3rd EDITION

Practical Guide to HIGH-RISK PREGNANCY & DELIVERY

A SOUTH ASIAN PERSPECTIVE

Fernando Arias
Shirish N Daftary
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Practical Guide to High-Risk Pregnancy and Delivery

A South Asian Perspective

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A South Asian Perspective

Third Edition

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In loving memory of

Dr Fernando Arias

June 11, 1943 – August 7, 2007

To our families

Dr (Mrs) Sindhu Daftary, Dr Gaurang Daftary,

Dr Ameet, and (Mrs) Aanal Mehta Daftary

Shirish N Daftary

To our families

Mr Govind Bhide, Mrs Manik Bhide, Dr (Mrs) Priya Bhide,

(Miss) Anuradha Bhide, and (Miss) Malvika Bhide

Amarnath G Bhide

Preface to the Third Edition

The second edition of this book was widely applauded by students in training and practitioners alike. It presented concisely the present-day trends in the management of pregnant women and provided guidance for the optimum care of high-risk pregnancies. An update of this treatise has been long awaited. In appreciation of the popularity of the book, Professor Fernando Arias was persuaded to revive it and bring it back to the offices of practicing obstetricians along with added observations and experiences of Indian workers. The experiences of the senior Indian author—an obstetrician practicing the art for over 40 years, author of several works in the specialty, and a teacher at the Seth GS Medical College and Nowrosjee Wadia Maternity Hospital, Mumbai for over 30 years—combined with the expertise of the joint author who has been professor of Obstetrics and Gynecology at the Seth GS Medical College and Nowrosjee Wadia Maternity Hospital, Mumbai for many years and is presently a consultant in maternal–fetal medicine at the well-known St. George's Hospital, London, UK, have provided fresh inputs to update this book to suit the Indian subcontinent.

A separate chapter on Tropical Diseases in Pregnancy has been added keeping in mind Indian conditions. Data of relevance to India has been added at relevant places in all the chapters. The addition of Indian experiences at the end of every chapter lends additional information about the experiences of practitioners in India, which may be of relevance to readers of the subcontinent.

Shirish N Daftary
Amarnath G Bhide

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Section I

FETAL MEDICINE

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Antepartum Care of the High-Risk Pregnancy

*Andres Sarmiento R**

CHAPTER OUTLINE

A high-risk pregnancy is that with a significant probability for a poor maternal or fetal outcome. In some cases, these patients are recognized in the initial prenatal office visit because they have a poor obstetrical history or a well-recognized medical complication. In other cases women become high-risk pregnancies because they develop unexpected complications in the course of otherwise normal pregnancies. These patients with unexpected complications are in a vulnerable emotional position due to the sudden loss of their expectations for a normal pregnancy and the lack of preparedness for invasive testing and obstetrical interventions. High-risk patients require sophisticated maternal and fetal surveillance and in many occasions difficult management decisions in order to optimize their outcome. This chapter provides (a) a description of the available systems to identify women at high risk for abnormal pregnancy outcomes, (b) a general description of prenatal care focused in the prevention of morbid outcomes not analyzed in other chapters of this book, and (c) an overview of the methods used for fetal surveillance in high-risk pregnancies, the rationale behind their use, the situations where their use is indicated, their limitations, their clinical usefulness, and their impact on the maternal and fetal outcome.

IDENTIFICATION OF THE HIGH-RISK PATIENT

A high-risk pregnancy can be identified only if the woman has access to prenatal care. Poverty—limiting access to the health care system—and lack of ability of societies and governments to provide medical coverage to those unable to pay for these services are powerful factors that prevent access to prenatal care. Once the woman has access to prenatal care, the second limiting factor preventing the identification of those at risk is the quality of the prenatal care

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itself, because in many cases the services provided are of marginal quality, and high-risk patients are not identified.

High-risk pregnancies are a small segment of the obstetrical population that produces the majority of the maternal and infant mortality and morbidity. This denomination includes women with chronic hypertension, pregestational diabetes, anemia, chronic lung disease, Rh alloimmunization, cardiac and renal disease, women at risk for congenital abnormalities in the offspring, and other conditions (Box 1-1) that place the pregnancy at risk (Martin et al., 2003). Women with a poor obstetrical history (Box 1-2) are also at high risk for abnormal outcomes.

To facilitate the identification of high-risk pregnancies, most prenatal records incorporate a list of high-risk factors that should be systematically checked during the first prenatal visit to find women at risk. Some of these systems assign a numerical value to the high-risk factors, depending on the potential severity of their effects on the pregnancy or the accuracy of the risk factor in predicting outcome, resulting in a numerical score that is supposed to be a quantitative reflection of the severity of the problems and their potential effects on the pregnancy. A potential benefit of this quantitative estimation of risk is that it may be useful to identify those cases that because of the severity of their problems require prenatal care under the direction of a specialist in Maternal Fetal Medicine. There are no adequate studies providing a basis for or demonstrating the benefits of referring women with high-risk factors to the specialists in Maternal Fetal Medicine, and the pattern of referral varies significantly between communities. Some suggestions on this respect are found in Box 1-3.

Unfortunately, most individual high-risk factors lack the necessary qualities to be adequate predictive tools. There are several methods to assess the accuracy or strength of a risk factor. One of these methods compares the frequency of a given outcome in patients with and without the risk factor (likelihood ratio), and the higher its value the stronger the association with the adverse outcome. However, even risk factors strongly associated with a given outcome may be poor predictors if the frequency of the outcome is low. For example, a cervical length of less than 1.5 cm is associated with preterm delivery within 7 days with a likelihood ratio of 8.7 (Gomez et al., 2005). The predictive value of this measurement will be much less in an unselected population with a frequency of preterm delivery of 11% than in a population at high risk with a frequency of preterm birth of 35%.

Another method to assess the predictive value of a high-risk factor is by analysis of its sensitivity and specificity. Sensitivity is the ability of the variable to identify patients who have the abnormal outcome and specificity is the ability of the same variable to identify patients who do not have the outcome. Most of the time when the sensitivity of a variable is high, the specificity decreases and the number of false positives increases. For example, uterine contractions are a sign with high sensitivity to predict the onset of preterm labor. However, the specificity of uterine contractions is low, and a large number of women with contractions will not deliver preterm. ROC (receiver

BOX 1-1

Partial list of medical conditions that place pregnancy at high risk for a poor outcome

- Malnutrition
- Anemia
- Chronic hypertension
- Diabetes
- Asthma
- Thrombophilia (history of DVT or PE)
- Cardiac disease
- Seizure disorder
- Family history of genetic disease
- Hemoglobinopathy
- Renal disease
- Psychiatric illness
- Lupus erythematosus and other connective tissue disorders
- Drug and alcohol abuse
- Smoking
- Rh alloimmunization
- Hepatitis B carrier
- Human immunodeficiency virus infection
- Syphilis
- Gonorrhea and Chlamydia infection
- Asymptomatic bacteriuria

BOX 1-2

Obstetrical high-risk factors

- History of previous prolonged labor—instrumental assisted delivery
- History of previous obstructed labor/rupture—uterus/traumatic delivery
- History of postpartum hemorrhage (high parity status)/obstetric shock
- History of puerperal sepsis
- Prior preterm birth (less than 36, less than 32, less than 28 weeks)
- History of birth asphyxia/neonatal convulsions/birth injuries
- Prior stillbirth
- Prior fetal growth restricted infant
- Second trimester pregnancy loss
- Prior neonatal death
- Prior infant with cerebral palsy
- Prior cesarean delivery
- Diagnosis of incompetent cervix in prior pregnancy
- History of preeclampsia before 32 weeks in prior pregnancy
- Prior fetus with chromosomal disorder or congenital anatomic abnormalities
- Anatomic abnormality of the uterus
- History of cervical trauma

BOX 1-3

High-risk patients that may benefit from referral or consultation with maternal fetal medicine

1. Women with conditions that may require invasive procedures for fetal diagnosis or treatment, such as:
   - Rh alloimmunization
   - Nonimmunologic fetal hydrops
   - Fetal urinary tract obstruction
   - Need for CVS
2. Women with severe medical complications affecting the pregnancy, such as:
   - Insulin-dependent diabetes
   - Artificial heart valves
   - Cardiomyopathy
   - Systemic lupus erythematosus
   - Sickle cell disease/thalassemia
   - Thromboembolic phenomena
   - Seizure disorder
3. Women with recurrent poor obstetrical outcome, such as:
   - Repetitive second trimester pregnancy losses
   - Recurrent stillbirths
   - Recurrent early preterm labor
   - Recurrent early rupture of membranes
4. Women with severe obstetrical complications, such as:
   - Preeclampsia/eclampsia with renal failure, pulmonary edema
   - Severe HELLP syndrome
   - Suspected cervical incompetence after 20 weeks' gestation
   - Suspected twin-to-twin transfusion
   - Multiple gestation of high order (3 and above)

operating characteristic) analysis is a plot of sensitivity on the y-axis versus 1– specificity (false positive results) on the x-axis. It is useful to determine if the high-risk factor discriminates better than chance alone and to find the threshold value with greater sensitivity and less false positive results which will be used to determine when the test is positive or negative.

For the individual patient and for the clinician taking care of patients, the positive and negative predictive values of the test are more significant and useful than their sensitivity and specificity. Positive predictive value is the probability that an individual who if tested positive is going to develop the condition he or she is being tested for. Negative predictive value is the probability that a negative test result truly predicts that the condition will not occur. The predictive value of any test is affected by the prevalence of the condition in the general population. A test may have a high sensitivity (ability to detect cases in the general population) but a low positive predictive value if that condition only affects a small segment of the population. Since abnormal and particularly catastrophic pregnancy outcomes occur infrequently, the majority of obstetrical tests are characterized by low positive and high negative predictive values.

Another tool to determine the predictive value of high-risk factors is the univariable analysis where all the variables significantly associated with a given outcome are used in a predictive model to determine which of them is the strongest predictor. Another method, the multivariable analysis, in particular logistic regression, performs a stepwise evaluation of the relative contribution of each variable to the prediction model and allows the investigator to determine if one or several of the variables under consideration are independent or not of each other. These are refined statistical techniques used to measure the accuracy of high-risk factors, laboratory tests and interventions in the prediction of outcomes. An excellent review of methods of clinical prediction is found in the article by Grobman and Stamilio (2006).

The use of individual or composite high-risk factors does not allow an accurate prediction of women who are going to deliver preterm because of preterm labor with intact membranes or because of premature rupture of membranes early in gestation. Similarly, there are no risk factors that predict with accuracy the occurrence of preeclampsia. This is unfortunate, because these two conditions, preterm delivery and preeclampsia affect close to 15% of all pregnancies, particularly in nulliparous patients, and the lack of adequate methods for their prediction and treatment poses a heavy burden on the discipline of Obstetrics.

PRECONCEPTIONAL COUNSELING

The best time to assess the potential impact of medical or obstetrical complications on the outcome of pregnancy is before pregnancy occurs. This is known as preconceptional counseling. Ideally a significant number of high-risk pregnancies can be identified before pregnancy occurs. When this happens, the woman will benefit considerably from a meeting with the obstetrician to analyze her high-risk factors and the life style modifications that she may adopt to maximize the outcome of pregnancy. In the course of this interview the following points should be methodically reviewed by the obstetrician:

1. The relative importance of each one of the high-risk factors identified through the history and examination of the patient.
2. The potential effects that each risk factor may have on the pregnancy.
3. The changes or effects that pregnancy may cause upon each risk factor.
4. The potential disability for the mother during pregnancy and the length of such disability.
5. The tests that will be required to monitor maternal and fetal well-being during pregnancy.
6. The prognosis for the outcome of the pregnancy.

7. The cost of the pregnancy particularly in terms of loss of revenue as a result of prolonged hospitalization and frequent testing, and the need for help at home with other children and the monetary and emotional costs of dealing with the effects of prematurity.

The ideal medical condition benefiting from preconceptional counseling is maternal diabetes. It includes education about the effects of diabetes on pregnancy and the effects of pregnancy on diabetes, advantages of rigorous metabolic control, and the importance of maintaining a low preconceptional level of glycosylated hemoglobin to decrease the incidence of congenital malformations. Other conditions that may benefit greatly from preconceptional counseling are Rh alloimmunization, history of recurrent stillbirths and patients at high risk for having fetuses with aneuploidy. Women with history of birth of a baby with neural tube defect should be prescribed folic acid supplements for 3 months prior to attempting subsequent pregnancy. In India, the practice of routine immunization of adolescents against rubella is not yet universally prevalent. Hence in present day practice, obstetricians are called upon to care for patients suffering from rubella during pregnancy with its potential to cause fetal malformations. Routine testing for rubella IgG antibodies prior to planning pregnancy is recommended. All susceptible patients should be immunized and advised against attempting pregnancy for the subsequent 3 months. Lastly, because of the high prevalence of thyroid disease in the sub-Himalayan region, the use of iodized salt and the practice of screening all patients for thyroid disorders are recommended. Thyroid insufficiency is an important cause of mental retardation in the offspring.

An important requirement of preconceptional counseling is that it should be nondirective. For example, when asked about the advisability of becoming pregnant, the obstetrician should provide information on the subject as factual as possible and avoid to tell the patient what to do. The decision to become pregnant despite significant risks is very personal and based on a multiplicity of variables and considerations that are known only by the patient and her partner.

Another important aspect of preconceptional counseling is to give consideration to the financial burden associated with the care of a high-risk pregnancy, particularly in terms of working disability. Many parents are not aware of the potential impact on the family unit and the personal cost that they assume when they get pregnant, specifically in terms of time off work and the need for help with children and household duties when they are admitted to the hospital or placed on bed rest at home.

PRENATAL CARE

Not too long ago the main objective of obstetrical practice was the prevention of maternal mortality. Improvements in the overall health conditions of women, obstetrical anesthesia, laboratory diagnosis, availability of blood transfusion, and improvements in surgical techniques resulted in significant advances in achieving this objective, and in industrialized societies maternal mortality became a rare event. Furthermore, maternal morbidity also markedly decreased. The significant improvements achieved in maternal outcomes were quickly followed by the adoption of a second paradigm of obstetrical care which was to obtain the best possible fetal outcome. Progress in achieving the fetal objective of obstetrical care has been amazingly rapid not only because of continuous technological developments but also due to the universal adoption of the concept of the "fetus as a patient" that clearly established the dual responsibility of the obstetrician as provider of care not only for the mother but also for the fetus. It was found soon that a small proportion of all pregnancies was responsible for the large majority of poor fetal outcomes, and in the last 30 years an explosion of knowledge about these pregnancies at risk has affected all aspects of prenatal care and has been responsible for the development of a new medical speciality in Maternal and Fetal Medicine.

One of the most significant achievements of the new discipline in Maternal and Fetal Medicine has been the discovery and subsequent integration to obstetrical care of new methods for the surveillance of the high-risk pregnancy. Unfortunately, many of these tests have been adopted into the regular obstetrical care of low-risk pregnancies without studies demonstrating their usefulness in this particular population. This has increased the cost of pregnancy care, burdened specialized laboratories with unnecessary tests, and has had little to do in improving the outcome of low risk women.

In summary, the main objective of prenatal care is the prevention and treatment of abnormal maternal and fetal outcomes. Prenatal care offers a unique opportunity to detect pathological conditions affecting the pregnancy and implement interventions that may positively affect these outcomes.

Determination of Gestational Age

An accurate determination of the gestational age and the expected date of delivery (EDD) is fundamental to the management of high-risk pregnancies. Proper assignment of the EDD is necessary in order to obtain and appropriately interpret laboratory tests, to plan and execute therapeutic maneuvers, and to determine the optimal management in certain difficult situations.

It is generally accepted that the best method to determine gestational age is through neonatal evaluation. Unfortunately, neonatal evaluation is not useful to the obstetrician, and there are data suggesting that overestimation of

gestational age in very preterm babies and underestimation of gestational age in post-term pregnancies occurs frequently when the neonate is evaluated by the Ballard's method as compared with early ultrasound examination (Alexander et al., 1992). Despite these deficiencies neonatal evaluation of gestational age is the "gold standard" to determine the accuracy of any other method.

Clinical dating

Clinical dating has limited value. Even women who conceive in the course of infertility protocols may have significant errors in the estimation of their EDDs. Therefore, all pregnant women including those with reliable clinical criteria pointing to a given EDD should have ultrasound examination for confirmation of their gestational age.

The variables necessary for clinical estimation of gestational age are the timing and characteristics of the last menstrual period (LMP), the findings on the initial pelvic examination, the date on which fetal heart tones are first heard, and the relation between the date of the first positive pregnancy test and the menstrual history.

The patient's menstrual history is considered adequate for the purpose of establishing the EDD only if the LMP was normal in duration and amount of flow, if the prior menstrual periods came at regular intervals, and if the patient did not use oral contraceptives within 3 months of her last period. Unfortunately, 30% of patients do not fulfill those criteria, thus making estimation of the EDD based on their LMPs unreliable. In a study of more than 11,000 pregnancies at McGill University, it was shown that LMP estimates were particularly inaccurate in patients with preterm and post-term pregnancies (Kramer et al., 1988).

The evaluation of uterine size has limited value for accurate clinical dating. Among the many variables that make assessment of the uterine size unreliable are maternal obesity, observer experience, position of the uterus, amount of amniotic fluid, multiple gestation, presence of uterine myomas, and fetal growth disorders. Studies have demonstrated that physician's measurements tend to underestimate the gestational age and have a preference for even numbers (Alexander et al., 1989).

The date on which fetal heart tones are first audible with Doppler ultrasound devices (10 weeks) or with standard obstetrical stethoscopes (20 weeks) has also been used to determine gestational age. Similar to other clinical parameters to evaluate gestational age, the time at which fetal heart sounds are first heard is an ineffective way to assess gestational age. It has value only when it agrees with other clinical indicators and with the ultrasound measurements.

In some patients, the time at which the first positive pregnancy test was obtained may be useful to establish the EDD. The sensitivity of the available over-the-counter pregnancy tests allows the diagnosis of pregnancy at 4–5 postmenstrual weeks. Thus, if a patient has a positive pregnancy test 4–5 weeks' after her LMP the patient's dates become firmly established.

Dating by ultrasound

The ability to visualize with ultrasound different fetal anatomic landmarks and to follow their growth during gestation is one of the most important tools that the obstetrician has acquired for the evaluation of the fetus. Fetal biometry has made it possible to accurately determine the gestational age of the fetus and the adequacy of the fetal growth. The methods most commonly used to determine the gestational age and EDD involve measurement of the crown–rump length (CRL) in the first trimester and the biparietal diameter (BPD), head circumference (HC), femur length (FL), humerus length (HL), and abdominal circumference (AC) in the second trimester. Cross-sectional or longitudinal measurements of these variables are plotted in scattergrams and the data analyzed by polynomial regression to obtain a curvilinear graph. By convention, the 5th and 95th percentiles above and below the curve are used to measure the normal dispersion or confidence limits around the mean. The measurements obtained in a given patient can be compared with the norms, and deviations from normality can be recognized.

Fetal biometry has been fundamental for determining the gestational age and to follow the fetal growth, but this is not without problems. One of these problems is inadequate interpretation of fetal measurements which are thought to reveal an error in the patient's gestational age when in fact they are indicative of abnormalities of the fetal growth, either fetal growth restriction (FGR) or a large for gestational age fetus. This error may have serious implications because FGR may not be discovered until late stages, when fetal hypoxia and acidosis may have already occurred, and also because an undiscovered large for gestational age infant may have serious intrapartum problems. The opposite mistake may also occur and normal fetuses may be classified as growth restricted and submitted to unnecessary testing and intervention. Despite these problems, fetal biometry remains one of the most important tools for following the high-risk pregnancy patient.

Determination of gestational age by ultrasound has similar accuracy when performed between 11–14 weeks of gestation and 18–22 weeks of gestation. This was demonstrated in a study of 104 singleton, 81 twins, and 33 triplet pregnancies conceived by in vitro fertilization (Kalish et al., 2004). After 22 weeks the margin of error increases, and it is necessary to obtain serial measurements 3–4 weeks apart to avoid a significant error. The reliability of the EDD may be categorized as excellent,

BOX 1-4

Reliability of the expected date of delivery

Excellent dates

1. Patients with adequate clinical information (known, normal LMP; 28–30-day cycles; no recent use of oral contraceptives; uterine size in agreement with dates) plus ultrasound examination between 16 and 24 weeks indicating that the fetal measurements are in agreement with the clinical estimation of gestational age.
2. Patients with inadequate or incomplete clinical information but with two ultrasound exams between 16 and 24 weeks showing linear fetal growth and similar EDD.

Good dates

1. Patients with adequate clinical information (as defined above) and one confirming ultrasound examination obtained after 24 weeks of gestation.
2. Patients with inadequate or incomplete clinical information and two or more ultrasound exams showing adequate growth and similar EDD.

Poor dates

Any clinical situation different from those listed above.

good, or poor by using the set of clinical and ultrasound criteria shown in Box 1-4.

Crown–rump length

Measurement of the CRL in the first trimester of pregnancy is the most accurate method to determine gestational age. The image should show a longitudinal view of the embryo and the calipers should be placed at the outer edge of the cephalic pole and the embryonic rump (Figure 1-1). The measurements are more accurate when the embryo is visualized with high-frequency vaginal ultrasound (Lasser et al., 1993). The CRL is accurate and predicts the menstrual age with a variation of + 3 days when it is obtained between 7 and 10 weeks. The variation increases with gestation and is + 5 days between 10 and 14 weeks. The practical implication of this information is that between 7 and 10 weeks' gestation, a discrepancy of more than 3 days between the gestational age calculated from clinical information and the gestational age calculated from the CRL indicates that the gestational age determined by the CRL is the true gestational age and the EDD must be changed. The same rule applies to a difference of

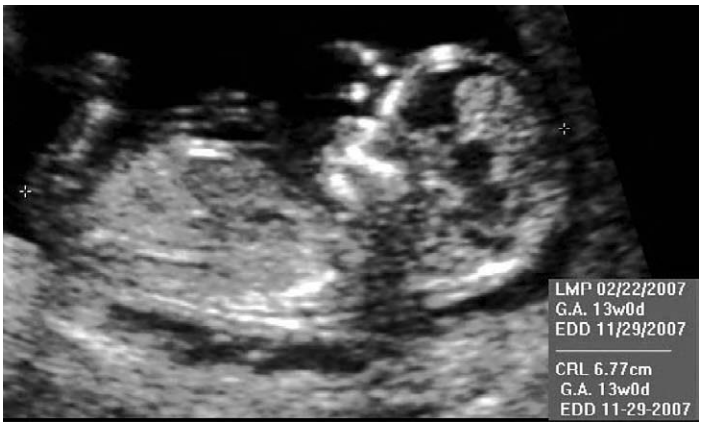


Figure 1-1. Crown–rump length.

Table 1-1. Gestational age by crown–rump length (6–15 weeks)

CRL (mm)	Gestational age (weeks)	CRL (mm)	Gestational age (weeks)	CRL (mm)	Gestational age (weeks)	CRL (mm)	Gestational age (weeks)	CRL (mm)	Gestational age (week)
3	5.9	21	8.7	39	10.8	57	12.3	75	13.6
4	6.1	22	8.9	40	10.9	58	12.3	76	13.7
5	6.2	23	9.0	41	11.0	59	12.4	77	13.7
6	6.3	24	9.1	42	11.1	60	12.5	78	13.8
7	6.4	25	9.2	43	11.2	61	12.6	79	13.9
8	6.5	26	9.4	44	11.2	62	12.6	80	14.0
9	6.9	27	9.5	45	11.3	63	12.7	81	14.1
10	7.1	28	9.6	46	11.4	64	12.8	82	14.2
11	7.2	29	9.7	47	11.5	65	12.8	83	14.2
12	7.4	30	9.9	48	11.6	66	12.9	84	14.3
13	7.5	31	10.0	49	11.7	67	13.0	85	14.4
14	7.7	32	10.1	50	11.7	68	13.1	86	14.5
15	7.9	33	10.2	51	11.8	69	13.1	87	14.6
16	8.0	34	10.3	52	11.9	70	13.2	88	14.7
17	8.1	35	10.4	53	12.0	71	13.3	89	14.8
18	8.3	36	10.5	54	12.0	72	13.4	90	14.9
19	8.4	37	10.6	55	12.1	73	13.4	91	15.0
20	8.6	38	10.7	56	12.2	74	13.5		

From Hadlock FP, Shah YP, Kanon DJ, et al. Fetal crown–rump length: reevaluation of relation to menstrual age (5–18 weeks) with high-resolution real-time US. Radiology 1992; 182: 501–5.

Table 1-2. Gestational age by BPD measurements

BPD (mm)	Gestational age (weeks)			BPD (mm)	Gestational age (weeks)		
	10th percentile	50th percentile	90th percentile		10th percentile	50th percentile	90th percentile
20	12	12	12	60	22.3	23.8	25.5
21	12	12	12	61	22.6	24.2	25.8
22	12.2	12.7	13.2	62	23.1	24.6	26.1
23	12.4	13.0	13.6	63	23.4	24.9	26.4
24	12.6	13.2	13.8	64	23.8	25.3	26.8
25	12.9	13.5	14.1	65	24.1	25.6	27.1
26	13.1	13.7	14.3	66	24.5	26.0	27.5
27	13.4	14.0	14.6	67	25.0	26.4	27.8
28	13.6	14.3	15.0	68	25.3	26.7	28.1
29	13.9	14.5	15.2	69	25.8	27.1	28.4
30	14.1	14.8	15.5	70	26.3	27.5	28.7
31	14.3	15.1	15.9	71	26.7	27.9	29.1
32	14.5	15.3	16.1	72	27.2	28.3	29.4
33	14.7	15.6	16.5	73	27.6	28.7	29.8
34	15.0	15.9	16.8	74	28.1	29.1	30.1
35	15.2	16.2	17.2	75	28.5	29.5	30.5
36	15.4	16.4	17.4	76	29.0	30.0	31.0
37	15.6	16.7	17.8	77	29.2	30.3	31.4
38	15.9	17.0	18.1	78	29.6	30.8	32.0
39	16.1	17.3	18.5	79	29.9	31.1	32.5
40	16.4	17.6	18.8	80	30.2	31.6	33.0
41	16.5	17.9	19.3	81	30.7	32.1	35.5
42	16.6	18.1	19.8	82	31.2	32.6	34.0
43	16.8	18.4	20.2	83	31.5	33.0	34.5
44	16.9	18.8	20.7	84	31.9	33.4	35.1
45	17.0	19.1	21.2	85	32.3	34.0	35.7
46	17.4	19.4	21.4	86	32.8	34.3	36.2
47	17.8	19.7	21.6	87	33.4	35.0	36.6
48	18.2	20.0	21.8	88	33.9	35.4	36.6
49	18.6	20.3	22.0	89	34.6	36.1	37.6
50	19.0	20.6	22.2	90	35.1	36.6	38.1
51	19.3	20.9	22.5	91	35.9	37.2	28.5
52	19.5	21.2	22.9	92	36.7	37.8	38.9
53	19.8	21.5	23.2	93	37.3	38.8	39.3
54	20.1	21.9	23.7	94	37.9	39.0	40.1
55	20.4	22.2	24.0	95	38.5	39.7	40.9
56	20.7	22.5	24.3	96	39.1	40.6	41.5
57	21.1	22.2	24.5	97	39.9	41.0	42.1
58	21.5	23.2	24.9	98	40.5	41.8	43.1
59	21.9	23.5	25.1				

From Kurtz AB, Needleman L. Ultrasound assessment of fetal age. In: Cullen PW, ed. Ultrasonography in Obstetrics and Gynecology (2nd edn). Philadelphia: Saunders, 1988: 47–64.

5 or more days for pregnancies between 10 and 14 weeks' gestation. One of the implications of accurate determination of gestational age by CRL is that the rate of induction for post-term pregnancy is significantly less when the gestational age is based on CRL than when it is based on second trimester biometry (Bennett et al., 2004). A possible source of error in the determination of gestational age by using the CRL is the presence of an embryo with chromosomal abnormalities, because abnormal embryos may be smaller than expected. Table 1-1 shows the gestational age by CRL between 6 and 15 weeks of gestation.

Biparietal diameter

The BPD is the most accurate measurement to determine the gestational age in the second trimester of pregnancy. In the majority of cases the BPD is relatively easy to obtain. It is measured in a transverse image of the head at the level of the thalamus with the calipers placed in the outer edge of the skull surface near to the transducer and in the inner edge of the distal skull (Figure 1-2). Fetuses in breech presentation may have a flattened head (dolichocephaly). If the fetal head looks flattened and elongated,

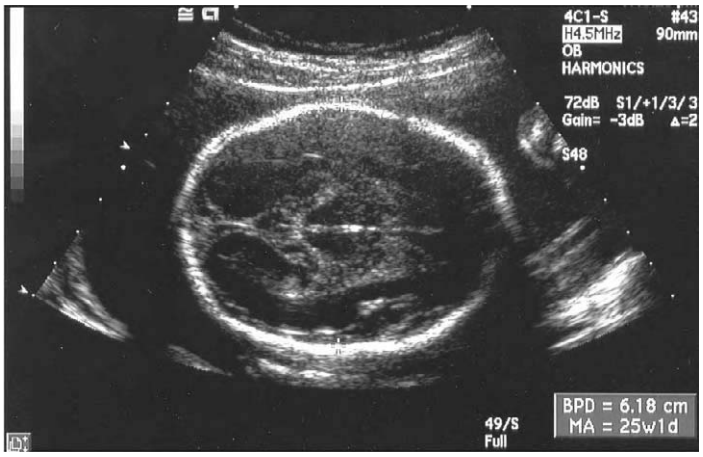


Figure 1-2. Biparietal diameter.

it is necessary to measure the cephalic index which is the ratio of the BPD divided by the occipitofrontal diameter (OFD). The cephalic index normal range is between 0.75 and 0.85, and when the value is less than 0.75 the HC should be used instead of the BPD to calculate the gestational age. It is frequently difficult to obtain adequate visualization of the transverse plane of the head when the fetal head is in occiput posterior position. In this case it is better to determine the gestational age using the femur or the HL. Table 1-2 shows the gestational age by BPD between 12 and 40 weeks.

Head circumference

The HC is measured in the same transverse plane as used to measure the BPD and it is not altered by dolichocephaly or brachycephaly of the fetal head. Most ultrasound machines measure the HC by means of electronic calipers but it can be calculated from the BPD and the OFD of the head, using the equation HC = BPD + OFD/2.

Femur length

The FL is an excellent parameter to calculate the gestational age, because it is not significantly affected by alterations in the fetal growth. It is measured in the bone closer to the transducer from the origin to the end of the bone' shaft without including the femoral head or the distal epiphysis (Figure 1-3). Table 1-3 shows the gestational age according to the FL.

Humerus length

The HL is another parameter, relatively easy to obtain, that is used for determination of the gestational age. It is measured in a similar way as the FL is measured.

Abdominal circumference

The AC is a less reliable parameter when used to determine gestational age because it is very sensitive to alterations in fetal growth. For the same reason the AC is the most important parameter in the estimation of fetal weight. The AC should be measured in a transverse plane at the

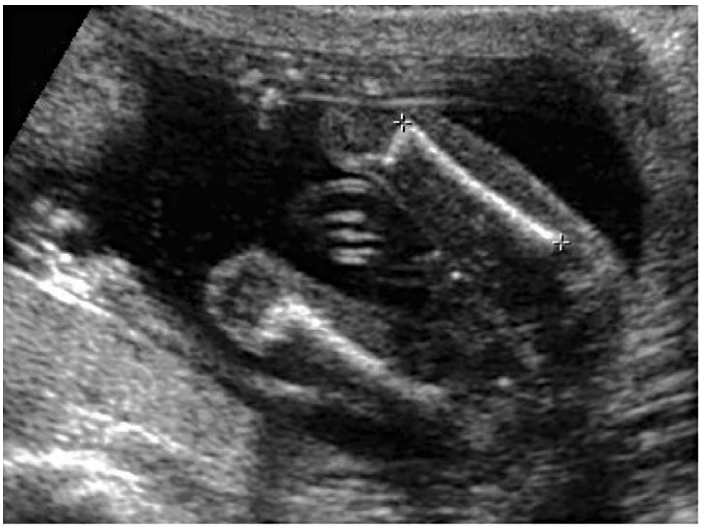


Figure 1-3. Femur length.

Table 1-3. Gestational age by femur length measurements

Gestational age (weeks)	Femur percentile		
	5	50	95
12	4	8	13
13	6	11	16
14	9	14	18
15	12	17	21
16	15	20	24
17	18	23	27
18	21	25	30
19	24	28	33
20	26	31	36
21	29	34	38
22	32	36	41
23	35	39	44
24	37	42	46
25	40	44	49
26	42	47	51
27	45	49	54
28	47	52	56
29	50	54	59
30	52	56	61
31	54	59	63
32	56	61	65
33	58	63	67
34	60	65	69
35	62	67	71
36	64	68	73
37	65	70	74
38	67	71	76
39	68	73	77
40	70	74	79

From Jeanty P, Cousaert E, Cantraine F, et al. A longitudinal study of fetal limb growth. Am J Perinatol 1984; 1: 136–44.

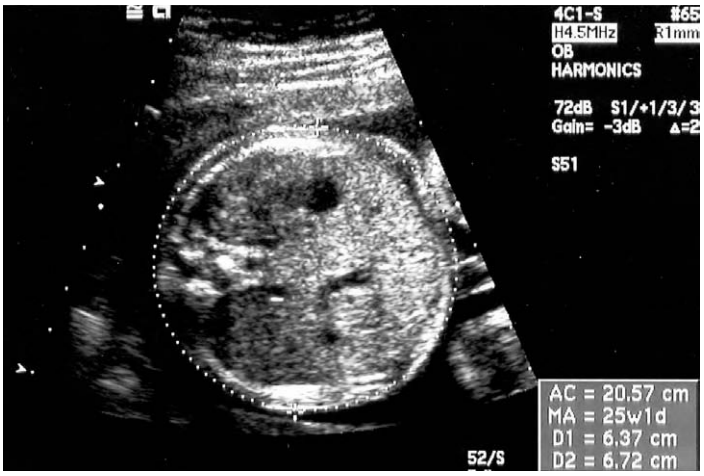


Figure 1-4. Abdominal circumference.

Table 1-4. Gestational age by abdominal circumference measurements

Gestational age (weeks)	–2SD	Mean	+2SD
12	31	56	81
13	44	69	94
14	56	81	106
15	68	93	118
16	80	105	130
17	92	117	142
18	104	129	154
19	116	141	166
20	127	152	177
21	139	164	189
22	150	175	200
23	161	186	211
24	172	197	220
25	183	208	233
26	194	219	244
27	204	229	254
28	215	240	265
29	225	250	275
30	235	260	285
31	245	270	295
32	255	280	305
33	265	290	315
34	275	300	325
35	284	309	334
36	293	318	343
37	302	327	352
38	311	336	361
39	320	345	370
40	329	354	379

From Hadlock FP, Deter RL, Harrist RB, et al. Fetal abdominal circumference as a predictor of menstrual age. Am J Roentgenol 1982; 139: 367–70.

level of the intrahepatic course of the umbilical vein. The ribs should be present at the sides of the image and the view should include the stomach bubble (Figure 1-4). When the umbilical vein is seen at its entrance in the abdomen, the plane is oblique and the measurement is not accurate. Table 1-4 show the gestational age in relation to AC measurements.

Other parameters used to determine gestational age

Other parameters are not commonly used to determine the fetal gestational age. These include the length of the tibia, the radius, the ulna, the clavicle, the foot, the binocular diameter, the sacrum and the transverse cerebellar diameter.

Determination of gestational age

Most ultrasound machines have incorporated into their software nomograms to calculate the gestational age using the BPD, HC, AC, FL, CRL, and HL. Some equipment includes nomograms for gestational age using the transverse diameter of the cerebellum and the size of the gestational sac. The estimated gestational age calculated from several of these variables is averaged and the result expressed as weeks and days of gestation. The EDD is then calculated automatically. Most of the equipment also calculates the gestational age and the EDD from the patient's menstrual history and so discrepancies in this information can be apparent to the examiner.

Prevention of Abnormal Maternal and Fetal Outcomes

The prevention of adverse maternal and fetal outcomes is the fundamental objective of prenatal care. The worse adverse outcomes are maternal and fetal death. Other poor outcomes are the birth of an infant with chromosomal abnormalities or congenital defects and the birth of a premature infant. The birth of an asphyxiated infant that later develops cerebral palsy is another tragic outcome. These outcomes have devastating consequences for the pregnant woman, her family and for society in general. Unfortunately, the frequency of these outcomes is unacceptable, particularly in developing countries, and most investigators agree that it is necessary to implement a multidisciplinary approach involving health care providers, community leaders, local governments, and the international community to have an impact on this problem. This book is entirely dedicated to the description and analysis of conditions causing abnormal pregnancy outcomes. This chapter is limited to the analysis of severe poor outcomes that are not covered in other chapters of the book, particularly maternal and fetal death.

Maternal death

Maternal death is the worst possible outcome of pregnancy. In industrialized countries, access to prenatal care and availability of legal abortion have been responsible for a significant decrease in the frequency of maternal deaths to about 8 per 100,000 live births. This is in dramatic contrast to developing countries, like Ethiopia, where the frequency of maternal deaths has been calculated at 1528 per 100,000 births (Jowett, 2000).

Worldwide figures are impressive and it has been estimated that one woman dies every minute from the effects of pregnancy or childbirth (Tracy and Tomich, 2002). Maternal mortality rates (MMRs) have been lowered dramatically in the developed world, but continue to remain appallingly high in the underdeveloped countries as shown in Table 1-5.

MMR in India continues to be unacceptably high; however, the MMR reveals wide regional variations as given in Table 1-6.

The low MMR achieved in Kerala (southern India) is the result of high literacy rate, better nutrition, improved status of women in society, and their demand for better health care. In the lesser progressive states of northern India, MMR continues to remain high. The mean MMR for India is 407 per 100,000 live births (Dutta, 2004). A great deal needs to be accomplished in the field of maternal health and welfare.

Table 1-5. Global perspective of MMR

S. No.	Developed countries	MMR/ 100,000 LB	Developing countries	MMR/ 100,000 LB
1.	USA	9.1	India	407
2.	Scandinavia	7.4	Pakistan	580
3.	United Kingdom	9	Bangladesh	850
4.	Japan	9.1	Nepal	1240
5.	Canada	4	Sri Lanka	26
6.	Germany	10	Myanmar	270
7.	Hong Kong	5	Malaysia	69
8.	Singapore	6	China	95

LB = live births

Table 1-6. MMR in different parts of India (mean MMR for India: 407/10,000 LB)

Indian state	MMR	Indian state	MMR
Andhra Pradesh	436	Karnataka	250
Assam	544	Kerala	67
Bihar	470	Madhya Pradesh	498
Gujarat	189	Maharashtra	236
Haryana	236	Orissa	738
Himachal Pradesh	356	Punjab	269
Rajasthan	625	Tamil Nadu	76
Uttar Pradesh	704	West Bengal	264

The Center for Disease Control (CDC) and the American College of Obstetricians and Gynecologists (ACOG) have defined pregnancy-associated deaths as those that occur during pregnancy or after 1 year of delivery. Pregnancy-associated deaths are pregnancy-related if the death resulted from complications of pregnancy, was the result of a chain of events initiated by pregnancy, or was due to an unrelated event aggravated by pregnancy or its management. If the cause of the death is not related to pregnancy, it is considered nonpregnancy-related. The International Classification of Diseases defines maternal death as the death of a woman while pregnant or after 42 days (or 1 year for late maternal deaths) of delivery, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by pregnancy, but not from accidental or incidental causes.

It is clear from these figures that the frequency of maternal deaths is similar in industrialized countries. Also similar are the main causes of maternal death (Table 1-7). In order of frequency the most important causes of maternal death in industrialized countries are hypertensive disorders, thromboembolism, bleeding, and abortion (Khan et al., 2006). Approximately 10% of maternal deaths occur during labor, 60% during the first postpartum week, and 25% during the second postpartum week (Berg et al., 1996). Even minimal prenatal care seems to be associated with a significant decrease in maternal mortality, but this association disappears when the data are corrected by income and education attainment (Harper et al., 2003). In USA, pregnancy-related mortality occurs significantly more frequently in African-American mothers.

Table 1-7. Causes of maternal death by geographical criteria

Developed countries:	
■ Hypertensive disorders	16.1%
■ Embolism	14.9%
■ Hemorrhage	13.4%
■ Abortion	8.2%
Africa:	
■ Hemorrhage	33.9%
■ Sepsis/infection	9.7%
■ HIV/AIDS	6.2%
■ Obstructed labor	4.1%
Asia:	
■ Hemorrhage	30.8%
■ Anemia	12.8%
■ Sepsis/infection	11.6%
■ Obstructed labor	9.4%
Latin America and the Caribbean:	
■ Hypertensive disorders	25.7%
■ Hemorrhage	20.8%
■ Obstructed labor	13.4%
■ Abortion	12.0%

According to the last WHO systematic review, hypertensive disorders are the most frequent cause of death in developed countries and in Latin America and the Caribbean (Khan et al., 2006). In India, the leading direct causes of maternal mortality are hemorrhage, sepsis, preeclampsia and eclampsia, unsafe abortion, and obstructed labor. To decrease maternal deaths secondary to preeclampsia/eclampsia/HELLP syndrome in developing countries, it is necessary to increase access to prenatal care. Since access to care is not a limiting factor in industrialized nations, maternal mortality secondary to preeclampsia may be related to inadequate diagnosis and therapy. It is also important that death as a result of hypertension during pregnancy is age related and occurs more frequently in older women than in those aged < 25 years. The reader will find more information about this subject in the chapter on hypertension during pregnancy.

Prevention of maternal death due to thromboembolic disease requires search for all known thrombophilias before or at the beginning of prenatal care. Unfortunately, these tests are expensive and have limited positive predictive value. A single laboratory test capable of detecting multiple thrombophilias would be ideal for the screening of the obstetrical population. A test with these characteristics, thrombin generation, has been used prospectively in a nonpregnant population at high risk for recurrent venous thromboembolism and was found to be a good discriminator between patients at high and low risk of recurrent deep vein thrombosis (Hron et al., 2006). A significant number of cases of thromboembolic disease during pregnancy can be prevented by the liberal use of pneumatic compression stockings in women who rest in bed for prolonged periods of time, such as those with threatened preterm labor, preeclampsia, and premature rupture of the membranes. Prophylactic heparinization with low-dose fractionated or unfractionated heparin in women with risk factors for thromboembolization will also be useful to decrease the incidence of this problem. The reader will find more information about this subject in the chapter about hematologic complications of pregnancy.

In industrialized countries where patient access to care is not a limiting factor, the majority of maternal deaths due to bleeding are preventable and are due to substandard care (de Swiet, 2000). Despite multiple advances in diagnostic tools, blood banking, interventional radiology, drug therapy, mechanical devices, and surgical techniques for bleeding control, women continue to die from obstetrical hemorrhage. Obviously, there is a problem with the application of technology and with adequate use of resources in cases of obstetrical hemorrhage—an area where continuous education of health care providers may have a significant effect. The interested reader will find more information about this subject in the chapter about bleeding during pregnancy.

Maternal death secondary to infection exhibited a significant decrease with the availability of legal abortion but is on the rise again. This trend is more apparent in developing countries with a high frequency of infections by the human immunodeficiency virus (HIV). In industrialized countries, overwhelming sepsis caused by antibiotic-resistant bacteria is responsible for a significant proportion of infection-related deaths.

Maternal death secondary to abortion is still a significant problem in developing and industrialized countries. According to the last WHO systematic review, 8.2% of maternal deaths in developed countries are secondary to abortion—a figure that is only surpassed by Latin-American and Caribbean nations with an incidence of 12% (Khan et al., 2006) and 13% in India. In contradistinction, the frequency of maternal deaths secondary to abortion is 3.9% in Africa and 5.7% in Asia. This is an alarming problem that can be explained partially by the lack of availability of legal abortion in developing countries but has no adequate explanation in industrialized countries where abortion is legal. Direct obstetric causes relate to maternal deaths resulting from complications of pregnancy, labor, puerperium due to interventions, omissions, or incorrect treatments, or from a chain of events resulting from any of the above.

In summary, maternal death is an untenable public health problem that requires priority attention. Most maternal deaths directly or indirectly related to pregnancy are preventable, but this requires significant social and governmental efforts to eliminate poverty and restrictions to human rights and individual efforts from health care providers, taking care of pregnant women to keep up with the methods to identify women at risk and to aggressively treat those complications that may result in maternal death.

Stillbirth

Stillbirth is a fetal death occurring after 20 weeks' gestation or when the fetus weighs more than 500 g. The stillbirth rate in USA in 2002 was 6.4 per 1000 births. Black women have more than twice the rate of stillbirth than that of Caucasian females (Silver, 2007). A stillbirth is a major obstetrical catastrophe at any gestational age but the emotional pain and distress caused by this event increases in direct relation to the duration of pregnancy.

Some of the risk factors associated with fetal death are the presence of maternal medical complications, advanced maternal age, Black race, low socioeconomic status, obesity, high cigarette use, history of prematurity, and adverse outcome in a prior pregnancy (Huang et al., 2000; Froen et al., 2001; Vintzileos et al., 2002a; Kahn et al., 2003; Fretts, 2005). Few of these high-risk factors can be modified during prenatal care. However, their identification makes it possible to follow these women with frequent

clinical and laboratory assessments in the hope of preventing an abnormal outcome. One study of 98 stillbirths (Chibber, 2005) identified several risk factors for fetal death. The most frequent were nulliparity, multiparity (more than five pregnancies), low socioeconomic status, maternal age less than 18 or greater than 40 years, preconceptional weight greater than 70 kilograms (155 lbs), less than three prenatal office visits, and late prenatal care. These are factors that cannot be modified during prenatal care and have only prognostic importance. A recent systematic review (Fretts, 2005) identified 15 risk factors for stillbirth. The 3 occurring most frequently were preconceptional obesity, socioeconomic status, and advanced maternal age. These are variables that cannot be corrected during prenatal care.

In Latin-American countries the lack of prenatal care increases four times (RR 4.26, 95% CI 3.84–4.71) the risk of fetal death (Conde-Agudelo et al., 2000). In USA absence of prenatal care increases the relative risk (RR) of fetal death 2.9 times in the African-American and 3.4 times in the Caucasian population. Prenatal care decreases the possibility of fetal death even if other high-risk factors are present (Vintzileos et al., 2002b). The absence of prenatal care also affects the RR of neonatal death which increases 1.4 times for African-American and 1.5 times for Caucasians (Vintzileos et al., 2002b). As little as one prenatal visit improves the outcome of pregnancy and may decrease the risk of perinatal death by 20% (Mondestin et al., 2001).

The known causes of stillbirth are fetal, placental, and maternal (Table 1-8). However, the etiology of between 25 and 40% of stillbirths remains unknown despite careful search for an explanation. At present only approximately 25% of stillbirths can be prevented. The most important preventable category is placental insufficiency, which may be secondary to abnormal placentation, thrombophilia, or other factors. Placental insufficiency is also the main cause of stillbirth when medical conditions such as hypertension or diabetes affect the mother and when the obstetrical history reveals placental insufficiency in a prior pregnancy. For this reason the large majority of tests for antepartum fetal surveillance are designed to investigate the possibility of placental insufficiency and the fetal response to hypoxia.

Table 1-8. Etiology of stillbirth

Fetal	
■ Multifactorial genetic defects	16%
■ Aneuploidy	5%
■ Other genetic defects	2%
■ Fetal infection	5%
Placenta	
■ Placental insufficiency	14%
■ Abruptio placenta	12%
■ Cord accidents	4%
■ Fetomaternal bleeding	5%
Maternal	
■ Diabetes	3%
■ Hypertension	5%
■ Other maternal diseases	3%
Unknown	25%

The relative frequency of the causes of stillbirth is different depending on the gestational age when the fetal death occurs. Between 24 and 28 weeks the most common causes of fetal death are infection, abruptio placenta, congenital fetal abnormalities, and "unexplained" fetal death. Between 28 and 36 weeks the most common reasons are "unexplained", FGR, and abruptio placenta. After 37 weeks the most common etiologies are "unexplained", FGR, and abruption but the frequency of "unexplained" stillbirths increases markedly when compared with the 28–36 weeks' group (Fretts, 2005).

The role of the obstetrician in the prevention of stillbirth starts with the identification of patients at risk for this outcome: advanced maternal age, obesity, high cigarette use, low socioeconomic status, late and limited prenatal care, and women with medical complications such as diabetes, hypertension, connective tissue disorder, thyroid gland dysfunction, cardiac or renal disease, and severe asthma (Huang et al., 2000; Froen et al., 2001). All of these patients should have a first trimester screening for aneuploidy and a second trimester quad screening for the prediction of pregnancy outcome. Women with elevated concentrations of serum alpha-fetoprotein (MSAFP) in the second trimester of pregnancy unexplained by sonography are at increased risk for fetal death, FGR, preeclampsia, and premature rupture of membranes (Waller et al., 1991; Simpson et al., 1995). The risk is higher if the MSAFP concentration is greater than 3 multiples of the mean (MoM), but women with MSAFP between 2.0 and 3.0 MoMs are also at high risk. Women with low concentrations of MSAFP, equal or less than 0.25 MoMs, are also at risk for fetal loss (Burton, 1988). Unexplained elevations of maternal serum hCG (human chorionic gonadotropin) in the second trimester are also associated with poor pregnancy outcomes, including preeclampsia, growth restriction, preterm delivery, and fetal death. The association is strongest when the hCG concentration is equal to or greater than 4.0 MoMs, but values equal to or larger than 3.0 MoMs are of concern (Gonen et al., 1992; Towner et al., 2006). Low unconjugated estriol, undetectable or less than 0.15 MoMs, is also associated with fetal death, growth restriction, placental sulfatase deficiency, and Smith–Lemli–Opitz syndrome (Kowalczyk et al., 1998; Schoen et al., 2003). Increased maternal serum concentration of inhibin A in the second trimester is associated with the development of severe preeclampsia (Kim et al., 2006).

Women with risk factors for stillbirth and abnormal values of one or several analytes in the second trimester quad screening require careful and systematic follow-up clinically and with serial ultrasound examinations. The ultrasound follow-up of the fetal growth is important because the incidence of stillbirth in fetuses small for gestational age is 46.8 per 1000 live birth as compared with 4 per 1000 in fetuses growing appropriately. Uterine and umbilical Doppler should be measured starting at 24 weeks of gestation and further fetal evaluation dictated by the result of these exams and the pattern of fetal growth by ultrasound examination. Early delivery may be necessary if there is clear evidence of fetal compromise.

Post-term pregnancy is a condition associated with stillbirth. The incidence of fetal deaths is more than double when the gestational age is 40 weeks or more as compared with pregnancies between 38 and 40 weeks. The increase in mortality associated with post-term pregnancy is quite evident when the stillbirth rate is calculated correctly, using the number of undelivered fetuses as the denominator rather than the number of live births (Divon et al., 2004). Preventative intervention consists of delivery when the pregnancy reaches 40 weeks if the cervix is ripe and delivery at 41 weeks in all other cases.

It is important to investigate the cause of a stillbirth. If the cause of a fetal death can be identified, the family will have answers about the possibility of recurrence and the availability of medical treatment to prevent recurrence. There is no universally accepted evaluation plan to determine the cause of stillbirth, but it is widely accepted that pathological examination of the placenta, fetal autopsy, and karyotype are the most important elements of that assessment. The usefulness of the Kleihauer–Betke test for fetal–maternal hemorrhage, anticardiolipin antibodies, thrombophilia, and TORCH titer is limited.

Neonatal death

Neonatal death is another catastrophic outcome that in many occasions is a direct consequence of antepartum and intrapartum conditions. The incidence of neonatal deaths in USA is approximately 4.5 per 1000 live births. There are significant regional variations in the neonatal death rate that are a reflection of the quality of neonatal care. The neonatal mortality figures are much better for infants born in hospitals with Newborn Intensive care Units (NICU) than in hospitals with no NICU or small community NICUs (Cifuentes et al., 2002). There are racial differences as well and the neonatal mortality for Black infants is more than twofold greater than that in Caucasians. The Center for Vital Statistics of the United States classifies infant deaths as all those that occur within 1 year of birth. Neonatal deaths are subdivided into early neonatal (0–6 days), late neonatal (7–27 days), and postneonatal (28 days to 11 months). Early neonatal deaths constitute 80% of all neonatal deaths and late neonatal most of the remaining 20%.

The most frequent causes of neonatal deaths in USA are congenital malformations and chromosomal disorders (37%), prematurity (18.2%), complications of pregnancy, labor and delivery (15.4%), maternal complications of pregnancy (8.2%), placental and cord abnormalities (5.5%), and intrauterine hypoxia or birth asphyxia (2.9%). The number of neonatal deaths secondary to antepartum and intrapartum asphyxia has decreased substantially in USA. Similarly, with the generalized use of antepartum glucocorticoids and neonatal surfactant the number of respiratory deaths associated with prematurity has also markedly decreased. The overwhelming majority of neonatal deaths worldwide occur in developing countries, with the largest neonatal mortality rates in sub-Saharan Africa and south-central Asia. The main causes of neonatal mortality in developing countries are prematurity, infection, and birth asphyxia.

Obstetrical prevention of neonatal mortality is a complex task. The largest contributors in USA are congenital malformations. The effect of these conditions on neonatal mortality can be reduced by early diagnosis and pregnancy termination. Also, some of these conditions (neural tube defects) can be prevented with adequate ingestion of folic acid in the periconceptional period. Prevention of prematurity has been unsuccessful so far. However, a frequent contributor to preterm birth is the significant increase in multifetal gestations due to the use of ovulation-inducing agents and assisted reproductive techniques. A serious and generalized effort to avoid iatrogenic multifetal gestations will have an impact on neonatal mortality rates.

The perinatal mortality rates (PNMRs) in countries of the Indian subcontinent (India, Pakistan, and Bangladesh) are three- to fivefold higher than in the developed countries. Lack of antenatal care, lack of patient compliance, lack of facilities for prenatal fetal health monitoring and institutional care, and deficient neonatal care services contribute to the persistent high PNMRs in the developing countries. The PNMRs per 1000 births from different parts of India ranged from 34.16 in Mumbai (Daftary and Mehta, 1994) to 107 in north Bengal (Saha and Saha, 2002). PNMRs vary in different parts of India depending on the socioeconomic strata, literacy, nutritional status, quality of prenatal care, urban or rural setting, and facilities available for neonatal care. The common causes of perinatal mortality (based on the surveys by Rao et al. (2001), Jotwani et al., (2001), and Gaddi and Seetharam (2001)) include prematurity (27%), low birth weight (16%), birth asphyxia (17%), infections (12%), congenital malformations (7%), birth trauma (5%), respiratory distress syndrome (13%), and the rest (3%).

Preterm delivery and preeclampsia

Preterm delivery and severe preeclampsia are two frequent poor pregnancy outcomes. An accurate test for the prediction of women destined to deliver prematurely or to develop preeclampsia will be extremely valuable even in the absence of adequate means to treat those conditions. Such a test or tests will permit the selection of a cohort of patients that can be systematically analyzed to better study the disease and to develop adequate therapies. More information about the prediction of preterm delivery and preeclampsia will be found in the corresponding chapters of this book. At this time it is sufficient to say that the advent of cervical length measurements by ultrasound and the determination of fetal fibronectin in the vaginal secretions have been important steps in the prediction of women destined to deliver prematurely. Similarly, the combination of maternal serum inhibin A, activin A, and uterine artery Doppler at 23 weeks of gestation has a sensitivity between 75 and 92% for detecting women that will develop preeclampsia, with a false positive rate of 5 and 10%, respectively (Spencer et al., 2006). These developments raise hopes of rapid advancements in the upcoming years in the identification and treatment of these serious obstetrical complications.

Low-risk pregnancies

One question without answer at this time is if low-risk pregnant women need to be screened for abnormal outcomes. More than 20% of women with negative personal and family history have abnormal outcomes, particularly preterm labor, FGR, and preeclampsia (Moutquin et al., 1987). The high incidence of abnormal outcomes clearly justifies the screening of low-risk women. Although there are no adequate preventive measures for any of these three frequent obstetrical complications, knowledge of a high probability of disease will be valuable because fetal, neonatal, and maternal deaths may be prevented by closer surveillance and early pregnancy interruption.

ANTEPARTUM FETAL SURVEILLANCE

The timely detection of morbid changes in the fetal status followed by adequate interventions to avoid death or disability is one of the most important objectives of prenatal care. Unfortunately, despite all the advances of the last 40 years this goal remains an unfulfilled promise and some, mostly acute, catastrophic changes in fetal status remain unpredictable and nonpreventable. The largest advances have been made in the assessment of the fetus at risk of death and morbidity secondary to placental insufficiency, and there are numerous tests available for that purpose. One of these tests, Doppler studies of the maternal–placental and placental–fetal circulation, has acquired significant importance in the assessment of placental insufficiency because Doppler abnormalities are detectable days before the onset of more apparent clinical changes. Doppler evaluation of the fetal middle cerebral artery (MCA) in the assessment of fetal anemia is another example of the value of this technology for fetal surveillance.

There are limitations to the generalized use of tests of fetal well being in obstetrical practice. In the first place, there is no ideal single test that can detect all fetal problems. In the second place, none of the tests for fetal surveillance are absolutely specific and interventions due to a false positive test may lead to iatrogenic preterm delivery and increased neonatal morbidity. Finally, on many occasions the tests of fetal well-being are unable to timely detect the fetal problem and intervention has no beneficial effect. Unfortunately, patients are not adequately informed about the limitations of these tests and have unreasonable expectations that when unfulfilled generate animosity toward the obstetrician and are the source of medical legal problems.

The methods used to detect and evaluate the severity of acute or chronic fetal hypoxia are biophysical in nature. The tests used at present are:

1. Fetal movement count
2. The nonstress test (NST)
3. The contraction stress test (CST)
4. The fetal biophysical profile (BPP)
5. The modified biophysical profile (MBPP)
6. Umbilical, cerebral, uterine, and venous Doppler
7. Percutaneous umbilical blood sampling

Fetal Movement Count

Maternal perception of fetal movements has been a traditional indication of fetal well-being. In contrast, a decrease or cessation of fetal movements has ominous implications and is associated with fetal compromise and death. Maternal assessment of the frequency of the fetal movements is the simplest and least costly method for the evaluation of fetal well-being in the second half of pregnancy. Several studies have demonstrated a good correlation between fetal movements perceived by the mother between 28 and 43 weeks of gestation and fetal movements detected by real-time ultrasound. The periods of fetal activity last for about 40 minutes and the periods of rest about 20 minutes. The mother usually perceives between 70 and 80% of these movements. Observations by ultrasound indicate that the fetus has gross movements approximately 10% of the time and as many as 30 movements may occur in 1 hour. The peak activity is between 9:00 pm and 1:00 am, a time that usually coincides with a period of low maternal plasma glucose levels.

Several factors influence the perception of fetal movements including maternal obesity, excessive amount of

amniotic fluid, and ingestion of medications. These factors cause significant subjective variability in the perception of movements. For this reason investigators have developed methods with a more quantitative value. The method most commonly used is the "count to 10" (Moore et al., 1989) which is preferred by the patients over other methods (Christensen et al., 2003). Patients are instructed to begin counting fetal movements until they reach 10 movements. If the 10 movements are noticed in 10 hours or less, the fetus most probably is in good health. If the mother notices less than 10 movements in 10 hours, she should have further evaluation. Also, the patient should have additional evaluation if there is a doubling in the number of hours that are usually required to complete the 10 movements. Clinical trials on the usefulness of fetal movement counting in preventing fetal death have produced contradictory results. A study (Moore et al., 1989) concluded that screening with the "count to 10" method was effective in reducing fetal mortality. Another study in a large population (Grant et al., 1989) found no decrease in antepartum fetal death rate between no counting and routine counting of fetal movements.

The Nonstress Test

The test most commonly used for antepartum evaluation of the fetal status is the NST. The NST is noninvasive, easily performed and interpreted, and readily accepted by patients. The test looks for the presence of temporary accelerations of the fetal heart rate (FHR) associated with fetal movement. Heart rate acceleration with movement is a reflex that involves the cerebral cortex and is affected by physiologic or pathologic influences on the fetal brain. The most common physiologic situation suppressing this reflex is fetal sleep and the most common pathologic condition is fetal hypoxia. For this reason, the absence of accelerations during a NST must be considered a consequence of fetal hypoxia unless it can be explained otherwise.

NSTs are categorized as reactive or nonreactive. A reactive or normal NST (Figure 1-5A) is characterized by two or more FHR accelerations of at least 15 beats per minute (bpm) and lasting at least 15 seconds from baseline to baseline within a 20-minute period with or without association with fetal movements as perceived by the woman. A nonreactive NST (Figure 1-5B) is characterized by lack of accelerations, as previously described, for a period of 40 minutes. The NST is performed as described in Box 1-5. Vibroacoustic stimulation (VAS) also elicits acceleration of the FHR and has been added to the protocol to perform the NST (Zimmer et al., 1993). FHR reactivity, spontaneous or obtained with VAS, is a solid indicator of fetal health and absence of acidosis. VAS uses stimulation with an artificial larynx (sold in USA by A T & T) over the fetal head during 1–3 seconds. The instrument produces a vibratory acoustic

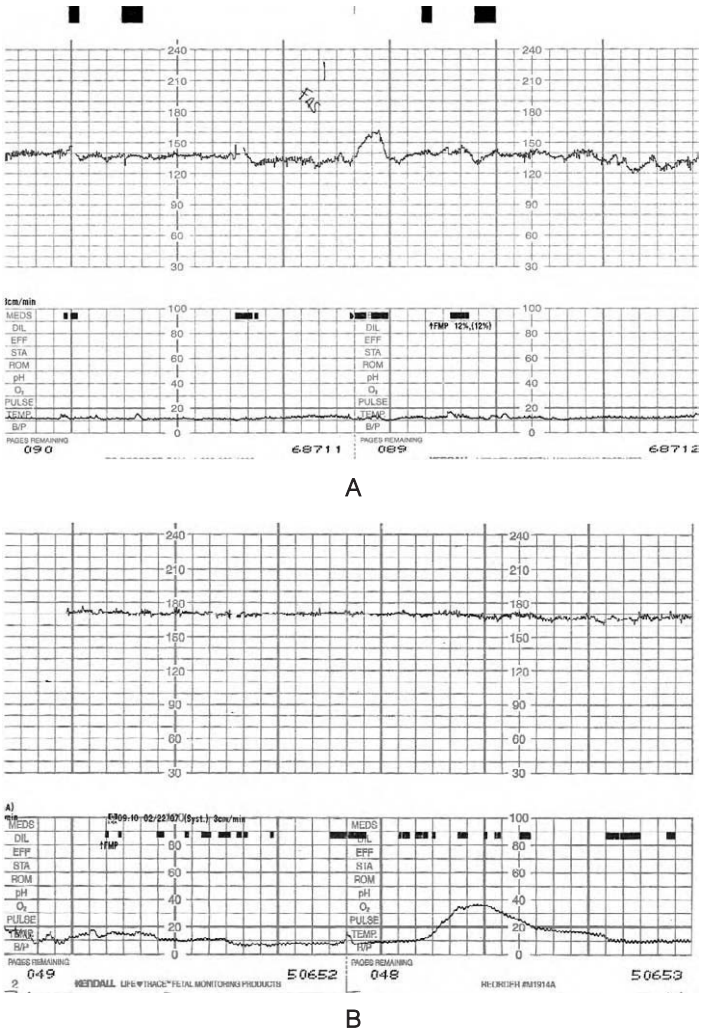


Figure 1-5. Reactive and non-reactive non-stress tests. A, Reactive NST. Acceleration of the fetal heart of 15 or more bpm, lasting 15 or more seconds following vibroacoustic stimulation. B, Nonreactive NST. There is decreased variability; no acceleration in association with contraction.

stimulus of approximately 80 Hz and 82 db. A healthy fetus will respond with sudden movement (startle response) followed by acceleration of the FHR. VAS was originally designed to decrease the time spent in the performance of the NST that is frequently prolonged because of episodes of fetal sleep, and soon the NST with VAS became the predominant method to perform the NST. The response to VAS is gestational age dependent. Fetuses of less than 24 weeks do not respond to VAS. Between 24 and 27, 27–30, and >31 weeks, 30, 86, and 96% of the fetuses will respond to the vibroacoustic stimulus, respectively. In the majority of cases, the acceleration of the FHR that follows stimulation lasts for several minutes. Other normal fetuses respond with a series of 2–5 accelerations lasting 20–60 seconds each. Maternal perception of fetal movement following VAS is another indicator of fetal well-being. However, if the mother does not feel the baby moving following VAS but

BOX 1-5

How to perform a nonstress test

1. Place patient in the semi-Fowler's position. Use pillows under one of the hips to displace the weight of the uterus away from the inferior vena cava. Take the patient's blood pressure every 10 or 15 minutes during the procedure because supine hypotension may cause a nonreactive result.
2. Apply the tococardiographic equipment to the maternal abdomen and observe the uterine activity and FHR for 10 minutes. Instruct the patient to push the calibration button of the uterine contraction tracing every time she feels fetal movement (FM).
3. A reactive test is present when two or more FHR accelerations are clearly recorded during a 20-minute period, each of 15 or more bpm and lasting 15 or more seconds, usually occurring simultaneously with episodes of fetal activity.
4. If no spontaneous FM occurs during the initial 20 minutes of observation, the test is continued for another 20 minutes, and during this period FM is provoked by external manipulation. If there is no acceleration with spontaneous or repeated external stimuli during a 40-minute period, the test is considered nonreactive.
5. The test is unsatisfactory (equivocal) if the quality of the monitor tracing is inadequate for interpretation.

there is a clear accelerative response of the FHR, the test is normal. An abnormal response to VAS, found in fetuses with chronic asphyxia, consists of no acceleration or deceleration of the FHR. VAS is safe, and no evidence of hearing impairment or other abnormality has been reported in neonates exposed to VAS in utero.

There are several factors that may influence the result of VAS. Some of them are the thickness of the maternal abdominal wall, the amount of amniotic fluid, the pressure exerted by the examiner in holding the artificial larynx against the abdomen, and the intensity of the stimulation. The influence of these factors is relatively small, and only 2% of NSTs are nonreactive following VAS. Of those NSTs that are nonreactive to VAS, 17% are followed by positive CSTs or by BPPs equal to or less than 4. Another area of application of VAS is in the management of intrapartum non-reassuring FHR tracings. In these cases, a positive response to VAS stimulation indicates that the fetus is not acidotic.

The NST is markedly influenced by the gestational age and approximately 50 and 15% of the NSTs performed in healthy, noncompromised fetuses 24–28 and 28–32 weeks, respectively, are nonreactive. Less false positive results will occur if the definition of reactivity is modified for women between 24 and 32 weeks and the NST is accepted as reactive if the peak of the accelerations reaches at least 10 bpm and the accelerations have a duration of at least 10 seconds.

The false negative rate of the test (reactive NST in a fetus who is actually in distress) is 3.2 per 1000, indicating that the likelihood of fetal death or serious fetal morbidity following a reactive test is very low. The frequency of stillbirth with reactive NST performed every week is 6.1 per 1000. When the frequency of testing is increased to twice weekly, the frequency of false negatives is substantially less, 1.9 per 1000 (Boehm et al., 1986). The false positive rate (nonreactive results in normal patients) is very high: 50% for morbidity and 80% for mortality, indicating that the probability of serious fetal problems when the test is nonreactive is also low. The high number of false positive results makes necessary to use additional corroborative testing before intervening in the majority of nonreactive NST. The large number of false positive results and the possibility that the test cannot recognize early stages of fetal compromise are the main concerns surrounding the use of the NST.

One of the reasons behind the high frequency of false positive results with the NST is that its interpretation relies on only one variable, the presence of accelerations of the FHR associated with fetal movement, and it ignores other important information such as FHR variability and the presence or absence of decelerations. These observations are of value in determining the true significance of a "nonreactive" result. A "nonreactive" result in the presence of poor FHR variability or decelerations strongly suggests fetal compromise. On the other hand, a "nonreactive" result when the FHR variability is normal and decelerations are absent most probably is a false positive result. The NST should be analyzed taking into consideration all the factors that provide information about the fetal well-being. An interpretation based solely on "reactivity" is incomplete and increases the incidence of false positive results. The variables that must be evaluated in the NST are:

1. Baseline FHR
2. Variability of the FHR
3. Presence or absence of accelerations
4. Presence or absence of decelerations

Each of these variables should be analyzed separately. A normal baseline heart rate frequency is between 110 and 160 bpm. Abnormalities in this variable are tachycardia (frequency greater than 160 bpm) and bradycardia (frequency less than 110 bpm). Alterations of the baseline frequency are most frequently due to maternal medications and maternal temperature but tachycardia and bradycardia may also occur with fetal hypoxia. Variability is of the utmost importance in the evaluation of the NST. Modern fetal heart monitoring equipment allows, under most circumstances, adequate evaluation of variability using indirect recording of the FHR obtained with Doppler ultrasound. FHR variability depends on the interaction of the fetal sympathetic and parasympathetic nervous systems and is influenced by gestational age, maternal medications, fetal congenital anomalies, fetal acidosis, and fetal tachycardia. A nonreactive NST in the presence of adequate variability most probably corresponds to a false positive result. In

contradistinction, a nonreactive NST associated with decreased or absent variability most probably is abnormal and caused by fetal hypoxia. The presence of accelerations of the FHR associated with fetal movements or in response to fetal stimulation is a reliable sign of fetal health and, as mentioned before, they occur more frequently as the pregnancy approaches term. The absence of accelerations in the NST may be a sign of fetal compromise but most commonly corresponds to periods of fetal sleep. The absence of decelerations in the NST is reassuring. The presence of spontaneous severe variable or late decelerations is worrisome and suggests fetal compromise. Variable decelerations may be seen in up to 50% of NSTs and if they are mild and nonrepetitive, do not suggest fetal compromise. However, repetitive variable decelerations are important and suggest fetal compromise even if the FHR pattern is reactive.

One concern about the use of the NST for primary fetal surveillance is that the test cannot recognize early stages of fetal compromise. This consideration has not been supported by clinical trials and has not impacted the increasing use of the NST as the primary tool for fetal surveillance in USA. Another problem with the generalized use of the NST for primary fetal surveillance is the tendency to use the test for all patients with high-risk pregnancies without understanding that, in some situations, other tests may be more useful (Kontopoulos and Vintzileos, 2004). One example of this situation is the use of the NST to follow patients with post-term pregnancies, without simultaneous evaluation of the amniotic fluid volume by ultrasound, or the use of the NST alone, instead of combining its use with umbilical artery (UA) Doppler, for the follow-up of fetuses with growth restriction.

Purandare (2003) mentioned that of all the various methods of antepartum fetal surveillance that are in use today, the nonprovocative tests (NST, BPP, and MBPP) are safe and effective for use in an outpatient setting. Whereas the NST is primarily an indicator of fetal health, the CST is an indicator of uteroplacental function. The slower the interruption of oxygen delivery to the fetus, the more likely that there will be an adaptation by the fetus to the hypoxic state, reflecting in loss of beat to beat variability, diminished accelerations, and late decelerations while the baseline FHR is maintained. Acute hypoxia (placental abruption) leads to marked fetal bradycardia. In patients with postdatism, the NST should be interpreted in light of the amniotic fluid index. Whereas in case of suspected IUGR, reduced accelerations in spite of fetal movements, FHR decelerations with uterine contractions, diminished variability with baseline tachycardia are indicative of poor placental reserve. Vibroacoustic stimulation during the NST has high specificity for negative predictive value and accuracy for prediction of poor perinatal outcome.

NST has a major role to play in the currently existing antepartum care system. Fetal death rate is lower in populations undergoing antepartum testing as compared to the general untested population. Protocols using adjunctive tests (BPP, color Doppler) help to further improve obstetric outcomes. Gandhi (2003) emphasizes that though the false positivity of NST ranges between 65 and 70%, a cumulative review of 50,000 cases (Ware and Devoe, 1994) revealed a perinatal mortality of 6.2/1000. The false negative rates remain low, indicating it to be a good predictor of fetal outcome. Further, Gandhi (2003) states that the diagnostic value of NST remains as good as CST and is simpler to perform.

The Contraction Stress Test

The CST is one of the best available tests for the primary fetal surveillance of high-risk pregnancies. The test is based on experimental evidence showing that the uteroplacental blood flow decreases markedly or ceases during uterine contractions. Therefore, uterine contractions cause a hypoxic stress that a normal, healthy fetus can tolerate without difficulty (Figure 1-6A). In contrast, a fetus with chronic or acute problems will not be able to tolerate such a decrease in oxygen supply and will demonstrate this by decelerations of the FHR following contractions (Figure 1-6B). The protocol for performing a CST is described in Box 1-6. On many occasions the patient is having spontaneous contractions and it is not necessary to administer uterine stimulants. In the absence of spontaneous contractions, nipple stimulation may be used to elicit uterine activity but the response is unpredictable, and it is better to use oxytocin for this purpose.

The end point of the CST is the presence or absence of late decelerations of the FHR following uterine contractions. Late decelerations are one of the earliest indicators of fetal compromise and they appear prior to loss of variability, decreased movement, or lack of tone. However, a positive test is falsely positive in 50% of the cases, and an important reason for this is the use of a single variable to classify the test as negative or positive. A positive CST associated with poor variability and lack of accelerations is more likely to be a true positive than a positive CST in the context of adequate variability and accelerations.

The CST is used infrequently for primary fetal surveillance. This is due to the long duration of the test, the requirement for continuous supervision by trained personnel, and the existence of risks and contraindications associated with its performance (Box 1-7). Presently, the CST is most commonly used to follow a "nonreactive" NST. The false negative rate of the CST is 0.4 per 1000, significantly better than that of the NST.

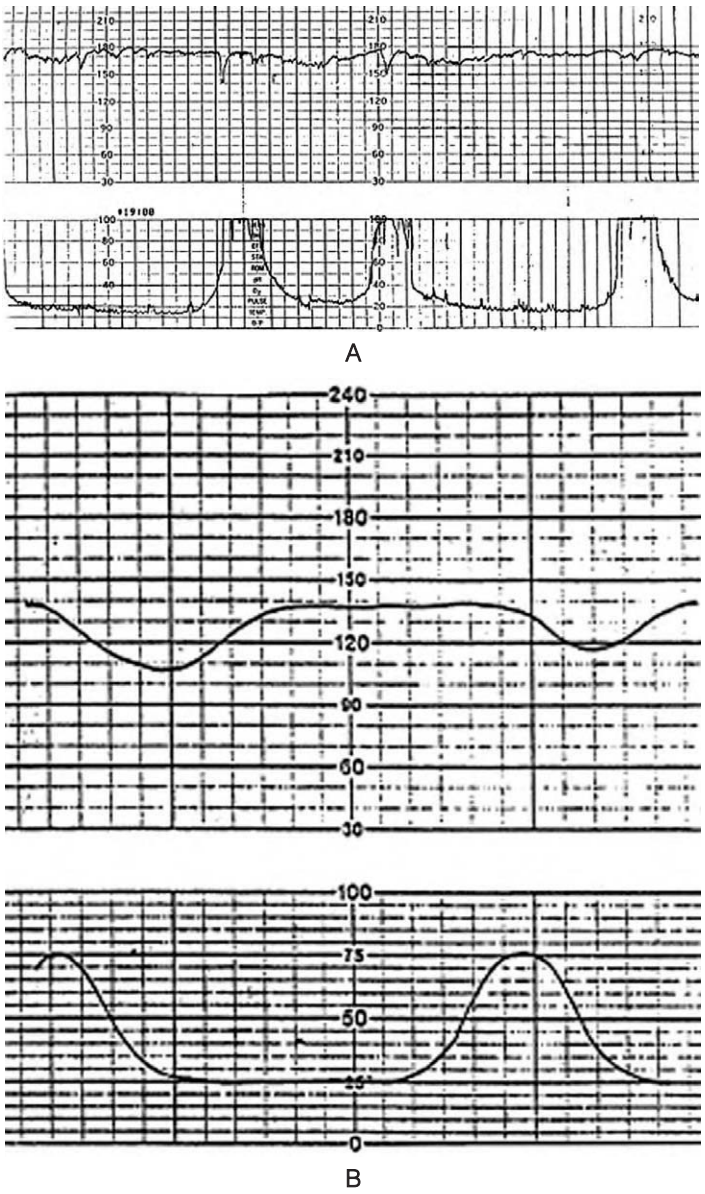


Figure 1-6. Negative and positive contraction stress test (CST). A, Negative CST: adequate variability. There are no decelerations associated with uterine contractions. B, Positive CST: absent variability. Every uterine contraction is followed by a deceleration of the fetal heart rate.

The Biophysical Profile

The BPP is another test for the evaluation of fetal well-being. It combines the NST with the observation by ultrasound of four variables: fetal breathing movements, fetal body movements, fetal tone, and amniotic fluid volume (Box 1-8). These variables are dependent on the integrity of the fetal central nervous system and are affected in situations of fetal compromise. The test is time consuming and requires some ultrasound training, but has no contraindications and no risk for the mother or the fetus.

Each of the five components of the BPP is assigned a numerical value of 2 (if present or normal) or 0 (if absent

BOX 1-6

How to perform a contraction stress test

1. Place the patient in semi-Fowler's position. Use pillows under the patient's hip or side to displace the weight of the uterus away from the inferior vena cava. Take the patient's blood pressure every 10 minutes through the test.
2. Apply the tococardiographic equipment to the maternal abdomen and observe the uterine activity and the FHR for approximately 15–20 minutes. Many patients who are receiving the test because of a nonreactive NST show adequate fetal reactivity during this observation period and do not require oxytocin stimulation. Other patients show spontaneous uterine activity of sufficient frequency and duration and do not require oxytocin administration.
3. Start intravenous oxytocin administration at 0.5 mU/minute using a pump. Double the rate every 15–20 minutes until three contractions lasting 40–60 seconds occur within a 10-minute period. If late decelerations appear before this duration and frequency of contractions has been achieved, the administration of oxytocin must be interrupted. Massage of the nipples with a warm towel by the patient may be all that is necessary to provoke uterine contractions and avoid the use of oxytocin.
4. Usually the test requires between 1½ and 2 hours. The amount of oxytocin required to obtain adequate uterine contractility is generally below 16 mU/minute.
5. After completing the test, monitoring of FHR and uterine contractions should continue until they return to baseline. If uterine activity persists, the subcutaneous administration of 250 mg of terbutaline is usually sufficient to paralyze the uterus.

BOX 1-7

Contraindications to the contraction stress test

- Placenta previa
- Prior classical cesarean section
- Prior extensive uterine surgery
- Preterm labor
- High-risk for preterm labor
- Preterm rupture of membranes

BOX 1-8

Biophysical profile

1. *Fetal breathing movement*
   Thirty seconds of sustained breathing movement during a 30-minute-observation period
2. *Fetal movement*
   Three or more gross body movements in a 30-minute-observation period
3. *Fetal tone*
   One or more episodes of limb motion from a position of flexion to extension and a rapid return to flexion
4. *Fetal heart rate reactivity*
   Two or more fetal heart rate accelerations associated with fetal movement of at least 15 bpm and lasting at least 15 seconds in 10 minutes (reactive NST)
5. *Fluid volume*
   Presence of a pocket of amniotic fluid that measures at least 2 cm in two perpendicular planes

or abnormal). A composite value of 8 or 10 indicates that the fetal status is reassuring or normal as long as the score of 8 does not include an abnormal fluid volume. The presence of oligohydramnios demands further testing, irrespective of the composite score value. A score of 6 is equivocal and requires further testing to verify fetal well-being. A score of 4 or less is suggestive of fetal compromise. The false negative rate of the BPP is 0.7 per 1000, a value better than that of the NST and similar to that of the CST. The false positive rate of the BPP is approximately 30%, better than the NST or the CST. The negative predictive value of the BPP is similar to that of the NST (98% for the NST, 98.5% for the BPP) but the positive predictive value of an abnormal BPP (50.8%) is better than that of a nonreactive NST.

The main problem with the BPP is the structure of the test because each of the five variables assessed in the test (fetal breathing movements, fetal body movements, fetal tone, amniotic fluid volume, and FHR reactivity) is assigned a score of either 0 or 2 although each one has a different predictive value for assessing the fetal situation. The BPP variables are dependent on the activity of certain areas of the fetal central nervous system that become functional at different gestational ages. Fetal tone and movement appear between 7 and 9 weeks and require activity of the brain cortex. Fetal breathing movements begin at 20–21 weeks and depend on centers in the ventral surface of the fourth ventricle. FHR reactivity appears between 28 and 30 weeks and stems from function of the posterior hypothalamus and nucleus in the upper medulla. The sensitivity of each of these centers to hypoxia is different and those that become functional earlier in fetal development are more resistant to changes in fetal oxygenation. Therefore, each fetal function evaluated in the BPP has a different predictive value for fetal hypoxia, and serious consequences may ensue from improper management decisions based on the total BPP score rather than on careful evaluation of the individual test components. For example, a fetus with a BPP of four, consisting of two points for a reactive NST and two points because of normal amniotic fluid volume is most likely normal, and unnecessary intervention because of the low total score may lead to a poor perinatal outcome.

Another problem with the BPP is that alterations in some of the test's criteria occur relatively late in the process of fetal asphyxia. This was demonstrated in studies measuring umbilical cord gases in women with abnormal BPP delivered by cesarean section after the abnormal test (Vintzileos et al., 1987). The first manifestations of fetal acidosis were nonreactive NST and lack of fetal breathing movements. Decreased body movement and decreased fetal tone were found only when the fetal compromise was severe. Other problems with the BPP are the difficulties in evaluating fetal tone, the definition of decreased amniotic fluid volume, the lack of data on the use of VAS to shorten the duration of the test, and whether prolonging the test time to increase the possibility of an adequate fetal response is permissible.

The Modified Biophysical Profile

Vintzileos et al. (1987) were the first to propose a modification of the biophysical profile for evaluation of fetal well-being. They monitored 6543 high-risk fetuses with NST (using VAS) and estimation of amniotic fluid volume and reported no deaths of structurally normal fetuses within 1 week of their biophysical assessment. Subsequent work by Clark et al. (1989) and Miller et al. (1996) further demonstrated the advantages of this method (Box 1-9).

The MBPP is an excellent test for primary fetal surveillance. It combines the observation of an index of acute fetal hypoxia, the NST with VAST, with a second index indicative of chronic fetal problems, the amniotic fluid volume. The test has excellent negative and positive predictive values, is easy to interpret, has clearly defined end points, and can be performed in an average of 20 minutes.

The following guidelines are useful when the MBPP is used as the primary test for fetal surveillance:

1. If both the NST and the fluid volume are normal, weekly fetal surveillance with MBPP is continued.
2. If both tests are abnormal (nonreactive NST, decreased amniotic fluid volume) and the pregnancy is of 36 weeks or more, the best option may be delivery. If the pregnancy is of less than 36 weeks, the management is individualized. Doppler studies, full BPP, performance of CST, or delivery may be used depending on the circumstances.
3. If the amniotic fluid volume is decreased but the NST is reactive, a search for indicators of placental

BOX 1-9

Modified biophysical profile

1. Start NST in the standard manner. If a spontaneous acceleration is not seen within 5 minutes, a single 1–2-second sound stimulation is applied in the lower abdomen with the artificial larynx. This stimulus may be repeated up to three times if necessary. Since this procedure requires two accelerations within 10 minutes, for a definition of reactivity, a second stimulus is applied if 9 minutes have elapsed since the first acceleration. Accelerations are defined in the standard manner of 15 bpm amplitude from an established baseline lasting 15 seconds.
2. A four-quadrant amniotic fluid volume is assessed by placing an ultrasound transducer perpendicular to the wall of the uterus in four abdominal quadrants and measuring the largest vertical amniotic fluid pocket. Pockets consisting primarily of umbilical cord are disregarded. A four-quadrant sum of 5 cm or greater is considered normal.

insufficiency or undiagnosed rupture of membranes needs to be undertaken and management will depend on the final diagnosis.

4. If the amniotic fluid volume is normal and the NST is nonreactive, further testing with Doppler, CST, or full BPP is indicated.

Jyotsna Gandhi (2003) states that MBPP is widely used as a primary modality of antenatal fetal testing in many centers in USA; it has a false positive rate of only 0.05%.

Doppler Velocimetry

The use of Doppler ultrasound for the evaluation of the fetal circulation is based on the physical principle of change in frequency of a sound wave when it is reflected by a moving object. This principle was described in 1842 by the Austrian physicist and mathematician Johann Christian Doppler. Doppler observed that the frequency of sound waves reflected by a static object was identical to that before being reflected. In contrast, the frequency of the sound waves reflected from a moving object, such as blood inside a blood vessel, was different from the original frequency and proportional to the velocity of the moving object (Doppler effect). Therefore, blood velocity and resistance to flow can be evaluated using the Doppler effect—a method that has significantly impacted the evaluation and management of the fetus at risk of hypoxia secondary to placental insufficiency. During Doppler studies fetal and maternal vessels are interrogated with ultrasound waves. The Doppler frequency shift caused by the moving red cells is submitted to spectrographic analysis and represented graphically as a waveform. These waveforms represent changes in the velocity of the blood flowing through the vessels. Velocity is greater in systole than in diastole. When peripheral vascular resistance is low, a good amount of the blood flow occurs during diastole but when resistance is high, most of the blood flow will occur during systole and diastolic flow will be minimal. For that reason, a simple visual analysis of the waveforms provides a qualitative measurement of the resistance to flow in the vessels that are being examined.

The role of umbilical and MCA Doppler in the evaluation of fetuses at high risk for poor outcomes has been adequately assessed in randomized clinical trials, and the method has been found to be useful (a) in complementing other methods of fetal surveillance such as the NST or the BPP to determine more precisely the degree of fetal compromise, (b) as a follow-up test when other tests of fetal well-being give ambiguous results or the clinical condition of mother or fetus is unstable, (c) to determine with more precision the need to deliver, (d) to identify a group of women at high risk of placental insufficiency and low risk for fetal complications, and (e) to evaluate the presence and severity of fetal anemia.

Doppler of the uterine arteries is an index of the quality of the uteroplacental circulation and reflects the condition of the maternal side of the placental circulation. Interrogation of these arteries at 23–25 weeks of gestation has been proposed as a useful test for the screening and selection of women at risk for preeclampsia and FGR.

Fetal–placental circulation

An adequate understanding of the use of Doppler in obstetrics requires a correct understanding of the fetal–placental and maternal–placental circulations and the pathophysiology of fetal hypoxia. The fetal circulation has three arterial-venous shunts that are of fundamental importance to the maintenance of fetal oxygenation and disappear shortly after birth. These shunts are (a) the ductus venosus (DV) that carries oxygenated blood from the umbilical vein into the inferior vena cava (IVC) and the right atrium (RA), (b) the foramen ovale that allows the passage of blood from the right to the left atrium, and (c) the ductus arteriosus that carries blood from the pulmonary artery into the aorta, effectively bypassing the pulmonary circulation.

Oxygenated blood comes from the placenta through the umbilical vein with a velocity of approximately 15 cm/second. Inside the fetal liver the umbilical vein becomes the portal sinus that is the origin of the portal veins and the DV. The DV brings oxygenated blood to the upper part of the IVC and its funnel-like structure causes an increase in the velocity of blood flow from 15 to 40 cm/second. A fold in the IVC, known as the Eustachian valve, directs the flow of blood coming from the DV toward the posterior side of the IVC and from there, without mixing with the blood coming from the lowers extremities, the DV blood enters the RA. This highly oxygenated blood (70% oxygen saturation) does not mix with other blood—thanks to the high velocity of flow through the DV. A second fold, the "crista dividens," directs the flow of blood coming from the DV into the RA toward the foramen ovale and the left atrium and from there to the aorta, the heart, and the brain. In other words, this "preferential flow" of the umbilical vein blood takes oxygenated blood from the placenta into the left atrium to be utilized mainly in the irrigation of the brain and myocardium. Other blood coming from the placenta that does not follow the "preferential flow" goes to the IVC via the hepatic veins and mixes with blood coming from the lower extremities, resulting in an oxygen saturation of 53%. This mixture of blood coming from the lower extremities and from the placenta will go to from the IVC to the RA, the RV (right ventricle), the pulmonary artery, and the aorta, via the ductus arteriosus. With modern 2-D and 3-D ultrasound equipment, color Doppler, and angio-Doppler, it is possible to identify the vascular structures and the velocity waveforms that characterize

normal and abnormal flow of the umbilical vein blood in the fetus.

Pathophysiology of fetal hypoxia

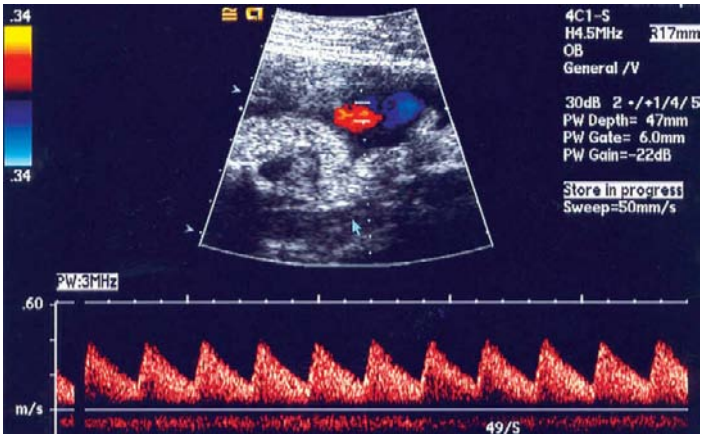
The primary adaptive response of the fetus to placental insufficiency is a decrease in growth. If placental insufficiency persists, there are secondary adaptive responses consisting in decrease in fetal movements to conserve energy, hemodynamic redistribution to favor the oxygenation of organs critical to the economy such as the brain and the heart, and attempts to improve the efficacy of the placental gas exchange by increasing the heart rate and the synthesis of red cells. Persistence and aggravation of placental insufficiency will lead to progressive decompensation with respiratory and metabolic acidosis, increase impedance in the fetal–placental circulation, renal insufficiency with decreased amniotic fluid volume, myocardial compromise with absent or reversed atrial flow in the DV, late decelerations in the FHR monitoring tracing, and fetal death. It would be ideal that this sequence of pathophysiologic changes elicited by placental insufficiency and fetal hypoxia could be identified in each of its different stages by a single test. This goal has not been achieved and it has been suggested that in the growth-restricted fetus the best perinatal outcome can be obtained with the simultaneous use of biophysical and hemodynamic parameters (Baschat, 2006).

UA Doppler

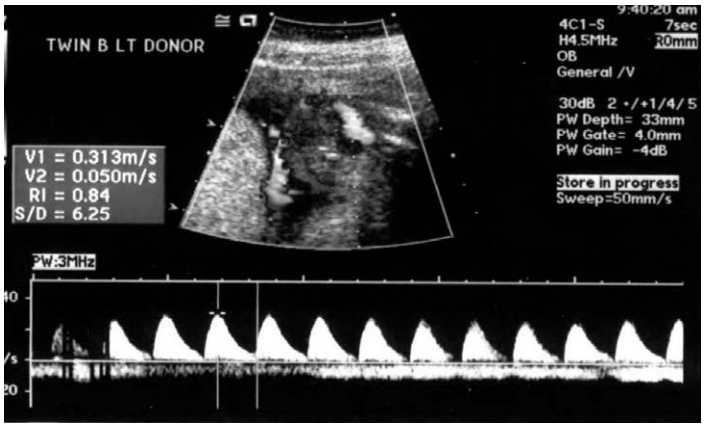
UA Doppler is a powerful tool that allows the obstetrician to follow a sequence of fetal hemodynamic events that happen in response to placental insufficiency. There are several methods of analyzing the UA waveforms to provide the clinician with a quantitative index of vascular resistance. In USA the most commonly used system is the systolic to diastolic ratio (S/D ratio) while in Europe is the pulsatility index or PI (systolic – diastolic/mean). With the PI it is possible to obtain a numerical value in the absence of diastolic flow or in cases of reversed diastolic flow. Another index frequently used is the resistance index or RI (systolic – diastolic/systolic). In this chapter we will use the S/D ratio as index of vascular impedance, but any of the other indices (PI or RI) can be used. The objective of these methods is to obtain numerical information from the waveform that reflects the resistance to the blood flow in the vessel being examined. All these ratios are independent of the angle of insonation. The best place to obtain UA waveforms is in the middle of the cord in one of the many loops floating in the amniotic fluid. Measurements closer to the fetal insertion of the umbilical cord will show higher resistance than measurements closer to the placental insertion. The waveforms should be obtained when the fetus is not moving and particularly in the absence of respiratory movements. Several measurements should be taken in different loops of the cord and the S/D ratio of at least four waveforms should be averaged to obtain a result.

The UA Doppler provides a clinician with an index of the resistance to flow in the fetal side of the placenta. An elevated UA S/D ratio (Figure 1-7B) is the result of a reduced number of arteries in the tertiary stem villi affecting the placental capacity to provide oxygen, glucose, and other nutrients to the fetus (Giles et al., 1985). With progression of the placental lesion or with increased fetal demands the limited availability of substrates for fetal growth will determine a compensatory hemodynamic response, known as centralization of flow, that can be appreciated by Doppler assessment of the MCA. With further aggravation of the problem the compensatory response will be exceeded and more severe changes will be apparent in the UA waveforms and in the venous side of the fetal circulation.

The sequence of events observable by Doppler studies of the UA and the venous system in the course of



A



B

Figure 1-7. Normal and abnormal umbilical artery waveforms. A, Normal umbilical waveforms: normal diastolic flow. B, Abnormal umbilical waveforms: decreased to absent diastolic flow.

progressive fetal compromise secondary to placental insufficiency is as follows: (a) increased UA resistance without centralization of flow, (b) increased UA resistance with centralization of flow, (c) absent umbilical artery diastolic flow (AUADF), (d) reversed umbilical artery diastolic flow (RUADF), and (e) alterations in the venous circulation.

Significance of umbilical artery velocimetry in predicting perinatal outcome of growth restricted fetuses was reported from Mumbai by Arora et al., (2005). Fetuses with abnormal umbilical artery flow velocimetry were associated with oligohydramnios, abnormal NST, low birth weight, lowered average diagnosis to delivery interval and fetal gestation age, and a higher incidence of neonatal admission to special neonatal care units. Bhatt et al. (2003) reported that abnormal umbilical artery flow velocimetry in growth-retarded fetuses was a predictor of high risk for necrotizing enterocolitis.

Increased UA resistance

The normal values of the UA S/D ratio in relation to gestational age are shown in Table 1-9. In the course of fetal compromise, secondary to placental insufficiency, the first sign is a progressive increase in S/D ratio in the UA without centralization of flow. This means that the UA S/D ratio will be above the normal limits and the S/D ratio in the MCA will remain normal. The S/D ratio of the MCA remains greater than the S/D ratio of the UA, indicating that the MCA maintains its normal characteristic of high resistance to flow. An increase in UA resistance without centralization of flow is less worrisome than increased UA resistance with centralization and indicates that there is a need for closer, frequent fetal surveillance to determine whether or not there is further fetal deterioration.

Centralization of flow

Centralization of flow or "brain sparing effect" is a fetal hemodynamic change characterized by increased blood flow and oxygen supply to the fetal brain to compensate for a decreased transfer of oxygen through the placenta. The MCA S/D ratio will be lower than the UA S/D ratio, indicating that the MCA has become a low-resistance vessel (Figure 1-8). This dramatic change in fetal hemodynamics is not, however, an indication for immediate delivery. It means that closer surveillance should continue to determine when the mechanisms of compensation are exhausted and delivery is necessary.

Absent umbilical artery diastolic flow

AUADF is a stage of further fetal deterioration in fetuses that have centralization of flow. It means that the placental vascular resistance has reached a point where the UA blood flow occurs only during systole. As a result the oxygen supply to the fetus is decreased and there is mild metabolic acidosis. At this point in the evolution of the problem, serious consideration should be given to delivery of the fetus and intrauterine life should be maintained only if there are compelling arguments suggesting that expectancy is better than delivery. In a hospital with a neonatal intensive care unit the only reason to delay delivery is the administration of steroids to improve the neonatal outcome. To condition the delivery of a compromised fetus to reach a given gestational age or to achieve fetal pulmonary maturity is a formula for disaster. In the rare case where expectancy is necessary, the fetal status requires monitoring with daily NSTs and frequent Dopplers.

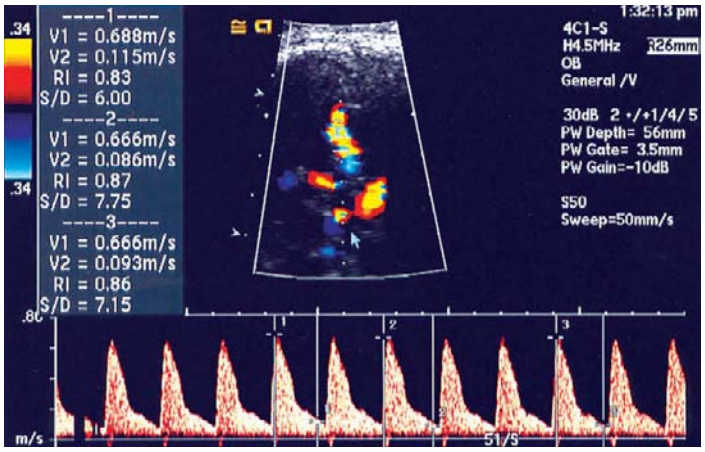
Table 1-9. Umbilical artery systolic to diastolic (S/D) ratio and gestational age

Gestational age (weeks)	5th percentile	50th percentile	95th percentile
16	3.33	5.00	10.0
17	3.23	4.76	9.09
18	3.13	4.55	8.33
19	3.03	4.35	7.69
20	2.94	4.17	7.14
21	2.86	4.0	6.67
22	2.78	3.85	6.25
23	2.70	3.70	5.88
24	2.63	3.57	5.56
25	2.56	3.45	5.26
26	2.50	3.33	5.00
27	2.44	3.23	4.76
28	2.38	3.13	4.55
29	2.33	3.03	4.35
30	2.27	2.94	4.17
31	2.22	2.86	4.00
32	2.17	2.78	3.85
33	2.13	2.7	3.7
34	2.08	2.63	3.57
35	2.04	2.56	3.45
36	2.00	2.50	3.33
37	1.96	2.44	3.23
38	1.89	2.33	3.03
39	1.85	2.27	2.94
40	1.82	2.22	2.86
41	1.79	2.17	2.78
42	1.75	2.13	2.70

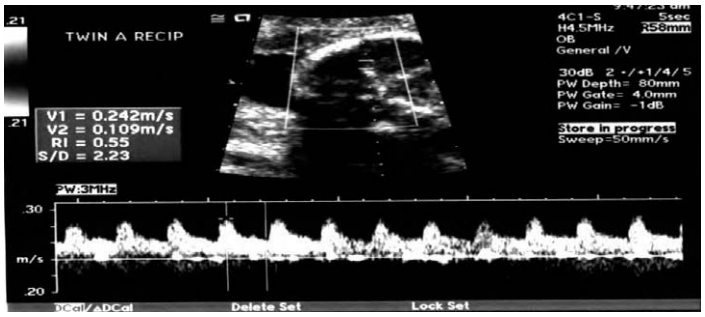
From Kofinas AD, Espeland MA, Penry M, et al. Uteroplacental Doppler flow velocity waveform indices in normal pregnancy: a statistical exercise and the development of appropriate reference values. Am J Perinatol 1992; 9: 94–101.

Reversed umbilical artery diastolic flow

The presence of RUADF is an ominous sign indicating that the vascular resistance has reached a point where the blood flow is reversed during diastole (Figure 1-9). Fetuses with RUADF are acidotic and need to be delivered



A



B

Figure 1-8. Changes in middle cerebral artery diastolic flow reflecting centralization of flow. A, Normal MCA Doppler waveforms showing high resistance to flow. B, Abundant diastolic flow in the middle cerebral artery waveforms indicating low resistance and centralization of flow.

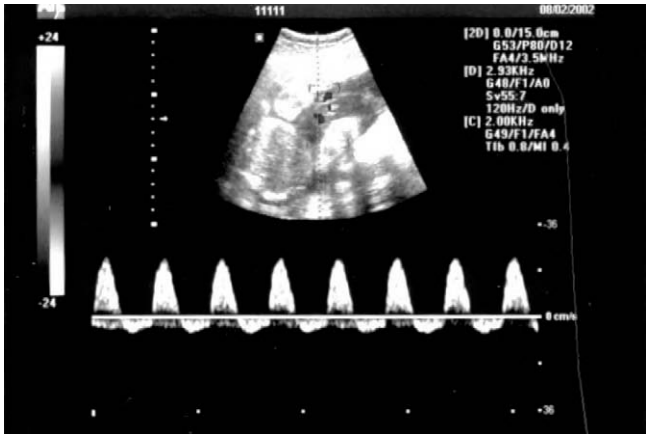
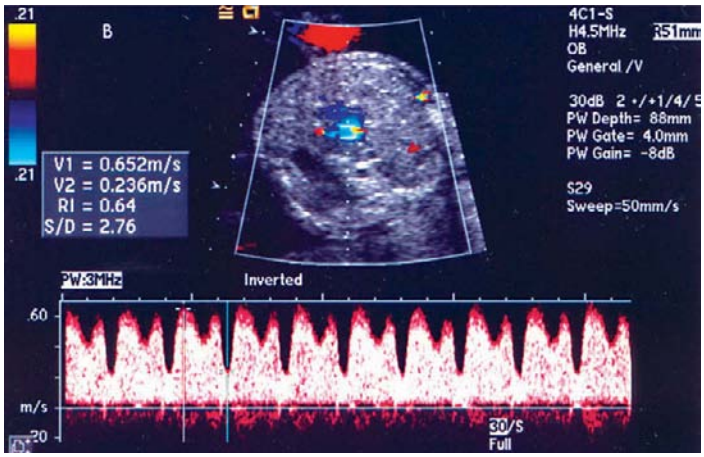


Figure 1-9. Reversed umbilical artery diastolic flow.

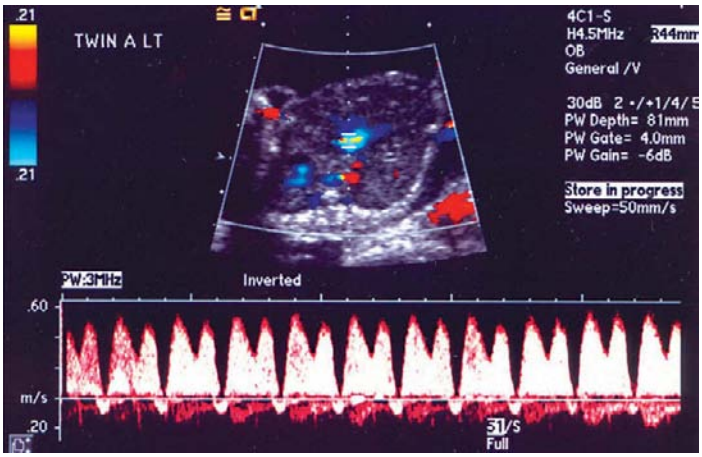
promptly. There is general agreement that fetuses exhibiting this abnormality are at a very high risk of death and significant neonatal morbidity.

Ductus venosus Doppler

Assessment of the DV waveforms is one of the best methods to obtain information about the venous side of the fetal circulation. The passage of blood through the



A



B

Figure 1-10. Normal and abnormal ductus venosus waveforms. A, Normal ductus venosus waveforms. B, Abnormal ductus venosus waveforms showing interrupted and reversed forward flow during atrial systole.

narrow part of the DV gives a unique appearance of turbulence with color Doppler, facilitating identification of the vessel. The DV waveforms show continuous uninterrupted forward flow during the systolic and diastolic phases of the cardiac cycle (Figure 1-10A). During ventricular systole, there is atrial relaxation and the velocity through the ductus increases, resulting in a peak systolic velocity (PSV). The velocity increases again during the passive filling of the ventricles (peak diastolic velocity or PDV) and drops to a nadir during the phase of atrial contraction and active ventricular filling. The maximal velocity in the waveform corresponds to the ventricular systole and the minimum velocity to the right atrial contraction. The PSV in the DV is in the range of 40–80 cm/second, approximately three times higher than the flow velocity in the umbilical vein or the IVC. When the foramen ovale closes during atrial contraction the DV waveform reflects the pressure on the RA and the atrial contraction in the waveform is a reflection of the right ventricular preload.

In the final stages of fetal compromise, secondary to placental insufficiency, the oxygen deficit and the acidemia affect the fetal cardiac function, causing an increase in right ventricular preload. This will result in interrupted forward flow due to absent or reversed flow during atrial contraction (Figure 1-10B), which is an ominous sign of poor fetal health and morbid neonatal outcome.

Uterine arteries Doppler

The uterine arteries originate in the internal iliac artery and run along each side of the uterus, branching into the arcuate arteries that circumferentially involve the corpus of the uterus. The radial arteries originate from the arcuate arteries and perpendicularly penetrate the external third of the myometrium, giving origin to the basal arteries. The spiral arteries originate from the basal arteries and supply blood to the endometrium and during pregnancy to the decidua and the intervillous space. One of the most important physiologic adaptations of pregnancy is the invasion of the spiral arteries by the cytotrophoblast. This physiological process results in a 10-fold increase in the blood flow in nonpregnant women through these vessels which is necessary to respond to the nutritional and respiratory needs of the fetal–placental unit. It is therefore not surprising that abnormalities in this fundamental component of normal placentation are associated with severe pregnancy complications such as preeclampsia, FGR, preterm labor, preterm rupture of membranes, and fetal death.

Trophoblastic invasion of the spiral arteries increases their diameter from 15–20 μm to approximately 300–500 μm. The elastic and muscular layers of the spiral arteries are replaced by hyaline material and the endothelial layer is replaced by trophoblast. This process occurs in two stages. The first trophoblastic invasion happens during the first trimester of pregnancy and involves the decidual portion of the spiral arteries. The second invasion occurs after 16 weeks of gestation and involves the myometrial portion of these vessels. The overall result of this process is the transformation of a high resistance vascular system to one of low resistance and high capacitance, characteristics that are ideal to maintain an adequate blood flow to the intervillous space. As a consequence of the trophoblastic invasion of the spiral arteries, the resistance to blood flow in the uterine arteries decreases dramatically after 10–12 weeks of gestation. The change in vascular resistance is more marked in the uterine artery closer to the placental implantation site.

Doppler interrogation of the uterine arteries is usually performed with transabdominal ultrasound but a transvaginal approach is occasionally necessary in obese patients. In both cases the uterine artery is identified with color Doppler shortly after its origin when it seems to cross the internal iliac artery (Figure 1-11). Several indices are available to assess the changes in resistance to flow in the uterine arteries. They are similar to those used in the evaluation of UA flow (S/D ratio, PI, RI) plus the observation of early diastolic notching (Figure 1-12). The notch is an index of increased impedance to flow and corresponds to a brief sharp decrease in velocity at the beginning of diastole with a nadir smaller than the peak diastolic velocity. Box 1-10 shows the pathological threshold values for different indices of uterine artery resistance.

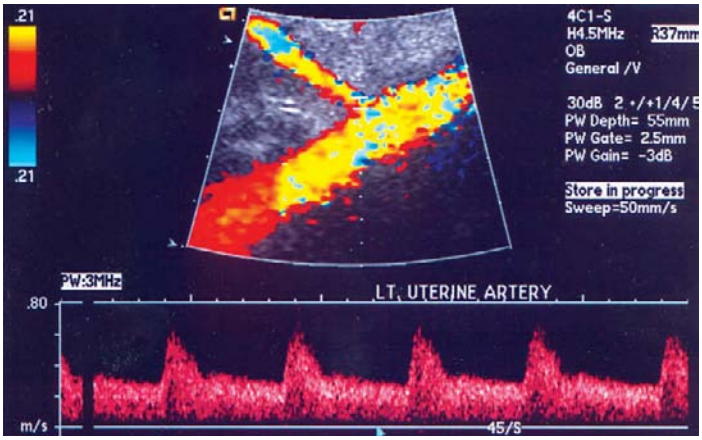


Figure 1-11. Normal uterine artery Doppler waveforms.

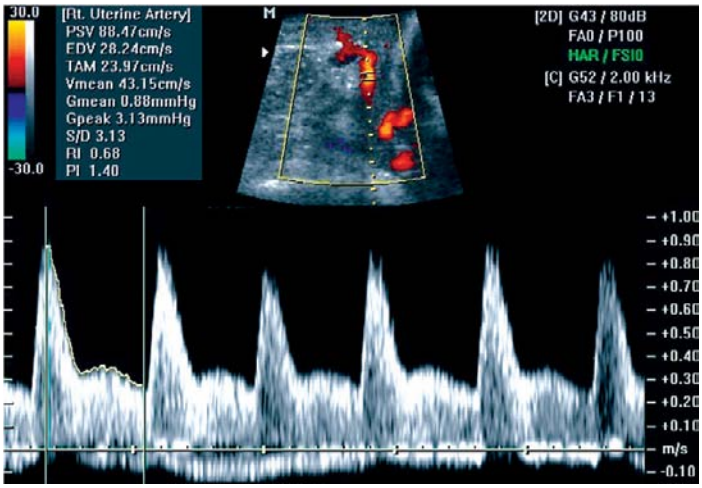


Figure 1-12. Uterine artery waveforms showing early diastolic notching.

BOX 1-10

Upper limit of normal for different methods of evaluation of uterine artery resistance

- Systolic to diastolic (S/D) ratio > 3.0 after 30 weeks
- Resistance index (RI) > 0.56
- Presence of protodiastolic notch in the placental ipsilateral side at 20 weeks or in the contralateral side after 26 weeks
- Pulsatility index (PI) > 1.56

An important variable in the interpretation of uterine artery Doppler is the gestational age at the time the test is performed. When the test is done before 20 weeks of gestation the number of false positive results is high. After 24 weeks of gestation, trophoblastic invasion has ended and false positive results will decrease. The decrease in uterine vascular resistance is not exactly equal bilaterally and the uterine artery in the ipsilateral side of the placental implantation usually shows decreased resistance before the artery in the contralateral side. For example, a notch in the ipsilateral artery usually disappears by 20 weeks while it may remain up to 26 weeks in the contralateral side.

Abnormal placentation occurs long before the clinical appearance of obstetrical complications. This has generated a great interest in the possibility of using uterine artery Doppler as screening test particularly for preeclampsia, FGR, and abnormal pregnancy outcome (Albaiges et al., 2000). The sensitivity of uterine artery Doppler in the prediction of preeclampsia and FGR is approximately 70%. Unfortunately the positive predictive value is poor (<10%), limiting its use as screening test in the general obstetrical population. However, in high-risk pregnancies an abnormal uterine Doppler is an indication for a closer prenatal follow-up. In the same high-risk population, a normal uterine artery Doppler is reassuring and allows a less frequent fetal surveillance than when the test is positive. When the uterine artery Doppler results are combined with clinical high-risk factors, there is an increase in the diagnostic value of the test (Papageorghiou, 2005). The accuracy of uterine artery Doppler in the prediction of preeclampsia is significantly increased when combined with the results of inhibin A and activin A concentrations in the maternal serum (Spencer et al., 2006). Another promising combination is the use of uterine artery Doppler in the first trimester with maternal plasmatic protein 13 (PP13) (Nicolaides, 2006).

Another potential use of uterine artery Doppler is in the evaluation of the severity of a pathological placental process. In patients with preeclampsia or FGR the depth of the protodiastolic notch may be an index of the severity of placental compromise (Park et al., 2000). In situations where the estimated fetal weight is below the 10th percentile and the UA Doppler is normal, the presence of an abnormal uterine Doppler indicates that a pathological process is affecting the maternal side of the placenta.

In summary, uterine artery Doppler is valuable as predictive index but has limited value for management purposes. Abnormal uterine arteries waveforms after 24 weeks of gestation are associated with the development of preeclampsia and FGR. However, the positive predictive value of the test is low and there is no universal agreement about the usefulness of uterine artery Doppler as a screening test for preeclampsia and IUGR (intrauterine growth restriction). The test has a high negative predictive value and the pregnancy outcome is excellent if both the umbilical and the uterine Doppler waveforms are normal. Ideally, uterine artery Doppler screening should be done at 24 weeks during the examination to measure cervical length and assess the risk for preterm delivery.

Fetal Blood Sampling

The introduction of percutaneous umbilical blood sampling (cordocentesis) by F. Daffos in 1983, and the confirmation by the same investigator in 1985 of the safety of the procedure, opened new avenues to the field of fetal diagnosis (Daffos et al., 1985). The availability of this technique changed the management of patients with Rh isoimmunization, idiopathic thrombocytopenic purpura, toxoplasmosis, and hereditary blood disorders.

Cordocentesis can be easily performed after 24 weeks of gestation. Attempts are being made in many centers to perform the procedure as early as 16 weeks, but in most cases it can consistently be done only after 18 weeks. Cordocentesis can be performed at any site on the umbilical cord but the placental insertion site is preferred. The procedure requires the use of high-resolution ultrasound equipment. Most maternal–fetal medicine specialists use sector scanning, free-hand technique, and a 22-G needle. However, others have similar success with linear scanning, ultrasonic needle guidance, and a 20-G needle.

The main risks of cordocentesis are bleeding from the puncture site and vagal reflex causing severe fetal bradycardia. The risk of fetal death associated with the procedure is usually quoted as 1 per 100 cases but the mortality may be higher in certain subgroups of patients, particularly those with FGR. The incidence of complications is also operator-dependent and is higher when the procedure is not performed frequently.

The indications for the use of cordocentesis have declined with the development of less invasive technology for fetal diagnosis. The use of PCR of the amniotic fluid and better bacteriologic culture techniques have made rare the use of cordocentesis in the diagnosis of fetal infection. Improvements in cytogenetics have made the rapid

BOX 1-11

Indications for cordocentesis

1. Rapid karyotype in fetuses with structural abnormalities discovered during ultrasound examination
2. Fetal hemolytic disease
3. Suspected fetal viral infection
4. Nonimmunologic hydrops fetalis
5. Suspected fetal thrombocytopenia
6. Diagnosis of twin-to-twin transfusion
7. Suspected fetal hemoglobinopathy

determination of fetal karyotype using amniotic fluid cells possible. The evaluation of MCA PSV is a sensitive index of fetal anemia. These developments have decreased the use of cordocentesis for the rapid diagnosis of chromosomal abnormalities and fetal anemia. However, cordocentesis is still an important tool for fetal diagnosis, and there are indications for the procedure as shown in Box 1-11.

INDIAN EXPERIENCE OF ANTEPARTUM SURVEILLANCE

A survey by the Indian council of Medical Research (ICMR, Bedi et al., 2001) revealed that antenatal deaths accounted for 43.8% of all maternal deaths. On analysis of the booking status of mothers dying in pregnancy and delivery, it was obvious that lack of antenatal supervision constituted an important contributory factor accounting for 70.0–89.0% of all maternal deaths as shown in various Indian studies (Shanker and Seetharam, 2001; Sharma, 2001; Roy and Pandey, 2002; Doke and Salunkhe, 2006). The major factors responsible for the prevailing high MMRs included poverty, ignorance, malnutrition, illiteracy, cultural traditions, unregulated fertility, and gender discrimination according females an inferior status in society. Dutta (2004) reported an MMR in India of 407 per 100,000 live births. Majority of women in India continue to live in rural areas where delivery conducted at home by a traditional birth attendant is common and qualified supervision and institutional care is meager. Government health care centers often exist at far off distances; travel and transport facilities are often primitive or nonexistent and private health care is expensive and beyond the reach of many. Chatterjee and Mukhopadhyaya (2003) described that 80% of maternal deaths are due to direct causes. Their distribution is as follows: sepsis including unsafe abortions (28%), obstetric hemorrhage (25%), pregnancy-induced hypertension and eclampsia (12%), accidents of pregnancy (8%), and others (8%). Many of these are preventable factors.

High-risk pregnancy and delivery pose high risk to the fetus as well. Table 1-10 presents a comparison of the perinatal outcome in booked and unbooked emergency admissions from various centers in India.

It is clear that antenatal care is the preventive and prophylactic arm of obstetric practice. It helps to detect high-risk factors and guides the clinician in adopting necessary tests and implementing treatment modalities aimed at eradicating or ameliorating the risk factors.

Sociodemographic determinants of pregnancy wastage were scrutinized by Banerjee and Hazra (2004) and Rao and Inborag (1975). They reported an overall pregnancy wastage of 11.19%. Review of factors influencing obstetric outcome included the following:

1. *Maternal age:* Pregnancy wastage in women aged > 35 years (16.58%); it was least in the age group of 20–24 years (7.7%).
2. *Birth order:* It was highest in primiparae (17%) and declined thereafter to reach the lowest in para-3 and -4, and there was a steady rise thereafter, reaching its peak in para-8 and above.
3. *Interval between births:* It was up to 1 year (15.29%) or 8 years and more (14.29%).
4. *Literacy:* Illiterate were more (12%) as compared to literate people (8%).
5. *Employment status:* It was higher (17%) as compared to unemployed women (9.3%).
6. *Residence:* It was higher in younger women (age < 20 years) from rural settings and highest in elderly women (age > 35 years) of urban origin.

In 1988, FIGO launched the Safe Motherhood initiative. Government of India launched its version of safe motherhood (CSSM) program in 1992 to control the high maternal mortality prevailing in our country. The protocol for Essential Obstetric Care for All included the following strategies (Chatterjee and Mukhopadhyaya, 2003):

- Registration between 12–16 weeks
- Antenatal visits (minimum three) at 16, 28, and 38 weeks' gestation
- Document blood pressure, weight, and obstetric examination findings at each visit
- Mandatory investigations include Hb%, ABO, and Rh type, urine protein and sugar, stools, and postprandial blood sugar
- Medications: oral iron, folic acid, and deworming agents after 16 weeks' gestation
- Tetanus toxoid injection, two doses/4–6 weeks apart
- Timely reference for emergency obstetric care
- Use of clean pregnancy kit for conducting delivery. The aim was to provide the auxiliary nurse midwives/skilled birth attendants to conduct safe delivery under hygienic surroundings to minimize maternal deaths in rural settings.

Table 1-10. Comparison of perinatal outcome in booked and unbooked pregnancies

Authors	Place and year	PNMR	Booked cases	Unbooked cases
Agarwal et al.	Jaipur; 2000	156/1000	29.6/1000	126.52/1000
Kamat and Jindal	Goa; 2001	138.5/1000	14.9/1000	123.60/1000
Rao et al.	Mumbai; 2001	55.3/1000	18.8/1000	36.55/1000
Gaddi and Seetharam	Bellary; 2001	187.1/1000	57.1/1000	130.04/1000

Modern day investigations for monitoring fetal health and well-being (biophysical assessment) are now available in urban centers and well-equipped hospitals in India: fetal movement count, electronic FHR monitoring (NST, CST), BPP, and color Doppler (assessment of fetoplacental blood efficiency) help to identify the high-risk fetus and to adopt preventive measures to forestall an adverse perinatal outcome. Ultrasound scanning for fetal anomalies in the midtrimester, followed by monitoring of fetal growth parameters, placental grading, and serial assessment of the amniotic fluid index provide guidance to the clinician to judge the intrauterine fetal environment. Sympathetic responses are assessed by the startle response (acoustic test) or FHR accelerations with fetal movements during a routine NST, and fetal behavioral assessment (based on testing of fetal movements and breathing movement) on ultrasound during BPP testing, color Doppler assessment of fetoplacental blood flow parameters supplement the abovementioned information and provide valuable information about fetal well-being and the information needed to adopt appropriate obstetric interventions (Damania, 2001; Purandare, 2003). Advances in the field of neonatology and the increase in number of neonatal care centers now available in India for care of the newborns has enabled obstetricians to undertake preterm obstetric interventions with greater confidence and with the assurance about the ultimate favorable outcome of pregnancy.

IMPORTANT POINTS

1. Preconceptional counseling of high-risk patients is important. Patients with diabetes, Rh isoimmunization, history of recurrent preterm labor, history of recurrent pregnancy losses, and those who potentially can transfer genetic disorders to their offspring will benefit most from preconceptional counseling.
2. A careful history and physical examination of every obstetric patient is the best way to identify the high-risk patient.
3. The best time to determine the gestational age of the fetus by ultrasound measurements is by CRL measurement before 14 weeks of gestation.
4. The objective of pregnancy care is to avoid poor maternal and fetal outcomes. The most severe abnormal outcomes are maternal death, stillbirth, neonatal death, preterm delivery, and severe preeclampsia.
5. Most maternal deaths due to bleeding, hypertension, obstructed labor, infection, thromboembolism, and abortion are preventable.
6. Most stillbirths have unknown etiology or result from nonpreventable conditions such as aneuploidy, multifactorial defects, abruptio placenta, and cord accidents.
7. The variables to be evaluated in the NST are as follows: (a) baseline FHR, (b) variability of the FHR, (c) presence or absence of accelerations, and (d) presence or absence of decelerations.
8. The MBPP (NST with VAS plus evaluation of amniotic fluid volume) is an excellent test for evaluation of the fetal well-being.
9. Absent end diastolic flow in the UA waveforms obtained by Doppler ultrasound is important evidence of fetal compromise and demands frequent and intensive fetal surveillance.
10. Reversed end diastolic flow in the UA is an ominous sign that is shortly followed by fetal demise. Fetuses with reversed end diastolic flow in the UA are acidotic and require prompt delivery.
11. Abnormal uterine artery Doppler waveforms indicate increased resistance in the maternal side of the placenta and their main use is as a screening tool for preeclampsia and FGR.
12. The DV waveforms reflect the function of the right side of the fetal circulation. Interruption of the forward flow at the nadir of atrial contraction indicates increased preload and the beginning of congestive heart failure.
13. The most important indications for percutaneous umbilical blood sampling are the need for a rapid fetal karyotype and fetal evaluation in patients with fetal hemolytic disease, fetal thrombocytopenia, or suspected fetal infection.

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2

Prenatal Diagnosis of Chromosomal Abnormalities

CHAPTER OUTLINE

Approximately 1.5% of all infants born each year in USA exhibit anatomic malformations, chromosomal abnormalities, or other genetic disorders at the time of birth. A similar number are born with abnormalities that will be detected during childhood or at adult age. This high prevalence makes the development of systems to diagnose and treat genetic conditions imperative. Fortunately, the number of these conditions that can be detected antenatally is growing at a rapid pace. This is due to the widespread use of screening methods to identify pregnancies at risk, to the continuous improvement in ultrasonic imaging, and to rapid advances in molecular diagnosis. The role of the obstetrician in prenatal diagnosis of congenital diseases is of great importance and consists mainly, but not exclusively, of the following functions:

1. Discussion with all pregnant women about the implications of genetic conditions, the methods available for screening and diagnosis, and the alternatives available if a genetic disease is found.
2. To offer screening to all pregnant women during the first or second trimester of pregnancy for chromosome abnormalities and refer all patients with positive screening to adequate facilities for counseling and further testing.
3. To offer screening to all pregnant women for fetal anatomic abnormalities by means of comprehensive ultrasound examination at 18–20 weeks of gestation and refer all women with positive findings to adequate facilities for counseling and further testing.

Advances in ultrasound technology have facilitated the diagnosis of fetal congenital anatomic abnormalities. As a consequence, more fetuses with anatomic abnormalities and in need of special diagnostic and therapeutic procedures are being discovered every day. This subject will be treated in Chapter 3 of this book.

This chapter will review the chromosomal abnormalities most frequently found in obstetrical patients and the screening methods used for identification of women at risk. Since screening for open spine defects is an integral part of the second trimester screening, this topic will be

also reviewed in this chapter. Then we will review the techniques commonly used to obtain fetal tissue for genetic diagnosis—genetic amniocentesis, chorionic villus biopsy, and umbilical cord blood sampling.

CHROMOSOMAL ABNORMALITIES

The chromosomal abnormalities most commonly found in obstetrical practice are trisomy 21 (T21), trisomy 18 (T18), trisomy 13 (T13), triploidy, Turner's syndrome, and sex chromosome abnormalities.

Trisomy 21

T21 or Down syndrome is one of the most frequent chromosomal disorders affecting human pregnancy with a prevalence of 1 in 700 or 800 live births. The risk of having a child with T21 increases with maternal age and decreases with gestational age (Table 2-1). At 16 weeks of gestation, this risk is 1 in 1053 at age 20 and 1 out of 50 at age 41. In about 95% of the cases, Down syndrome is caused by nondisjunction during meiosis, resulting in the presence of an entire additional chromosome 21. In 3–5% of the cases, it results from translocation of a band from another chromosome, most commonly chromosome 14. Mosaic composition is the cause of only a few cases. Nondisjunctional Down syndrome is usually sporadic and shows a well-defined relationship to advanced maternal age whereas those cases involving translocations may be familial and unrelated to maternal age.

The cause of the meiotic nondisjunction resulting in Down syndrome is unknown. However, there is evidence that some mothers bearing children with Down syndrome have abnormalities in folic acid metabolism, particularly a genetic abnormality in the methylenetetrahydrofolate reductase (MTHFR) gene (James et al., 1999). Folic acid is an important enzymatic cofactor essential to methylation reactions, and its deficiency may result in abnormal methylation of DNA, causing impaired chromosomal segregation and aneuploidy. Also, there is strong evidence implicating folic acid deficiency in the origin of neural tube defects (NTD), and recent studies have demonstrated a link between Down syndrome and NTDs (Barkai et al., 2003). The implication of these studies is that folic acid supplementation before conception may be useful to prevent not only NTDs but also Down syndrome.

Live-borns with Down syndrome have a characteristic phenotype including flattened facial features, small and low-set ears, small nose, excess of nuchal skin, a protruding tongue, and a broad nasal bridge. They have short limbs, short fingers, especially the fifth digit, small hands, single palm creases and increased space between the first and the second toes. Associated anomalies are common, particularly congenital heart defects that affect approximately 50% of the cases. Gastrointestinal abnormalities are also common and include duodenal atresia, imperforated anus, and tracheoesophageal fistula. The phenotypic characteristics of newborns and fetuses with T21 are the basis for ultrasound screening for this abnormality. As it will be seen later, absence or hypoplasia of the nose

Table 2-1. Risk of Down syndrome by maternal age and gestational age

Maternal age (years)	Gestational age					
	10 weeks	12 weeks	14 weeks	16 weeks	20 weeks	40 weeks
20	1/983	0	0	0	0	0
25	1/870	1/946	0	0	0	0
30	1/576	1/626	1/668	1/703	1/759	1/895
31	1/500	1/543	1/580	1/610	1/658	1/776
32	1/424	1/461	1/492	1/518	1/559	1/659
33	1/352	1/383	1/409	1/430	1/464	1/547
34	1/287	1/312	1/333	1/350	1/378	1/446
35	1/229	1/249	1/266	1/280	1/302	1/356
36	1/180	1/196	1/209	1/220	1/238	1/280
37	1/140	1/152	1/163	1/171	1/185	1/218
38	1/108	1/117	1/125	1/131	1/142	1/167
39	1/82	1/89	1/95	1/100	1/108	1/128
40	1/62	1/68	1/72	1/76	1/82	1/97
41	1/47	1/51	1/54	1/57	1/62	1/73
42	1/35	1/38	1/41	1/43	1/46	1/55
43	1/26	1/29	1/30	1/32	1/35	1/41
44	1/20	1/21	1/23	1/24	1/26	1/30
45	1/15	1/16	1/17	1/18	1/19	1/23

From Snijders RJM, Sebire NJ, Cuckle H, et al. Maternal age and gestational age-specific risks for chromosomal defects. Fetal Diagn Ther 1995; 10: 356–67.

bone, increased nuchal fold thickness (NFT), cardiac abnormalities, short bones, and short digits are some of the ultrasound markers indicating an increased likelihood that the fetus has Down syndrome. Approximately 20–30% of these infants die during their 1st year of life mainly due to cardiac abnormalities. Fifty percent die by the age of 5 years, mainly due to respiratory infections. Those who survive infancy may reach 40 or 50 years of age and universally have mental retardation with IQ between 25 and 50.

When a pregnant woman has a history of a previous child with Down syndrome, it is important to know the type of chromosomal defect found in the affected child because the risk of recurrence in a future pregnancy will be different depending on the type of defect. The recurrence risk for nondisjunctional T21 is 0.75% higher than the maternal and gestational age-related risk (Nicolaides, 2003). For example, the background risk for a woman 25-year old at 16 weeks of gestation is 1 in 933 (0.10%). If she has a history of T21 in previous pregnancy, her risk will be 0.10 + 0.75 = 0.85% = 1 in 117. The recurrence risk when Down syndrome is caused by an unbalanced translocation varies depending on the chromosomal composition of the parents. If both parents have a normal karyotype, the translocation in the affected child occurred "de novo" and the risk of another affected child is less than 1%. If the mother's karyotype is normal but the father has a balanced 13/21, 14/21, 15/21, or 21/22 translocation, the risk of another affected child will be 2–3%. If the father's karyotype is normal and the mother is the carrier of a balanced 13/21, 14/21, 15/21, or 21/22 translocation, the probability of having another affected child is 11.9%, which is much less than the theoretical risk of 33%. If either parent has a balanced 21/21 translocation, the risk of having an affected child in a future pregnancy will be 100%. The risk of recurrence when a previous child has been born with Down syndrome resulting from mosaicism is unknown, but is probably small, 2–3%.

Trisomy 18

T18 or Edwards syndrome is another relatively frequent chromosomal abnormality with a prevalence of 1 in 3000 to 1 in 6000 births. Most of the cases are sporadic. Most cases of T18 are due to nondisjunction during meiosis, and the frequency of the condition increases with maternal age and decreases with gestational age (Table 2-2). The reason for the association between maternal age and increased frequency of meiotic nondisjunction is unknown.

T18 is a lethal abnormality and most affected individuals die before birth or in the first 3 months of life. Failure to thrive, feeding difficulties, and death from cardiac and gastrointestinal abnormalities are the usual course of the infants who survive the neonatal period. Survivors for more than 1 year are profoundly retarded in motor and intellectual development and are unable to talk or walk. The majority of fetuses with T18 present with phenotypic defects. They include severe fetal growth restriction, cardiac abnormalities, fawn-like and low-set ears, small biparietal diameter of the skull, single umbilical artery, rocker-bottom feet, clenched hands, and micrognathia. The hand abnormality is characteristic: the hands are

Table 2-2. Risk of trisomy 18 by maternal age and gestational age

Maternal age (years)	Gestational age					
	10 weeks	12 weeks	14 weeks	16 weeks	20 weeks	40 weeks
20	1/1993	1/2484	1/3015	1/3590	1/4897	1/18013
25	1/1765	1/2200	1/2670	1/3179	1/4336	1/15951
30	1/1168	1/1456	1/1766	1/2103	1/2869	1/10554
31	1/1014	1/1263	1/1533	1/1825	1/2490	1/9160
32	1/860	1/1072	1/1301	1/1549	1/2490	1/7775
33	1/715	1/891	1/1081	1/1287	1/1755	1/6458
34	1/582	1/725	1/880	1/1047	1/1429	1/5256
35	1/465	1/580	1/703	1/837	1/1142	1/4202
36	1/366	1/456	1/553	1/659	1/899	1/3307
37	1/284	1/354	1/430	1/512	1/698	1/2569
38	1/218	1/272	1/330	1/393	1/537	1/1974
39	1/167	1/208	1/252	1/300	1/409	1/1505
40	1/126	1/157	1/191	1/227	1/310	1/1139
41	1/95	1/118	1/144	1/171	1/233	1/858
42	1/71	1/89	1/108	1/128	1/175	1/644
43	1/53	1/66	1/81	1/96	1/131	1/481
44	1/40	1/50	1/60	1/72	1/98	1/359

From Snijders RJM, Sebire NJ, Cuckle H, et al. Maternal age and gestational age-specific risks for chromosomal defects. Fetal Diagn Ther 1995; 10: 356–67.

clenched and the third or fourth finger overrides the others. The occiput is prominent and the cisterna magna is enlarged. Choroid plexus cysts occur in approximately 40% of the cases. Cardiac defects are common especially ventricular septal defects and aortic coarctation. Renal malformations, especially horseshoe kidneys, occur in 50–80% of the cases.

Screening for T18 is performed by serology and ultrasound. Serologic screening is performed with the same analytes used for first trimester screening or for triple or quadruple screening in the second trimester. Ultrasound screening is done by nuchal translucency (NT) in the first trimester and genetic ultrasound in the second trimester. Diagnosis is by chorionic villus sampling (CVS) or amniocentesis. Similarly to what happens in Down syndrome, the risk of recurrence of T18 is 0.75% higher than the maternal and gestational age-associated risk for T18. However, the risk of T21 is not increased when the previous child had T18, indicating that the risk of recurrence is specific for each abnormality (Nicolaides, 2003).

Trisomy 13

T13 or Patau syndrome is another relatively frequent chromosome abnormality with an incidence of 1 in every 5000 births to 1 in 8000 births. It is a lethal condition with the majority of cases dying in utero or shortly after birth and very few survive after 1 year. In the large majority of cases, T13 is due to meiotic nondisjunction and its frequency increases with maternal age and decreases with gestational age (Table 2-3).

In the majority of cases, T13 is characterized by a triad of microphthalmia, cleft lip and palate, and polydactyly. However, some or all of these features may be absent. Other phenotypic features of fetuses and newborns with T13 include growth restriction, microcephaly, holoprosencephaly which is present in 40% of the cases, congenital cardiac abnormalities in 80% of the cases, and renal abnormalities in 80% of the cases, particularly polycystic kidneys dysplasia and hydronephrosis.

T13 can be suspected by ultrasound findings in the second trimester. Early detection can be achieved by further investigation of increased NT, cystic hygromas, or holoprosencephaly found by ultrasound examination between 11 and 14 weeks. First and second trimester serologic screening are not helpful for the detection of T13. Most cases of T13 are sporadic and the risk of recurrence is 1 in 100.

Turner's Syndrome

Turner's syndrome is a female chromosomal abnormality resulting from the total or partial absence of one of the X chromosomes (45XO). The incidence is 1 per 2500 to 1 in 3000 live-born girls, but this number is not representative of the real frequency of the abnormality since more than 90% of the fetuses with this abnormality are spontaneously aborted. The incidence of Turner's syndrome is not related to the maternal age. Cystic hygromas and cardiac abnormalities are the main features of fetal 45XO syndrome. Short stature, hearing impairment, gonadal dysgenesis with lack of secondary sexual characteristics and infertility are the predominant features in adulthood. Intelligence is normal. Congenital heart disease (CHD)

Table 2-3. Risk of trisomy 13 by maternal age and gestational age

Maternal age (years)	Gestational age					
	10 weeks	12 weeks	14 weeks	16 weeks	20 weeks	40 weeks
20	1/6347	1/7826	1/9389	1/11042	1/14656	1/42423
25	1/5621	1/6930	1/8314	1/9778	1/12978	1/37567
30	1/3719	1/4585	1/5501	1/6470	1/8587	1/24856
31	1/3228	1/3980	1/4774	1/5615	1/7453	1/21573
32	1/2740	1/3378	1/4052	1/4766	1/6326	1/18311
33	1/2275	1/2806	1/3366	1/3959	1/5254	1/15209
34	1/1852	1/2284	1/2740	1/3222	1/4277	1/12380
35	1/1481	1/1826	1/2190	1/2576	1/3419	1/9876
36	1/1165	1/1437	1/1724	1/2027	1/2691	1/7788
37	1/905	1/1116	1/1339	1/1575	1/2090	1/6050
38	1/696	1/858	1/1029	1/1210	1/1606	1/4650
39	1/530	1/654	1/784	1/922	1/1224	1/3544
40	1/401	1/495	1/594	1/698	1/927	1/2683
41	1/302	1/373	1/447	1/526	1/698	1/2020
42	1/227	1/280	1/335	1/395	1/524	1/1516
43	1/170	1/209	1/251	1/295	1/392	1/1134
44	1/127	1/156	1/187	1/220	1/292	1/846

From Snijders RJM, Sebire NJ, Cuckle H, et al. Maternal age and gestational age-specific risks for chromosomal defects. Fetal Diagn Ther 1995; 10: 356–67.

affects between 17 and 45% of girls with Turner's syndrome. Coarctation of the aorta and bicuspid aortic valve are the most frequent abnormalities. Antenatal diagnosis can be made in the first trimester by ultrasound visualization of a cystic hygroma followed by CVS, or in the second trimester by abnormal serologic screening (triple or quadruple test) followed by amniocentesis. In a recent study, 45XO was diagnosed in 41 fetuses. The main indication for diagnosis was an abnormal ultrasound, and in 93% of the cases the pregnancy was terminated (Brun et al., 2004).

Klinefelter's Syndrome

Klinefelter's syndrome (47XXY) is the most common of all sex chromosome abnormalities affecting 1 in 600 births. The adult phenotypic characteristics are tall stature, hypogonadism with azoospermia or oligospermia and decreased libido, osteoporosis, and cognitive and behavioral problems. In a series of 31 cases of Klinefelter's syndrome, the main indication for karyotyping was maternal age and the termination rate was 32% (Brun et al., 2004).

Fragile X Syndrome

Mutations in the X chromosome are the most frequent cause for mental retardation. One of these mutations affecting about 1 in 15,000 males and 1 in 2500 females is the fragile X syndrome—a name that originated in the demonstration of a fragile site in the long arm of the X chromosome under certain conditions in the tissue culture. The fragile X gene contains 200–2000 repeat triplets CGG compared to 6–45 in normal individuals. As a consequence, there is hypermethylation of the promoter region of the gene and blockage of the synthesis of the gene product. Individuals with fragile X have moderate to severe mental impairment and their IQ is between 20 and 50. The abnormality occurs frequently in autistic males and females.

Triploidy

Triploidy is a lethal malformation that consists of the presence of a complete additional set of chromosomes in each cell of the conceptus as a result of the fertilization of an egg by two spermatozoids or the fertilization of a diploid egg by one sperm. As a consequence the karyotype will be 69XXX or 69XXY. One percent of all human conceptuses are triploid, but most of them end in spontaneous abortion. The frequency of live-born triploids is 1 in 10,000 births. Survival after the neonatal period is rare. Cases of triploidy that are not aborted early in gestation are characterized by severe fetal growth restriction, central nervous system, cardiac, and limb abnormalities, and oligohydramnios. The placenta is usually enlarged and has areas of cystic degeneration, resembling molar pregnancy. Triploid cases are sporadic and recurrence risk is low.

SCREENING FOR CHROMOSOMAL ABNORMALITIES

Before the development of serologic screening, prenatal assessment for chromosomal abnormalities was limited to performing amniocentesis in women considered at high-risk. This mainly included pregnant women aged 35 years or older or women who had a newborn with aneuploidy in a previous pregnancy. With the development of screening methods, surveillance for aneuploidy has been extended to women of all ages. Screening for aneuploidy originated in the early 1980s when it was found that the serum from mothers having fetuses with aneuploidy frequently had low concentrations of alpha-fetoprotein (AFP), which was being measured to screen for the presence of open NTDs. This led to the discovery of other serum markers that are used in the first or second trimester of pregnancy to screen for aneuploidy. Parallel to the development of biochemical analytes were significant advances in the accuracy of fetal ultrasound in the identification of several markers of aneuploidy. At the present time, screening for aneuploidy can be performed in the first trimester, using ultrasound measurement of the NT alone or in combination with two biochemical analytes: the free beta subunit of human chorionic gonadotropin (free beta-hCG) and the pregnancy-associated plasma protein A (PAPP-A). Screening in the second trimester is performed using the triple test (maternal serum hCG, AFP, and uE3 (unconjugated estriol)) or the quadruple test (quad test) which involves determinations of maternal serum hCG, AFP, uE3, and inhA (inhibin A). A third method of second trimester screening is the "genetic" or "comprehensive"

BOX 2-1

Screening methods for chromosomal abnormalities

First trimester
- Maternal age
- NT
- NB (nasal bone)
- Free beta-hCG + PAPP-A
- NT + free beta-hCG + PAPP-A
- NT + NB + free beta-hCG + PAPP-A

Second trimester
- Triple test
- Quad test
- Genetic sonogram
- Quad test + genetic sonogram

First plus second trimester
- Integrated test
- Sequential test (stepwise or contingent)

ultrasound examination. Finally, ultrasound and biochemical markers obtained in the first and the second trimester may be integrated or used sequentially to obtain further accuracy in the assessment of risk (Box 2-1).

It is important to distinguish between screening tests and diagnostic tests. Screening tests provide an assessment of the risk of having a condition while diagnostic tests determine if the condition is present or not. In the particular case of fetal chromosomal abnormalities the diagnostic tests are CVS and amniocentesis. These diagnostic tests carry with them risks for the pregnancy and are usually reserved for subjects that test positive with the screening tests.

General Considerations

All pregnant women are at risk of carrying a fetus with genetic abnormalities. Therefore, screening for fetal genetic abnormalities should be an integral part of the prenatal care for all women. Limiting genetic screening to certain groups at higher than the usual background risk for abnormalities is a practice that should be abandoned and screening for fetal chromosomal abnormalities should be an integral part of the prenatal care for all women. This attitude toward antenatal screening has been recently recommended by ACOG (ACOG, 2007).

The background risk of having a baby with chromosome abnormalities depends on the maternal age and the gestational age at the time of evaluation (Tables 2-1–2-3). The increased risk associated with advanced maternal age has been recognized for many years. The decreased risk associated with gestational age occurs because fetuses with abnormalities tend to die "in utero" and when pregnancy advances, more of them will die and the risk of aneuploidy for the remaining fetal population will be less. The death rate for fetuses with Down syndrome between 12 weeks and term is 30%, for fetuses with T18 and T13 is about 80%, and for fetuses with triploidy is almost 100%. It is obvious that the risk for fetal aneuploidy of women having genetic screening in the first or second trimester of pregnancy is larger than the risk of delivering at term a fetus with aneuploidy. When counseling women about genetic screening, it is necessary to use the risk associated with maternal age and the risk associated with the gestational age at the time of the test.

The concentration of biochemical analytes used for prenatal screening changes with the gestational age, and it is expressed as multiples of the median (MoM). In order to do that, laboratories analyze thousands of serum samples and generate median values at different gestational ages. Then the serum concentration of one analyte in ng/ml or IU/ml is normalized and given to the clinician as MoM eliminating the variation associated with the gestational age. By definition the normal median value of an analyte at a specific gestational age is 1.0. A value of 1.5 MoMs means that the patient has a value that is 1.5 times the mean value for individuals of the same gestational age. Values at or above 2.0 MoMs are considered abnormal. Expressing the lab results as MoMs allows the clinician to compare the value obtained for an individual patient with that obtained for the overall obstetrical population.

When biochemical analytes are used to screen for fetal chromosomal abnormalities, it is necessary to define a cutoff risk for test interpretation. Values larger than the cutoff value are considered screen positives and values smaller than the cutoff will be screen negatives. A commonly used cutoff is 1:380, which is the risk for a 35-year-old woman of having a term newborn with T21. Studies on prenatal screening have used cutoff points between 1:190 and 1:385. Changes in the cutoff point affect the accuracy of the screening test, and adoption of a large cutoff will increase the detection rate, or DR, and the false positive results (FPR) while a smaller cutoff will have the opposite effect.

The two most important characteristics of a screening test are its sensitivity (detection rate) and its false positive rate. Sensitivity indicates how many of the affected fetuses in the population will be identified by a positive test result. This is important and the tendency is to use the screening test that identifies the highest possible number of abnormal fetuses. However, that tendency should be balanced against the false positive rate. The false positive rate indicates the number of normal fetus cases with positive test results and in the case of prenatal diagnosis is an indication of the number of unnecessary invasive procedures dictated by the screening test. This is important because both CVS and amniocentesis carry the risk of postprocedural pregnancy loss and the higher the false positive rate, the higher the number of normal fetuses that will be lost as a result of the diagnostic procedure. For example, a screening test with 83% sensitivity and 8% false positive rate will detect 830 fetuses with Down syndrome out of 1000 present in a population of 700,000 women assuming an incidence of Down syndrome of 1:700. To detect these abnormal fetuses it will be necessary to perform 56,000 amniocentesis and approximately 280 normal fetuses will be lost as a consequence of the procedure.

Screening for chromosome abnormalities is an effective method to decrease the number of live births with abnormalities. A study using data from the US National Center for Health Statistics demonstrated that the proportion of live births to women aged 35 years and older was 13.6% in 2001 but the rate of Down syndrome live births actually declined. Women aged 15–34 years had 45% and those aged 35–49 years had 53% fewer live births with Down syndrome in the same year (Egan et al., 2004). This decrease most probably is due to the use

of genetic screening, prenatal diagnosis, and terminations of the affected pregnancies.

First Trimester Screening

Screening during the first trimester is widely used in European countries and is being used increasingly in USA. First trimester screening may be performed using the ultrasound evaluation of NT alone or combined with the maternal serum concentration of free beta-hCG plus PAPP-A. The ultrasound finding of a hypoplastic or absent nasal bone (NB) is another powerful marker of aneuploidy in the first trimester that when combined with the first trimester screening offers the highest sensitivity for the detection of Down syndrome.

Nuchal translucency

The discovery that NT (Figure 2-1) is a sensitive marker of aneuploidy (Nicolaides et al., 1992) has been one of the most significant contributions to the advance of prenatal diagnosis. Embryos with aneuploidy have an increased amount of fluid in the neck region, resulting in increased NT measurements. This finding is not specific for aneuploidy and fetuses with CHD, genetic syndromes, and with some anatomic abnormalities also exhibit increased NT measurements. The abnormal accumulation of fluid in these cases may be due to embryonic heart failure, abnormal or delayed development of the fetal lymphatic system, hypoproteinemia with decreased plasma oncotic pressure, or altered composition of the connective tissue below the nuchal skin (von Kaisenberg et al., 1999). NT measurements should be obtained between 11 and 13 weeks of gestation (embryonic crown–rump length (CRL) between 45 and 84 mm). Obtaining accurate NT measurements requires strict adherence to the rules shown in Box 2-2. Individuals doing this measurement should ideally be certified by the Fetal Medicine Foundation in London—an entity that has been the pioneer in attempting to maintain the quality of the measurement by continuous assessment and supervision of the certified personnel.

BOX 2-2

Requirements for accurate NT measurements

- Crown–rump length between 45 and 85 mm
- A good midsagittal section of the fetus showing the facial profile
- Clear differentiation between the fetal skin and the amnion achieved by spontaneous or induced fetal movement
- Magnification of the image so that the fetal head, neck, and upper thorax occupy three-fourths of the screen
- Placing of the calipers on the border of the white lines (fetal skin and fetal skull) so that the maximal translucent area is measured
- The fetal head should be in a neutral position. Extended head will increase and flexed head will decrease the measurement
- The measurement should be performed in the line of the fetal mandible that usually corresponds to the area of widest nuchal translucency

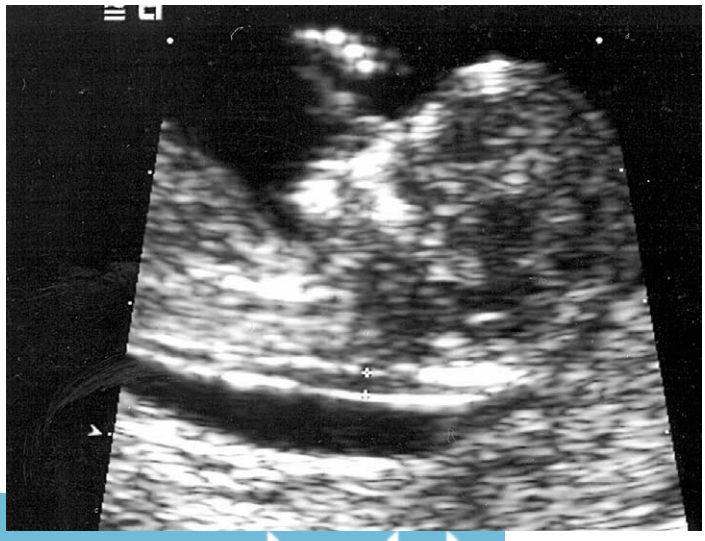

Figure 2-1. Nuchal translucency.

NT is gestational-age-dependent and the measurement increases with the gestational age. The median and 95th percentile of NT at a CRL of 38 mm are 1.3 mm and 2.2 mm, respectively, and 1.9 mm and 2.8 mm at a CRL of 84 mm (Snijders et al., 1998). NT is a powerful marker of aneuploidy and the number of abnormal fetuses increases in direct relationship to increases in NT value. When the NT is between 2.5 and 3.4 mm the frequency of abnormal fetuses is 8%. It increases to 29% when the NT is between 3.5 and 4.4 mm and to 48% when the NT is 4.5–5.4 mm. When the NT is greater than 6.5 mm, 87% of the fetuses will be abnormal. The measurement is above the 95th percentile in 71.8% of fetuses with T21, in 70.5% of fetuses with other chromosomal defects (T18, T13, Turner's syndrome, triploidy, others), and in 4.4% of normal fetuses. For a cutoff of 1 in 300, the sensitivity of NT plus maternal age is 82.2%, the false positive rate 8.3%, the positive predictive value 3.2%, and the negative predictive value 99.9% (Snijders et al., 1998). As it will be discussed later, when NT is used in combination with free beta-hCG and PAPP-A (combined first trimester screening) it has the capability to detect > 90% of Down syndrome cases with a false positive rate of 5%. When the NT is ≥ 4.0 mm the incidence of aneuploidy is so significant that it is appropriate to perform CVS without testing for biochemical analytes.

In addition to being useful for aneuploidy screening, NT is a marker of cardiac abnormalities, diaphragmatic hernia, skeletal dysplasias, genetic syndromes, and other fetal congenital abnormalities (Souka et al., 1998). In one study the incidence of abnormal outcomes in fetuses with normal karyotype and NT > 3 mm was 32% while it was only 7.5% in fetuses with NT < 3 mm (Bilardo et al., 1998).

Nasal bone

Absent NB is another important marker of Down syndrome in the first trimester of pregnancy (Cicero et al., 2001). The NB is absent in 68.8% of fetuses with Down syndrome and in 32.2 of fetuses with other chromosomal abnormalities. In the normal population the frequency of absent NB is related to the ethnic origin of the mother, and it is 2.2% in Caucasians, 9.0% in Afro-Caribbeans and 5% in Asians (Cicero et al., 2004). These normal variations need to be taken into consideration when evaluating a patient's individual risk of Down syndrome using the NB as a marker. The incidence of absent NB decreases with the CRL and increases with the NT of the fetus. The positive likelihood ratio, or LR (incidence of Down syndrome in fetuses with absent NB divided by the incidence of normal karyotype in fetuses with absent NB) will be higher in Caucasians (31.3) than in Afro-Caribbean (8.8), lower at CRL of 45–54 mm (17.6) than at a CRL of 75–84 mm (51.8) and higher when the NT is between the 95th percentile and 3.4 mm (25.1) than when the NT is ≥ 2.5 mm (5.3) (Cicero et al., 2004). For example, the positive likelihood ratio for a Caucasian mother (LR 31.3) with a CRL of 50 mm (LR 17.6) and an NT < 95th percentile (LR 37.1) will be 28.6. It has been calculated that for a false positive rate of 5% the detection rate for Down syndrome using NT alone will be 75%, for NT plus NB will be 90%, and for NT, plus NB, plus serum biochemical analytes will be 97%. If the false positive rate is fixed at 1% the detection rate will be 57, 86, and 93%, respectively (Cicero et al., 2004).

Similarly to the NT measurement, it is necessary to follow a strict set of rules for the ultrasound visualization of the NB (Box 2-3). The skin over the nasal bridge is parallel and almost as echogenic as the NB (Figure 2-2),

BOX 2-3

Requirements for accurate NB measurements

- The fetus needs to be facing the ultrasound transducer
- The magnification of the image should be such that the head and the thorax occupy the whole image (11–13 weeks scan)
- The angle of insonation should be 90° (face of the transducer should be parallel to the longitudinal axis of the nasal bone and the skin over the nasal bridge)
- In normal fetuses, three echogenic lines should be identified (the skin over the nasal bridge, a line below the skin that corresponds to the nasal bone, and a third line further away from the forehead than the nasal bone and at a slightly higher level that corresponds to the skin over the nasal tip)
- The two parallel lines representing the skin over the nasal bridge and the nasal bone compose the so-called "equal sign" (=)
- If the bottom part of the equal sign is missing, the nasal bone is considered to be absent

From Sonek J, Cicero S, Neiger R, et al. Nasal bone assessment in prenatal screening for trisomy 21. Am J Obstet Gynecol 2006; 195: 1219–30.

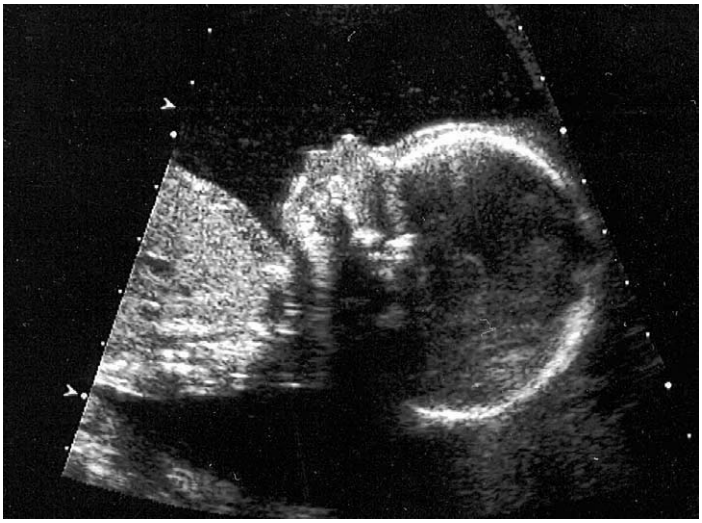

Figure 2-2. Nasal bone.

and when the NB is present the parallel lines of echogenicity have the shape of an "equal sign" (Sonek et al., 2006). If the bottom part of the equal sign is missing, the NB is considered to be absent. The average number of studies necessary to achieve proficiency in assessment of the NB between 11 and 14 weeks' gestation was 80 (Cicero et al., 2003a). Ideally, personnel performing this assessment should be certified and periodically supervised by the Fetal Medicine Foundation. Three-dimensional ultrasound is extremely useful in the assessment of confusing two-dimensional cases.

Free beta-hCG

Human chorionic gonadotropin, or hCG, is a glycoprotein made up of two alpha and beta subunits that may be bound to each other or free. Both free alpha and beta subunits are increased in Down syndrome but only the free beta subunit has been widely used for screening. The increase in free beta-hCG in fetuses with aneuploidy starts at the end of the first trimester and continues during the second trimester, making the test useful for both first and second trimester screening. Total hCG is also increased in aneuploid pregnancies but investigations have demonstrated that is a poor marker in the first trimester of pregnancy (Aitken et al., 1993). The MoM of free beta-hCG in aneuploid pregnancies is between 2.06 and 2.64. When used alone, free beta-hCG has a detection rate for Down syndrome of 33%, a value that increases to 46% when used in combination with maternal age. When free beta-hCG values are combined with maternal age and PAPP-A the detection rate increases to 67% (Spencer et al., 1999).

Pregnancy-associated plasma protein A

The majority of fetuses with aneuploidy exhibit reduced levels of PAPP-A in the first trimester of pregnancy. PAPP

is a glycoprotein containing 16 atoms of zinc. PAPP-A concentration is lower in fetuses with aneuploidy but the difference with normal pregnancies becomes smaller with advances in gestational age, making this analyte useful only in the 10–14-week interval. The median MoM concentration of PAPP-A is 0.48 in aneuploid pregnancies. When used alone, it has a detection rate of 38% that increases to 48% when combined with maternal age (Spencer et al., 1999).

Combined ultrasound and biochemical screening

One of the best available methods of screening for aneuploidy is the evaluation of NT by ultrasound and simultaneous determination of the concentration of free beta-hCG and PAPP-A (combined test). The combined ultrasound and serum screening has a detection rate for Down syndrome of 87.5% with a false positive rate of 4.5% in women younger than 35 years and a detection rate of 92% with a false positive rate of 14.3% in women older than 35 years using a cutoff of 1:300. In women younger than 35 years the detection rate of the combined test for T18 is approximately 100% with a false positive rate less than 1% using a risk cutoff of 1:150. In women older than 35 years the detection rate for T18 is similar but the FPRs increase to 1.4% (Krantz et al., 2000).

The NT is not used alone for aneuploidy screening with the exception of multifetal pregnancies. In these cases the maternal serum concentration of free beta-hCG and PAPP-A is the sum of the analytes produced by each pregnancy and it is impossible to know the relative contribution of each of the fetuses to the grand total. Therefore, it is better to use the NT alone than to risk a serious error by assuming that each fetus contributed a similar amount to the total concentration of maternal analytes.

In situations where it is not possible to obtain adequate NT measurements, screening may be postponed to the second trimester (quad test plus comprehensive ultrasound). Another option will be integrated screening using only first- and second-trimester serologic markers. This approach has 85–88% detection rate (Malone et al., 2005).

First trimester screening for aneuploidy has multiple advantages. The most important is a detection rate better or similar to that of second trimester screening. Also, the majority of women can be reassured early in gestation of the normalcy of the pregnancy and those found to have an affected fetus and who choose to terminate the pregnancy could have it done by a procedure much safer than that used later in gestation. Also, first trimester screening and termination of affected pregnancies protects the privacy of the pregnant women because it is done at a time when the physical manifestations of pregnancy are not apparent. Finally, the decision to terminate or not the pregnancy when the fetus is affected is not influenced by the maternal perception of fetal movements.

First trimester screening is not only an adequate method for early selection of the patients at risk for aneuploidy but also abnormal results in the absence of aneuploidy are associated with obstetrical complications. The National Institute of Child Health and Human Development study on first trimester maternal serum biochemistry and ultrasound NT screening for T21 and T18 demonstrated that PAPP-A and free beta-hCG values below the 1st percentile were associated with increased risk for fetal growth restriction. PAPP-A < 5th percentile and NT > 99th percentile were associated with increased risk of preterm delivery before 34 weeks (Krantz et al., 2004). Similar conclusions were found in the FASTER trial (Dugoff et al., 2004).

First trimester screening should be performed when the CRL is between 45 and 85 mm (10 weeks 4 days and 13 weeks 6 days of gestation). The NT measurement should be performed by a person trained and certified for the performance of the examination. Blood for measurement of the biochemical analytes can be collected by finger stick in specialized filter paper (Krantz et al., 2000). Follow-up of the first trimester screening results varies depending on the overall strategy adopted for the screening and diagnosis of chromosomal abnormalities, a topic that will be discussed later on in this chapter.

Second Trimester Screening

The maternal biochemical analytes used for second trimester screening with the triple test are AFP, hCG or free beta-hCG, and free estriol. The quad test includes a fourth analyte, inhA. The ultrasound screening method is called comprehensive or genetic ultrasound.

Alpha fetoprotein

AFP is a globulin produced in the liver and gastrointestinal tract of the fetus. The physiologic role of AFP is unknown. AFP is secreted in the fetal urine and then excreted in the amniotic fluid. The maternal serum concentration of AFP increases during pregnancy and reaches a peak between 28 and 32 weeks and is substantially greater when the fetus has an open NTD. Soon after the generalized use of maternal serum AFP (MSAFP) as a screening test for open spine defects, it was noticed that the concentration of MSAFP was about 25% lower in fetuses with Down syndrome. When the results of MSAFP were used in combination with the maternal age risk in women younger than 35 years, the detection rate for Down syndrome was 25% with 5% FPRs (New England Regional Genetics Group Prenatal Collaborative Study of Down Syndrome Screening, 1989).

Free beta-hCG

hCG is produced in the trophoblast cells and its maternal serum concentration reaches a peak at approximately 15 weeks, followed by a rapid decline until 17 weeks and a more gradual decrease between 17 and 22 weeks. The concentration of free beta-hCG is increased in aneuploid fetuses and is useful for screening in the first and the second trimester of pregnancy. Some laboratories use total hCG concentration instead of free beta-hCG and this may be acceptable for the second but not for first trimester screening. The levels of hCG and free beta-hCG are increased to about twice the normal value during the second trimester in fetuses with aneuploidy.

Unconjugated estriol

Estriol is a steroid molecule synthesized from the combined activity of the fetal adrenal gland and the placenta. The main precursor of estriol is dehydroepiandrosterone sulfate (DHEA-S) produced in the fetal adrenal gland. This precursor is transformed in estriol by the placenta. Estriol is mostly protein bound. The concentration of free estriol in the second trimester of pregnancy is decreased about 25% in aneuploid pregnancies, making it valuable as a screening analyte.

Very low levels of uE3 are associated with Smith–Lemli–Opitz syndrome, an autosomal recessive condition causing with moderate to severe mental retardation (Bradley et al., 1999). The reason for this is that individuals affected with Smith–Lemli–Opitz syndrome have a deficient cholesterol synthesis and cholesterol is a precursor of DHEA-S and estriol. Another condition resulting in undetectable low levels of uE3 is placental sulfatase deficiency which blocks the metabolic degradation of DHEA-S.

Inhibin A

Inhibin is a glycoprotein composed of one alpha and one of two beta subunits (beta-A and beta-B). In nonpregnant women inhibin is produced by the corpus luteum and inhibits the pituitary production of follicle-stimulating hormone, or FSH. InhA is made up of one alpha-A and one beta-A subunit and during pregnancy is produced by the placenta, reaching serum concentrations much higher than in the nonpregnant status. InhA levels are not discriminatory in the first trimester of pregnancy between fetuses affected by Down syndrome and normal ones, but in the second trimester affected fetuses show higher concentrations than normal ones. The increase in inhA levels associated with Down syndrome is about 1.77 MoMs. The concentration of inhA is not used to calculate the risk for T18.

Triple test

The triple test has been for many years the most commonly used screening test in the second trimester of pregnancy. It consists of measuring the serum concentration of MSAFP, beta-hCG, and uE3. The three variables are independent predictors of genetic risk and in combination with the maternal age generate a patient-specific risk of having a fetus with Down syndrome. The gestational age to perform the triple test is between 15 and 21 weeks. The test cutoff is 1:380. The detection rate is approximately 69% for a false positive rate of 5%. A meta-analysis of 20 series including close to 200,000 cases found detection rates of 67, 71, and 73% when the cutoffs used were 1:190–200, 1:250–295, and 1:350–380 (Conde-Agudelo and Kafury-Goeta, 1998). The triple test is being used less frequently due to the better detection rates obtained with the quad test and with first trimester screening.

The triple test is also useful to screen for T18 and the risk given by the test is an accurate reflection of the observed prevalence of the syndrome (Meier et al., 2003). When the fetus is at high risk for T18 the serum concentration of all three analytes is low. The cutoff for T18 is 1:100.

Quad test

The quad test consists of determining the maternal serum concentration of MSAFP, beta-hCG, free estriol, and inhA to assess the risk for Down syndrome. The addition of inhA improves the detection rate of Down syndrome in comparison with the triple test. The detection rate of the quad test in a population of 23,704 women using a cutoff of 1:270 was 85.8% with a false positive rate of 8.3% (Benn et al., 2003). In another study involving 46,193 pregnancies the detection rate was 81% with a false positive rate of 7% using a cutoff of 1:300 (Wald et al., 2003).

Genetic sonogram

With the discovery and generalized use of ultrasound markers of aneuploidy it is necessary to have adequate means to assess their impact in the evaluation of risk for individual patients. To use ultrasound markers correctly it is necessary to multiply the background risk or previous risk of the patient, usually the risk associated with the maternal age and the gestational age of the pregnancy, by the positive or negative likelihood ratios of each one of the markers assessed during the ultrasound examination. A positive likelihood ratio results from dividing the frequency that marker is found in fetuses with confirmed diagnosis of Down syndrome by the frequency of the same marker in fetuses with normal karyotype. A negative

likelihood ratio results from dividing the number of fetuses with Down syndrome that do not exhibit a given marker by the number of normal fetuses that do not exhibit such a marker. For example, an echogenic bowel is found in 13.3% of fetuses with Down syndrome and in 0.6% of normal fetuses. The positive likelihood ratio will be 13.3/0.6 = 22.0. The negative likelihood ratio will be 86.7/99.4 = 0.87.

Different ultrasound markers have different sensitivity (detection rate) for fetuses with Down syndrome and therefore different likelihood ratios (Table 2-4). The most powerful markers of aneuploidy in Caucasians are the absence of NB, increased NFT, and cardiac abnormalities. When one or several of the eight markers shown in Table 2-3 are present but the others are not, the likelihood ratio for that particular individual will be the product of the positive predictive value of the marker or markers that were found during the examination and the negative predictive values of the markers that were not found. For example, if a short humerus is found in the fetus of a Caucasian mother that otherwise has normal NB, normal nuchal fold, no major defects, normal kidneys, normal bowel, and no echogenic foci in the heart the likelihood ratio for that fetus of having Down syndrome will be 22.76 × 0.38 × 0.67 × 0.62 × 0.85 × 0.75 × 0.87 × 0.79 = 1.57. If the background risk is 1/1250 (0.0008) the new risk will be 0.0008 × 1.57 = 0.001256 (1/796).

A genetic sonogram without markers of aneuploidy reduces the background risk for Down syndrome determined by the maternal age and the gestational age at the time of the test. The magnitude of that reduction varies between investigators. The likelihood ratio when the genetic sonogram is normal and none of the markers is present is 0.2 for Bromley et al. (2002) and 0.11 for DeVore (2000). If the negative likelihood ratios shown in Table 2-4 are combined the likelihood ratio of a normal genetic sonogram will be 0.12 without including the NB in the calculation, 0.047 when the NB is included and the population is Caucasian, and 0.032 when the NB is included and the population is Afro-Caribbean.

Table 2-4. Positive and negative likelihood ratios for ultrasound markers of Down syndrome

	Positive LR	Negative LR
Nasal bone (Caucasians)	132.1	0.39
Nuchal fold	53.05	0.67
Major defect	32.96	0.79
Short humerus	22.76	0.68
Echogenic bowel	21.17	0.87
Nasal bone (Afro-Caribbeans)	8.5	0.27
Short femur	7.94	0.62
Hydronephrosis	6.77	0.85
Echogenic focus	6.41	0.75

From Nicolaides KH. Screening for chromosomal defects. Ultrasound Obstet Gynecol 2003; 21: 313–21.

Since CHD is present in approximately 50% of fetuses with Down syndrome, DeVore (2000) has emphasized the importance of searching for cardiovascular markers (right to left chamber disproportion, tricuspid regurgitation, mitral regurgitation, pericardial effusion, and outflow tract abnormalities). According to this investigator the likelihood ratio following a normal genetic sonogram without using the cardiovascular markers is 0.42 while it is 0.11 when the genetic sonogram includes a negative search for cardiovascular markers.

The reduction in background risk resulting from a normal genetic sonogram has made this method popular among women older than 35 years who want to avoid genetic amniocentesis (Vintzileos et al., 1997). In approximately 75% of these women, amniocentesis can be avoided because their risk of Down syndrome following a normal genetic sonogram is below the 1/270 threshold used to recommend this procedure.

A normal genetic ultrasound decreases the risk of Down syndrome given by an abnormal triple test screening. It has been calculated that when the genetic ultrasound is normal the risk given by the triple test needs to be 1:40 or greater in order for the overall risk to reach a level of 1:270 (Bahado-Sing et al., 1996). Since the positive predictive value of the triple test is low, a genetic ultrasound will help to estimate with more precision the possibility of aneuploidy. Ultrasound correction of the risk given by the triple test will decrease significantly the number of diagnostic amniocentesis and the loss of normal fetuses secondary to this procedure.

The ultrasound markers of fetal genetic disease with higher positive predictive value are the NFT, the NB, cardiac abnormalities, echogenic bowel and short digits. A brief review follows.

Nuchal fold thickness

NFT is the most important sonographic marker of aneuploidy in the second trimester (Figure 2-3). It should not be confused with NT that is a first trimester marker (Figure 2-1). While NT is measured from the external surface of the skull to the *internal* surface of the skin, NFT is measured from the *external* surface of the occipital bone to the external surface of the skin. The sensitivity (detection rate) and the false positive rate of isolated NFT have a wide variation in the literature from 21 to 75% and from 0.1 to 11.0%, respectively (Crane and Gray, 1991). The cutoff value most commonly used to determine if the NFT is abnormal is 5 mm (Nyberg and Souter, 2001). Table 2-5, from Locatelli et al. (2000), suggests that an upper limit of 4 mm is adequate threshold from 14.6 to 16.8 weeks (BPD, or biparietal diameter, 28–36 mm), 5 mm from 17.3 to 20.1 weeks (BPD

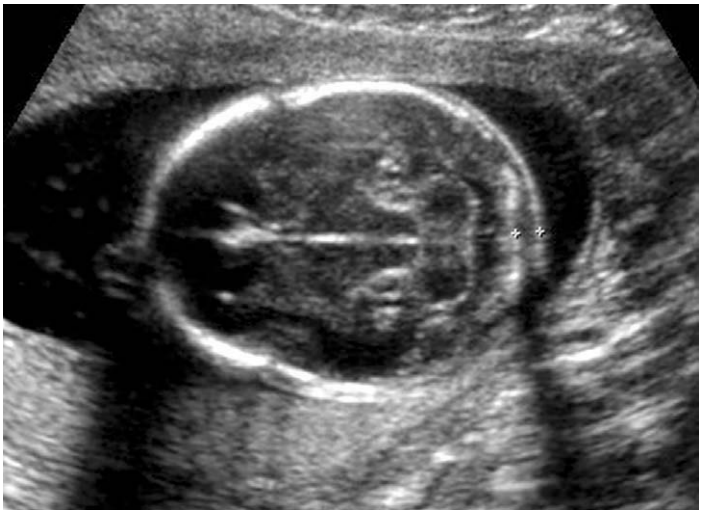

Figure 2-3. Nuchal fold thickness.

Table 2-5. Positive likelihood ratios for Down syndrome according to biparietal diameter and nuchal fold thickness

		Observed nuchal fold thickness			
BPD	GA	4–4.9 mm	5–5.9 mm	6–6.9 mm	>7 mm
28	14.6	2.75	17.78		
30	15.2	2.11	13.02		
32	15.7	1.64	9.57		
34	16.2	1.30	7.06		
36	16.8	1.05	5.23		
38	17.3		3.91	26.33	
40	17.9		2.95	19.23	
42	18.4		2.25	14.07	
44	19.0		1.74	10.33	
46	19.5		1.38	7.61	
48	20.1		1.11	5.64	
50	20.6			4.20	28.49
52	21.1			3.16	20.80
54	21.7			2.40	15.21
56	22.2			1.86	11.16
58	22.8			1.46	8.21
60	23.3			1.17	6.07

From Locatelli A, Piccoli MG, Vergani P, et al. Critical appraisal of the use of nuchal fold thickness measurements for the prediction of Down syndrome. Am J Obstet Gynecol 2000; 182: 192–7.

38–48 mm), and 6 mm from 20.6 to 23.3 weeks (BPD 50–60 mm). NFT is useful for screening between 14 and 23 weeks of gestation.

Nasal bone

Absence or hypoplasia of the NB (Figure 2-2) is a sensitive marker of aneuploidy in the second trimester of pregnancy (Odibo et al., 2006). The NB is considered to be hypoplastic if it is absent or measures less than 2.5 mm between 15 and 22 weeks of gestation (Cicero et al., 2003b). As it was mentioned before, there is a significant ethnic variation in the prevalence of hypoplastic bone in the normal population between Caucasians (0.5%) and Afro-Caribbeans (8.8%) and this impacts the sensitivity and false positive rate of this finding in the screening for Down syndrome.

Cardiac abnormalities

CHD is commonly associated with aneuploidy and specifically complicates 50% of the cases of Down syndrome. The detection of CHD by ultrasound was low until the development of color Doppler. With this technology the prenatal identification of CHD increased from 25 to 87% (DeVore and Alfi, 1995). The cardiac markers with highest positive likelihood ratio (DeVore, 2000) are the presence of right-to-left disproportion in the heart (LR 88.2), ventricular septal defect (LR 12.5), and pericardial effusion (LR 10.02).

Echogenic bowel

This marker is present in 0.6% of the normal population (Bromley et al., 1994) and therefore it is highly specific. In the majority of the cases, the presence of hyperechoic bowel is a normal finding but it may be associated with cystic fibrosis (CF), cytomegalovirus infection, intraamniotic bleeding, and severe placental insufficiency.

Short digits

Short fingers are one of the phenotypic characteristics of infants with Down syndrome. This is a feature that can be recognized in a good ultrasound examination between 16 and 22 weeks because frequently the hands of fetuses with Down syndrome are open. Hypoplasia of the middle phalanx of the fifth finger is one of the ultrasound markers of Down syndrome. However, the digit length quotient proposed by Hansmann (2004) is simple and easier to obtain. The quotient is calculated by measuring the length of digit three or two and dividing it by the transverse diameter of the hand measured between the external borders of the proximal end of the first phalanx of digits two and five. In normal fetuses the length of the fingers is always larger than the width of the hand. In Down syndrome fetuses the quotient is greater than 1, in the range 1.2–1.5.

Second trimester combined serologic screening and genetic ultrasound

Many pregnant women present for care after 14 weeks and require a screening method in the second trimester with similar sensitivity and false positive rate as that of

first trimester screening. One method consists in a combination of serologic screening and genetic ultrasound (DeVore and Romero, 2001). These investigators used mathematical modeling to compare women younger than 35 years with positive triple test screening who had amniocentesis with similar cases that had amniocentesis only when an abnormal sonographic finding was present and found that the second approach increased the detection rate of fetuses with T21 without increasing the loss rate of normal fetuses. The successful integration of genetic sonogram and second trimester serologic screening requires excellent diagnostic ability of the centers performing the comprehensive ultrasound examination of the fetus.

First Plus Second Trimester Aneuploidy Screening

The reasons for performing genetic screening in the first and the second trimester are varied. Some patients having first trimester screening ask for second trimester testing. Some of them want further reassurance when the first trimester screening is normal and others want further confirmation of abnormality before undergoing invasive diagnostic testing. Also, sometimes the results of the fist trimester screening are abnormal, but the risk is not extremely high (between 1:100 and 1:270) and it will be desirable to obtain further corroborative evidence before recommending amniocentesis. Several testing modalities have been proposed.

First trimester combined screening plus second trimester ultrasound examination

A large study of almost 15,000 patients studied the detection rate for Down syndrome of first trimester combined screening (NT plus free beta-hCG and PAPP-A) and routine 20–22 weeks' anomaly scan (Rozenberg et al., 2006). The detection rate and false positive rate of the first trimester combined scan were 79.6 and 2.7%, respectively, features that reached 89.7 and 4.2%, respectively, when combined with the second trimester ultrasound scan. A significant disadvantage of the method is that when the diagnosis of aneuploidy is made after 22 weeks of gestation the possibility of termination of pregnancy is limited.

Integrated test

The measurements of serum analytes in the first and second trimester and the NT obtained in the first trimester can be integrated in a single test to achieve a sensitivity of 85% with a false positive rate of 0.9%, using a cutoff of 1:120 (Wald et al., 1999). The integrated test achieves a rate of detection similar to that of the first trimester screening but the false positive rate is significantly lower, resulting in a significant reduction in the loss of unaffected fetuses. The main problem with this study is that the authors used information obtained from different groups of women rather than serum samples and ultrasound examination of the same population to calculate the accuracy of the test. Also, performance of the integrated test conveys the ethical difficulty of keeping the patient uninformed of abnormal test results in the first trimester screening.

Sequential test

Sequential testing has been studied in a large number of patients by Platt et al. (2004). These investigators demonstrated that sequential screening could detect 98% of pregnancies affected by T21. However, the false positive rate was 17%, a result that is not surprising since in sequential testing the false positive rate of both screens has to be combined. Sequential testing may be stepwise or contingent. In the sequential stepwise testing, a diagnostic test (CVS) is offered if the first trimester combined screening is positive. If the combined screening is negative, second trimester (quad test) will be offered. The final result will incorporate the results of the first and the second trimester tests. In the contingent sequential testing the results of the first trimester combined screening will be categorized into positive, negative, and intermediate. A diagnostic test will be offered for positive cases and no further testing for negative cases will be done. Patients in the intermediate group will be offered second trimester screening and the final result incorporates the results of the first and second trimester tests.

Screening Test Selection

With the availability of multiple screening methods the practitioner is faced with the decision of choosing the approach that will be more beneficial for the patients within the characteristics of his/her practice and the variation in gestational age when the patients present for prenatal care. The dominant consideration in this selection is to choose the test or tests offering greater sensitivity (detection rate) and the smallest rate of FPRs (Box 2-4). Other considerations are the availability of qualified personnel to measure NT and NB and to perform CVS as well as the gestational age when the patient enters the care system.

Figure 2-4 shows a contingent sequential approach to the problem of screening for aneuploidy for women presenting for prenatal care before 14 weeks of gestation. The first test is the combined (NT + free beta-hCG + PAPP-A) screening. The following steps will be contingent on the results of the combined screening. If the risk for aneuploidy is ≤ 1:1000, the only additional test will be an MSAFP or a comprehensive ultrasound examination

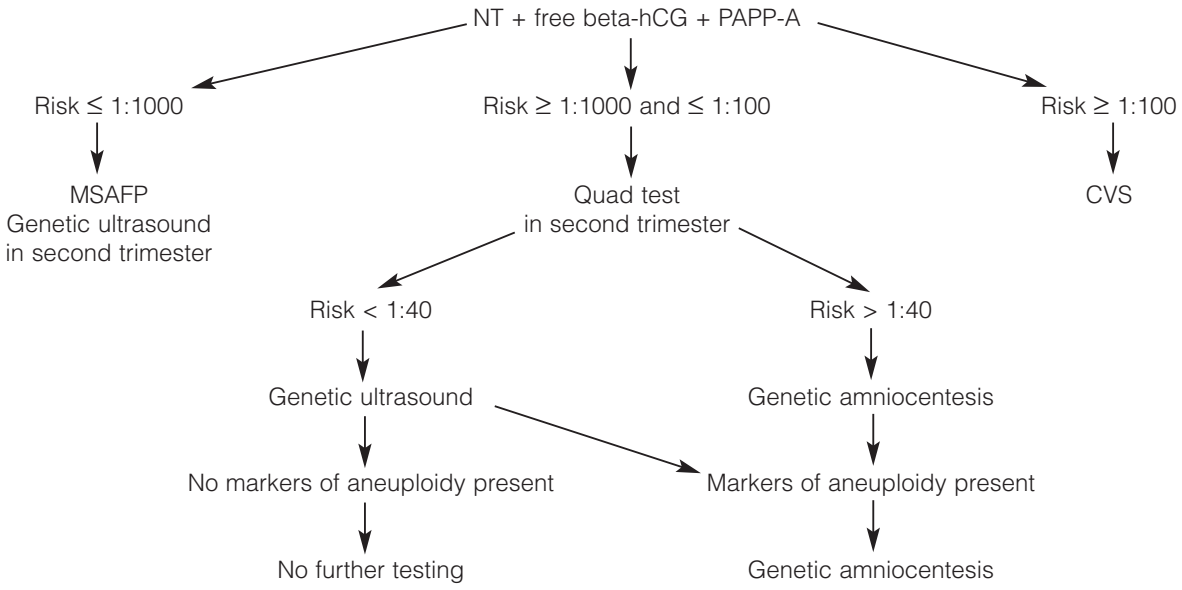

Figure 2-4. Sequential contingent first and second trimester screening for aneuploidy.

BOX 2-4

Detection rate and false positive rate of several tests for aneuploidy screening

Screening test	Detection rate (%)	False positive rate (%)
MA	50	14
MA + NT	77	4.7
Free beta-hCG + PAPP-A	63	5.0
MA + NT + free beta-hCG + PAPP-A	89.0	5
NB*	73.0	1
MA + NT + NB + free beta-hCG + PAPP-A	97.0	5
Triple test	63.0	5
Quad test	81	7
Genetic ultrasound	59	5
Integrated screening	85	0.9
Sequential screening	98	17

*In Caucasian population.
MA = maternal age; NT = nuchal translucency; PAPP-A = pregnancy-associated plasma protein A; NB = nasal bone.

between 16 and 20 weeks to rule out fetal congenital anatomic abnormalities, particularly open spine defects. If the risk for aneuploidy given by the combined test is ≥ 1:100, CVS will be recommended. If the risk is between 1:100 and 1:1000 the patient will have quad screening between 16 and 20 weeks. If the risk given by the quad screen is ≤ 1:40 the next step will be genetic amniocentesis. If the quad screening risk is < 1:40 the next step will be genetic ultrasound to look for markers of aneuploidy and to rule out congenital anatomic abnormalities.

Women presenting for prenatal care after 14 weeks of gestation or cases where the NT measurement could not be obtained will enter the scheme in Figure 2-3 at the level of the quad screening and if the risk is ≥ 1:40 the recommendation will be genetic amniocentesis. Any other result will be followed by a genetic ultrasound to search for markers of aneuploidy and to rule out congenital anatomic abnormalities of the fetus.

The sequential contingent screening shown in Figure 2-4 is based on the recent literature on this subject. The scheme incorporates thresholds for invasive diagnosis according to the results of the combined first trimester and the quad screening tests and the use of genetic ultrasound to rule out congenital anatomic abnormalities. This approach to genetic screening has not been endorsed by any authoritative body and the practitioner needs to decide if the conventional approach is better for his/her specific practice situation.

Once the background risk (maternal age-related risk) has been corrected by serologic testing and comprehensive ultrasound examination it is important to determine if the new risk is high enough to justify the performance of diagnostic procedures, i.e., CVS or amniocentesis. One fundamental point in deciding the cutoff to recommend invasive diagnosis is the procedure-related pregnancy loss following amniocentesis that was estimated to be approximately 1:200 in old studies. When age of 35 years was adopted as cutoff to recommend genetic amniocentesis it was assumed that the risk of having a miscarriage following the procedure was similar to the probability of carrying a fetus affected by aneuploidy and that women offered invasive diagnosis will give similar weight to the risk of having a baby with aneuploidy and the risk of losing a normal fetus because of the amniocentesis. This assumption has been proved to be incorrect, and the majority of

women do not weight equally these outcomes and a preference between these risks is different from one woman to the other.

GENETIC AMNIOCENTESIS

Genetic amniocentesis is an outpatient procedure usually performed at 16 weeks of gestation. Genetic amniocentesis is usually preceded by adequate counseling by a geneticist, a maternal–fetal medicine specialist, or by the obstetrician. Counseling includes, in addition to a discussion about the indications for the amniocentesis, a description of the procedure, its risks, and its complications. Genetic amniocentesis should also be preceded by determination of the maternal blood group and Rh factor. This is important in assessing the patient's eligibility for Rh immune globulin following the amniocentesis. The genetic amniocentesis should also be preceded by a comprehensive ultrasound examination to determine the number of fetuses, the gestational age, the placental localization, and to rule out the presence of congenital anatomic abnormalities and markers of aneuploidy.

It is important to know the placental location, and a search must be made for a place where the needle can be inserted without puncturing the placenta. If there is no area devoid of placenta, a thin placental area, away from the center of the organ and its large vessels, should be selected. Before an amniocentesis is performed, the area selected for inserting the needle should be examined with color Doppler to be certain that a large placental or uterine vessel is not present in that area. Once the comprehensive ultrasound examination is finished and an adequate puncture site has been selected, a sterile preparation of the maternal lower abdomen is performed. Local anesthesia is unnecessary. A 22-G needle should always be used since larger needles offer no advantages and are more painful and traumatic. Under continuous ultrasound visualization using sector or linear transducers placed inside a sterile plastic bag, the needle is inserted in two rapid, successive steps. The first step will carry the tip of the needle into the subcutaneous tissue. The second step will place the needle inside the amniotic cavity. The two steps are necessary because many patients involuntarily contract the muscles of the anterior abdominal wall when they feel the needle in contact with their skin, and this may cause the needle to deviate from its intended route. Thus, it is better to introduce the needle through the skin and the subcutaneous tissue first and after the patient relaxes the anterior abdominal wall, to insert the needle into the uterus. When a linear transducer is used for amniocentesis, only the tip of the needle is visualized. However, with the sector transducer the whole length of the needle can be seen. When the needle is inside the amniotic cavity, the stylet is removed and fluid should come out freely from the needle. Then a plastic connecting tube is placed between the hub of the needle and the 10-cc syringe used to aspirate the fluid. The connecting tube will avoid movements of the needle caused by the physician. The plastic connecting tube also allows the needle to move passively within the amniotic cavity, making extremely unlikely for the fetus to sustain a significant injury if the needle is hit by the fetus during episodes of fetal movements (Jeanty et al., 1983).

The fluid is aspirated with the sterile syringe and the first milliliter is discarded because of possible contamination with maternal cells. Two 10-ml aliquots of fluid are withdrawn, placed into two separate sterile plastic tubes, and transported to the laboratory for cytogenetic analysis and amniotic fluid AFP determination. After the fluid is removed, the needle is withdrawn and fetal heart motion is observed with real-time ultrasound.

When multiple sacs are present the amniocentesis involves separate puncture and analysis of the amniotic fluid of each sac. After drawing fluid from the first sac, 0.5–1.0 cc of indigo carmine and 0.1 cc of air are mixed into 5 cc of amniotic fluid and injected into the first sac. The bubbles contained in the fluid will delineate the first sac and will allow a better selection of the second needle insertion site. The withdrawal of clear fluid without dye will confirm insertion into the second sac. In some occasions it is possible to draw fluid from a first sac, advance the needle through the membrane separating the sacs, and draw amniotic fluid from the second sac without the need for a second needle insertion.

Genetic amniocentesis entails certain maternal and fetal risks as well as some potential technical problems. The main maternal risks associated with genetic amniocentesis are Rh isoimmunization in the Rh-negative mother and infection. To prevent Rh isoimmunization, the maternal Rh factor should always be known before the procedure and, if the patient is Rh negative, 150 mg of Rh immune globulin should be administered intramuscularly following the amniocentesis. The risk of maternal infection is very low, probably less than 1:1000.

One common concern of women considering genetic amniocentesis is the risk of losing the pregnancy as a consequence of the procedure. The risk changes with the gestational age, the preprocedure or concomitant use of ultrasound, the size of the needle and the number of needle insertions, the characteristics of the amniotic fluid, and the experience and ability of the individual performing the intervention. Another important risk that should be covered during the preprocedure counseling is amniotic fluid leakage, because a significant number of women experiencing leaking of amniotic fluid will end losing their pregnancies. Also, many women are concerned about the possibility of fetal trauma during the procedure.

The pregnancy loss rate after midtrimester amniocentesis is usually quoted to be 1 in 200 cases (5 per 1000). In

the Canadian trial of early and midtrimester amniocentesis the risk of pregnancy loss was 7.7 per 1000 women when the procedure was done at 15–16 weeks of gestation (Canadian Early and Mid-Trimester Amniocentesis Trial Group, 1998). In another study, 85% of the amniocenteses were performed between 13 and 14 weeks and the incidence of fluid leakage was 14 per 1000 cases and the pregnancy loss rate was 11 per 1000 (Saltvedt et al., 1999). The same study suggests that the risk of pregnancy loss when the amniocentesis is performed after 16–17 weeks approaches zero. Brumfield et al. (1996) compared amniocentesis at 11–14 weeks versus 16–19 weeks and found an incidence of pregnancy loss of 2 per 1000 cases in the later group. A recent review of 68,119 cases compared the pregnancy loss after amniocentesis in cases performed with concurrent ultrasound guidance and those where the ultrasound was used before but not during the procedure and found a significantly lower rate with the concurrent use of ultrasound, 1.4 versus 2.1% (Seeds, 2004). The same study compared the pregnancy loss following amniocentesis with the spontaneous loss without amniocentesis reported in five randomized clinical trials and found that with the procedure excess pregnancy loss was 0.6%. In a trial designed to compare first and second trimester screening for Down syndrome, 3096 cases had amniocentesis and 31,907 cases did not. The spontaneous pregnancy loss rate less than 24 weeks of gestation in the amniocentesis group was 1.0 and was 0.94% in the no amniocentesis group. Therefore, the pregnancy loss rate attributable to amniocentesis was 0.06% (Eddleman et al., 2006).

The risk of fetal loss is increased in women with brown and/or green amniotic fluid at the time of amniocentesis. This problem occurs in 1.6–6.7% of midtrimester amniocentesis. The discoloration of the fluid is due to the presence of blood breakdown products secondary to intra-amniotic bleeding. The majority of these patients had episodes of bleeding or spotting before the amniocentesis secondary to chorioamniotic separation. The fetal loss following amniocentesis in these patients varies from 5.0 to 9.0%. The risk of pregnancy loss seems to be greater if the needle used for the procedure is 18- or 20-G than that if it is 22-G. Multiple attempts also increase the probability of amniotic fluid leakage and pregnancy loss.

Amniotic fluid leakage is a significant complication because 12–40% of these cases end in pregnancy loss. In about half of the cases the leak is observed the same day of the procedure. In the majority of cases, if the patient remains in bed for 2 or 3 days, the fluid leakage will stop spontaneously and fluid reaccumulates. When the leakage does not stop after 3 days and there are no signs of infection, bleeding, or labor, it is possible to attempt sealing of the membranes using intra-amniotic infusion of platelets and cryoprecipitate (Quintero et al., 1999). Other investigators have used intra-amniotic injection of commercial fibrin tissue sealant (Sciscione et al., 2001). The main potential problem with these methods is the possibility of infection, and close monitoring is necessary.

Another risk associated with genetic amniocentesis is the possibility of fetal trauma with the needle. This rarely occurs. The most common fetal injury is a puncture of the fetal skin which happens in approximately 1 out of 1000 procedures.

The technical problems associated with genetic amniocentesis have to do with the extremely rare inaccuracy of the test and with the rare failure of the amniotic fluid cells to grow adequately in vitro. The test is extremely accurate, with an overall error rate of 0.4%. More than half of this error is caused by contamination of the cultures with maternal cells. The culture failure rate is about 3.2%. In these cases, a second genetic amniocenteses should be performed.

It is important to inform patients that the finding of a normal fetal karyotype and a normal amniotic fluid AFP level does not guarantee the birth of a normal newborn, since there are birth defects and mental retardation cases that cannot be detected through amniocentesis. The possibilities of this occurrence are, however, very low—most probably under 1%.

CHORIONIC VILLUS SAMPLING

CVS is a procedure for prenatal genetic diagnosis usually performed between 10 and 14 weeks. CVS avoids some of the problems associated with traditional amniocentesis at 16 weeks such as the advanced gestational age at which results are given to patient and the medical and emotional problems associated with late pregnancy termination. For these reasons, from its beginnings in the early 1980s, CVS has been performed more frequently, and it is used to diagnose more genetic conditions.

Chorionic villi for antenatal diagnosis can be obtained by transcervical catheter aspiration (transcervical CVS) or transabdominal needle aspiration (transabdominal CVS). Transvaginal aspiration (transvaginal CVS) is rarely done. The criterion to decide between transcervical or transabdominal CVS is the placenta localization. Fundal placentas and anterior, posterior, or lateral placentas located in the upper two-thirds of the uterus are better approached with transabdominal CVS. Anterior, posterior, or lateral placentas located in the lower one-third of the uterus can be sampled easily by transcervical CVS. Approximately 70–80% of all CVS are performed transabdominally.

Transcervical CVS

Similar to amniocentesis, CVS starts with a real-time ultrasound examination. The position of the uterus, the number of gestational sacs, the gestational age of the fetus, the presence of fetal heart activity, and the site of insertion of

the umbilical cord are determined. Two persons are required for the performance of CVS. One person does the sonography while the other performs the sampling. While the sonographer keeps the uterus visualized at all times, the operator inserts a sterile speculum in the patient's vagina and cleans the vagina and the cervix with an antiseptic solution. A sterile polyethylene catheter with a malleable metal obturator is inserted into the endocervical canal and advanced parallel to the chorion frondosum and toward the site of insertion of the umbilical cord. The position of the uterus and the angle between the cervix and the uterus can be modified by manipulating the speculum. The tip of the catheter should be away from the amnion, ideally in the center of the placenta. Occasionally a single-tooth tenaculum needs to be applied to the anterior lip of the cervix to help in the manipulation of the uterus. Once the tip of the catheter is in the desired position, the obturator of the catheter is removed, a syringe with a small amount of culture medium is connected to the catheter, and negative pressure is applied while the catheter is moved back and forth slowly three or four times. The sample of tissue obtained is analyzed immediately with the use of an inverted microscope. An adequate sample consists of 20 mg or more of placental tissue. Most patients report minimal or no discomfort during the procedure. Vaginal spotting occurs infrequently after CVS and usually disappears in 2–3 days.

The main risk associated with CVS is pregnancy loss following the procedure. A collaborative study in USA (Rhoads et al., 1989) and a randomized study in Canada (Canadian Collaborative CVS—Amniocentesis Clinical Trial Group, 1989) compared chorionic villus biopsy and amniocentesis at 16 weeks. They found a rate of fetal loss following transcervical CVS 0.8% and 0.6% greater than the rate after amniocentesis. It was also found that cramping, spotting, and bleeding following the procedure were more common after CVS. The conclusion was that CVS entails a slightly higher risk of fetal loss than does amniocentesis.

Another concern about transcervical CVS was the possibility of introducing bacteria into the uterus and causing chorioamnionitis. However, the incidence of infection has been lower than expected. Chorioamnionitis occurs in only 0.2–0.3% of patients undergoing CVS. Only two cases of life-threatening maternal infections following CVS have been reported.

Other potential risks of transcervical CVS are rupture of the membranes, which occurs in approximately 0.3% of patients, and severe vaginal bleeding, which occurs rarely. Rh-negative women may become immunized following CVS and should receive prophylactic Rh immune globulin. Also, it is possible that a large increase in Rh antibodies following CVS may have an unfavorable effect in women who have alloimmunization to the Rh factor, and CVS is not recommended in these cases. Immediately following CVS, 8.0% of the patients will experience light vaginal bleeding and by the end of the week following the procedure as many as 39% will have some spotting or bleeding. However, this is usually inconsequential.

The advantages and disadvantages of transcervical CVS are summarized in Box 2-5. The contraindications to transcervical CVS are summarized in Box 2-6.

BOX 2-5

Advantages and disadvantages of transcervical CVS

Advantages

1. Genetic diagnosis is achieved at an early gestational age, minimizing the anxiety of the parents and facilitating termination of pregnancy for patients who choose this option.
2. It is comfortable for the patient since no pain or discomfort is involved.
3. It is technically simple.

Disadvantages

1. It has a slightly higher risk of fetal loss (0.8%) than traditional amniocentesis.
2. The chromosome composition of the chorionic villus is occasionally (1.3% of the cases) different from the chromosome composition of the fetal cells.
3. The enzyme composition of the chorionic villus cells may be different from the fetal cells.
4. It is difficult if the placenta is above the lower one-third of the uterus.
5. There are contraindications to transcervical CVS.

BOX 2-6

Contraindications to transcervical CVS

- Positive *Neisseria gonorrhoeae* culture of the cervix
- Active genital herpes
- Active bleeding
- Maternal coagulopathy
- Cervical stenosis
- Severe cervicitis
- Uterine myomata
- IUD inside the pregnant uterus

Transabdominal CVS

Transabdominal CVS grew out of the need to obtain chorionic villi from patients who had contraindications to the performance of transcervical CVS, to reduce the potential risk of infection associated with the vaginal procedure and to facilitate the approach to placentas located in the upper two-thirds of the uterus. The transabdominal approach requires real-time ultrasound guidance and can be performed with one or two needles.

The single-needle technique is the method most commonly used. After preparation of the abdomen with antiseptic solution the insertion site is selected using ultrasound. Color Doppler is useful to find the placental insertion of the

umbilical cord that usually corresponds to the thickest part of the placenta. Ideally the area of the placenta selected for the biopsy will be such that the needle will be parallel to the long axis of the placenta. Local anesthesia is used on the skin and if possible on the area of the surface of the uterus where the needle is going to be inserted. Then an 18- or 19-G needle is inserted using a "free-hand" technique or a needle-guiding device which attaches to the ultrasound transducer. The needle is moved slowly back and forth several times in the chorion frondosum while negative pressure is applied with the syringe. The tissue obtained is placed in a Petri dish and examined with an inversion microscope. In most cases, one or two insertions of the second needle yield adequate amount of tissue. The tissue usually has little contamination with maternal decidua, blood, or mucus.

When two needles are used, an 18-G needle is inserted first into the chorion frondosum. The stylet of the needle is removed and a 20-G needle, 1.5 cm longer than the first one, is inserted through the first needle. The stylet of the second needle is removed and the needle is connected to a 20-cc syringe containing 2–5 ml of culture medium. Negative pressure is applied to the syringe, the needle is moved back and forth, and the tissue is removed. If the amount of tissue obtained is inadequate, the procedure can be easily repeated because the first needle remains in place.

The risk of fetal loss following transabdominal CVS is similar to or less than that of amniocentesis. The literature suggests that this risk may be minimized if transabdominal CVS is performed after 12 weeks (Saura et al., 1990). The advantages and disadvantages of transabdominal CVS are summarized in Box 2-7.

BOX 2-7

Advantages and disadvantages of transabdominal CVS

Advantages

1. There is minimal risk of infection.
2. It does not cause vaginal bleeding.
3. It can be performed in the second and third trimesters.

Disadvantages

1. The amount of tissue obtained is less than that with transcervical CVS.
2. Patient discomfort is greater than that with transcervical CVS or amniocentesis.
3. It is difficult to perform if the placenta is posterior.
4. It is technically more difficult than transcervical CVS.

Transvaginal CVS

There are some patients in whom transabdominal and transcervical CVS are difficult to perform due to extreme uterine retroversion, presence of myomas, or placental localization. In some of these patients, chorionic villi may be obtained using transvaginal aspiration under guidance with an endovaginal probe (Sidranski et al., 1990).

Laboratory Aspects of CVS

After chorionic villi are identified, they are washed, cleaned, and separated from any decidual tissue. The villi are now ready for direct cytogenetic analysis or for long-term tissue culture. Direct cytogenetic analysis of the chorionic villi is made possible by the presence of viable and actively dividing trophoblastic cells. The process of cell division is arrested by Colcemid and the cells in metaphase are analyzed after adequate staining. The original technique for direct analysis required approximately 4 hours between the time the tissue sample was obtained and the time of the result. This has been modified and most of the current techniques require 12–48 hours of incubation before the harvest of chromosomes. The morphology of the chromosomes obtained for direct analysis is slightly different from that of those obtained after prolonged tissue culture. However, chromosomes obtained from direct analysis are useful for detecting numeric abnormalities and major rearrangements.

The analysis of uncultured trophoblastic or amniotic cells is by means of polymerase chain reaction (PCR) using DNA extracted from those cells or most commonly by means of fluorescence in situ hybridization (FISH). These methods are much faster than the conventional cytogenetic analysis. The FISH technology is reliable for the detection of T21, T18, T13, and Turner's syndrome but it may miss as many as 15–30% of the abnormalities detected by the karyotype. For this reason replacement of the karyotype by PCR or FISH analysis of uncultured cells is not recommended (Caine et al., 2005)

A problem associated with CVS is the observation of chromosomal mosaicisms, complicating the interpretation of the test. Mosaicism is the presence of two or more different cell lines with different karyotypes. Mosaicism occurs in approximately 1.5% of CVS specimens. There are several mechanisms that may lead to mosaicism. One of these is contamination with maternal cells, which occurs more frequently in the cultured than in the direct preparations. Mosaicism also may result from in vitro influences on the growing cells, and in this case the problem will be apparent in the cell cultures and not in the direct preparations. Last, nondisjunction during embryogenesis with formation of aneuploid cells in the extraembryonic tissues but not in the fetus may cause mosaicism.

The majority of mosaics in CVS occur in the direct preparations and rarely are confirmed in the fetus. This suggests that the majority of CVS mosaics are limited to the extraembryonic tissues. Therefore, when a mosaic is present in the direct preparation it is necessary to wait for the culture results. If the mesenchymal cell culture is normal, the parents should be reassured that the fetal chromosomes

are also normal. If the cell culture also shows mosaicism, it is necessary to perform fetal blood sampling to confirm the diagnosis (Gosden et al., 1988). Fetal blood is necessary because even if the mosaicism is found in amniotic cells, it may not be confirmed in the fetus or in the neonate. The perinatal outcome of patients with placental mosaicism is guarded (Johnson et al., 1990).

PERCUTANEOUS UMBILICAL BLOOD SAMPLING

Percutaneous umbilical blood sampling or cordocentesis is a procedure to obtain fetal blood which was described in 1983 by Fernand Daffos and his collaborators (Daffos et al., 1983). Their initial report was followed 2 years later by a comprehensive description of the complications and risks associated with the procedure, based on their experience with more than 600 cases. Cordocentesis was originally designed to study the fetal transmission of toxoplasmosis, but it became evident that it could be used to investigate a wide range of fetal disorders. The most frequent indication for cordocentesis in USA is for the rapid karyotype of fetuses with anatomical deformities or other conditions associated with chromosomal abnormalities.

The main advantage of obtaining fetal blood instead of amniotic fluid for the diagnosis of chromosome abnormalities is that it is possible to obtain a high-quality karyotype in 48–72 hours (rapid karyotype) rather than in the 10–14 days that is needed for amniotic cell culture. Percutaneous umbilical blood sampling is useful for karyotype in patients who have fetal abnormalities detected by ultrasound, for cases of fetal growth retardation or polyhydramnios, and for the diagnosis of other genetic defects such as hereditary deficiencies of the hemostatic system, hemoglobinopathies, and metabolic disorders.

Cordocentesis is a procedure similar to amniocentesis. It is performed as an outpatient procedure and does not require local or regional anesthesia. It can be done easily after 24 weeks of gestation, and in the hands of skilled operators as early as 18 weeks of gestation. The procedure begins with an ultrasound examination to find the placental insertion of the umbilical cord that is the best place to obtain the blood sample. Color Doppler is invaluable for the correct localization of the cord origin. Once the placental insertion of the cord is found, a 22- or 20-G spinal needle of adequate length is inserted and advanced to the umbilical vein. Free-hand technique or a needle guide attached to the sector transducer may be used. The vessel is penetrated and after injecting 3–5 ml of normal saline to verify by ultrasound the correct intravascular placement of the needle, the necessary volume of blood for a rapid karyotype, usually 3 ml, is removed. Another small sample is sent to the laboratory for determination of the mean corpuscular volume (MCV) of the erythrocytes, which is always higher in fetal than in maternal blood.

The studies reported so far in the literature, involving more than 1400 cases, indicate that cordocentesis has a procedure-related fetal mortality rate of approximately 1%, but other investigators report up to 5% frequency of procedure-related deaths (Pielet et al., 1988). The complications most frequently observed with cordocentesis are bleeding from the puncture site, which occurs in approximately 30% of patients, and fetal bradycardia, which occurs in about 5%. Both are usually transient but occasionally they may be severe and require emergency cesarean delivery.

MOLECULAR GENETIC TESTING

In the last few years, a series of techniques used primarily in molecular biology research have been successfully applied to the solution of clinical problems in obstetrics and gynecology. The technological advances have led to a constantly increasing number of genetic conditions that can be diagnosed prenatally and to improvements in the accuracy of the diagnosis of many others. The impact of molecular genetics on prenatal diagnosis has been spectacular and with the completion of the human genome project, there is a realistic promise of further advances that may lead to the treatment and correction of genetic diseases.

For the obstetrician gynecologist the most important impact of molecular genetics is the availability of direct mutation, testing for several conditions. Direct testing is possible when the mutation causing a specific disorder is identified and can be detected using techniques that include among many others specific hybridization with radiolabeled DNA probes, PCR, restriction fragment length polymorphism (RFLP) analysis, and linkage analysis.

One popular method for detecting mutations is the Southern blot analysis. The DNA being investigated is extracted from the nucleus of the cells and digested with restriction endonucleases which are bacterial enzymes that recognize specific restriction sites in the double-stranded DNA chain of the gene and cleave the DNA molecule at that particular site. The restriction sites are made up of short nucleotide sequences. More than 100 different restriction endonucleases, each one recognizing specific base-pair sequences, have been discovered. These enzymes split the chromosomal DNA into similar fragments each time the DNA is incubated with the same restriction enzyme, and these fragments are separated according to their molecular size using gel electrophoresis and then converted from double- into single-stranded pieces by alkali treatment. The single-stranded DNA pieces are transferred to a nitrocellulose membrane and specific segments can be detected by hybridization with complementary radiolabeled DNA probes.

DNA microarrays is a method for prenatal diagnosis that extends the diagnostic scope of conventional karyotype. In this method, small pieces of DNA, associated or not with certain genetic disorders, are attached to a glass slide after being labeled with a fluorescent color. DNA from the fetus, labeled with a different fluorescent color is mixed and allowed to hybridize with the DNA of the array. A Laser scanner reads the slide and determines the relative strength of the two different colors on each piece of DNA attached to the array to determine if there is a duplication or deletion of genetic material. Unfortunately, microarray technology cannot identify inversions, balanced translocations, triploids, mosaicisms, and point mutations. Despite these limitations DNA microarray is a promising technique that is expanding rapidly the field of prenatal diagnosis. The prenatal diagnosis of more and more conditions is available every day, and to keep up with current developments the obstetrician should use online sources of information such as www.genetest.org.

Mutations may destroy or create a new restriction site and become available for diagnosis by RFLP analysis. If the genetic mutation results in the creation of a new restriction site, a normal individual will show a normal uncut fragment when the DNA is incubated with the corresponding endonuclease. A homozygous individual will show two cut DNA fragments and a heterozygous person will show one normal uncut fragment and two cut fragments. This method is used for the diagnosis of sickle cell disease because the single base pair substitution causing the disease results in the loss of a restriction site.

A molecular genetic technology frequently used for the diagnosis of known mutations is the PCR. This is a biochemical process that permits the exponential amplification of a given DNA segment. This selective amplification has been automatized and it is theoretically possible to obtain the necessary amounts of DNA for complex biochemical studies starting from the DNA of a single cell. The first step in PCR consists of denaturation of the DNA to make it single stranded. Then oligonucleotide primers complementary to the beginning and the end of the DNA segment to be amplified are hybridized with their complementary regions in the single-stranded DNA. Finally, copies of the DNA segment located between the PCR primers are obtained using the enzyme Taq polymerase and abundant amounts of nucleotide triphosphates. This reaction cycle is repeated many times to produce millions of copies of the targeted DNA segment.

Linkage analysis is another molecular technique frequently used for the diagnosis of mutations. Linkage analysis makes use of polymorphic markers that are DNA variations, usually a single nucleotide change without phenotypic expression, that are transmitted from parent to child as any other genetic marker. If a polymorphic marker is closely linked to an abnormal gene, both the polymorphic marker and the abnormal gene will be coinherited and the abnormal locus can be identified indirectly by recognizing the closely linked polymorphism. The use of polymorphisms for the diagnosis of genetic diseases depends on the recognition of particular patterns in a given family. Therefore, it requires the availability of DNA from an affected individual in the family under study. Once the polymorphic fragment containing the affected locus is characterized, other members of the family can be studied for carrier status and prenatal diagnosis becomes feasible for any pregnant member of the family.

SCREENING FOR HEMATOLOGIC DISORDERS

The American College of Obstetricians and Gynecology recommends screening for hemoglobinopathies for individuals of African-American, Southeast Asians, and Mediterranean ancestry. The usual screening is for sickle cell disease and the thalassemias.

Sickle Cell Disease

Sickle cell disease is an autosomal recessive disorder resulting in the synthesis of an abnormal hemoglobin. The difference between normal beta-globin and sickle cell globin is the substitution of glutamine for valine in the sixth amino acid position of the protein. This, in turn, is the result of a single nucleotide change in the DNA coding for the protein. The nucleotide sequence GAG, which codes for glutamine, suffers a mutation to GTG, which is the code for valine. Sickle cell disease may also occur in patients who have hemoglobin S in one beta-globin chain plus hemoglobin C or beta-thalassemia in the other globin chain. Ten percent of the Black population in USA is heterozygous for the hemoglobin S gene. If two heterozygous persons conceive, the probability for that child to have sickle cell disease is 25%. The interested reader will find more information about sickle cell disease in the chapter of this book about hematologic abnormalities in pregnancy.

The screening test for sickle cell disease is hemoglobin electrophoresis, a test that should be part of the initial evaluation of African-American pregnant women. This test should be used instead of the rapid test or solubility test because hemoglobin electrophoresis may reveal abnormalities not detected with the solubility test such as beta-thalassemia trait or hemoglobin B, C, D, and E traits. A mother with one of these conditions and a partner with sickle cell trait can have offspring with hemoglobin SC or with beta-thalassemia/hemoglobin S disease. If the hemoglobin electrophoresis reveals any of these abnormalities in the mother and the partner is African-American, he should have similar testing in order to assess the potential risk for the fetus.

Today, precise antenatal diagnosis of fetal sickle cell disease can be made by applying molecular genetic technology to fetal DNA obtained through chorionic villus biopsy or amniocentesis.

Alpha- and Beta-Thalassemia

Women of Southeast Asian descent are at increased risk for alpha-thalassemia and individuals of Mediterranean ancestry are at high risk for beta-thalassemia. The screening test to identify carriers of these abnormal genes is the mean red cell corpuscular volume, or MCV, that is usually reported in automated laboratory blood cell counts. An MCV < 80 μ^3 indicates microcytosis, a finding that when associated with a decrease in mean corpuscular hemoglobin concentration usually indicates the presence of a microcytic hypochromic iron deficiency anemia. However, if a low MCV is found in a mother of Mediterranean origin, the next step is to obtain a hemoglobin electrophoresis. If the concentration of hemoglobin A2 is greater than 3.5% the patient is a carrier of the beta-thalassemia gene and the partner should have similar testing to assess the probability of fetal disease. If both parents are heterozygous for the beta-thalassemia gene the probability that the fetus will be homozygous is 25% and the chances of being a carrier will be 50%.

When microcytosis is present in individuals of Southeast Asian origin in the absence of iron deficiency anemia and the hemoglobin electrophoresis is normal, the possibility of being a carrier of alpha-thalassemia should be considered. The diagnosis requires DNA testing (PCR) and if it is positive, evaluation of the partner is necessary for adequate counseling about the probability of fetal disease. If both parents are heterozygous for the alpha-thalassemia gene the probability that the fetus will be homozygous is 25% and the probability of being a carrier will be 50%.

SCREENING FOR METABOLIC DISORDERS

Inborn errors of metabolism are infrequent. However, there are a constantly increasing number of hereditary metabolic defects that can be diagnosed antenatally by amniocentesis, CVS, fetal biopsy, or fetal blood sampling. Prenatal diagnosis is useful because in some occasions the fetal condition may be altered by changes in the maternal diet and also because it makes possible to initiate adequate treatment of the newborn shortly after birth. The present recommendation of the American College of Obstetricians and Gynecologists is to screen individuals of Ashkenazy Jewish ancestry for Tay-Sachs and Canavan disease.

Tay-Sachs Disease

Tay-Sachs disease is an inborn error of metabolism characterized by the accumulation, primarily in the neurons, of a glycolipid identified as GM2-ganglioside. This substance accumulates due to a deficiency in the synthesis of the alpha subunit of the isoenzyme hexosaminidase A (Hexa-A). The disease causes a progressive deterioration of neurologic function until the child dies, usually between 3 and 4 years of age.

Tay-Sachs disease is a lysosomal storage disease occurring predominantly in Jews of Ashkenazi ancestry (Central and Eastern Europe). It is transmitted in autosomal recessive fashion. One of every 30 Ashkenazi Jews is a carrier for the abnormal gene, and well over 90% of all American Jews are of Ashkenazi origin. The heterozygous state can be recognized by measuring Hexa-A activity in a serum sample, and this makes possible to screen the population at risk. The fetal homozygous state can be recognized by amniocentesis, culture of fetal fibroblasts, and analysis of their production of Hexa-A. Fetal DNA analysis can identify any of the three specific mutations causing 90% of Tay-Sachs disease in Ashkenazi Jews: exon 11 4bp insertion mutation, intron 12 splice-junction mutation and exon 7 mutation (Triggs-Raine et al., 1990).

Ideally, all Jews of Ashkenazi ancestry, French-Canadians, and Cajun descendants should have preconceptional counseling. If this has not been done and the patient is already pregnant, the male partner should be screened. If the male has normal serum Hexa-A activity (more than 60% of total activity), there is no risk to the fetus. If the male is a carrier (less than 55% of total Hexa-A activity), it is necessary to determine the mother's status by measuring the enzyme activity in her leukocytes because serum screening is unreliable during pregnancy. If the mother is negative, there is no risk to the fetus. If she is positive, amniocentesis should be carried out to measure Hexa-A activity or to obtain fetal DNA to be analyzed for the presence of specific mutations.

Canavan Disease

Canavan disease is a severe progressive neurological condition caused by a deficiency of the enzyme aspartoacylase that leads to the accumulation of N-acetylaspartic acid (NAA) that in turn causes demyelination and spongy degeneration of the brain tissue. The disease is transmitted in an autosomal recessive fashion and affects mainly Ashkenazi Jews. The carrier frequency in this population is 1 in 40. Two mutations in codons 231 and 285 of the aspartoacylase gene account for 97% of the cases of Canavan disease and a third mutation in codon 305 accounts for 36% of the cases in non-Jewish individuals.

Carrier screening for Canavan disease requires DNA analysis (PCR) for the three most common mutations and should be offered to couples of Ashkenazi Jewish background simultaneously with the screening for Tay-Sachs disease. If both parents are carriers, prenatal diagnosis

can be performed by measuring the concentration of NAA in the amniotic fluid or by specific DNA analysis for the three most common mutations.

SCREENING FOR NTDS

NTDs is a generic name designating malformations resulting from the failure of the neural tube to close in the first four 4 weeks after conception. Anencephaly and spina bifida are the most common NTDs. They are among the most common major malformations of the central nervous system, and their incidence changes with geographic location. The incidence of NTDs in USA has decreased from 3.1 per 1000 births in the 1970s to 0.4 per 1000 births in 1997. In Wales and Ireland the prevalence of anencephaly and spina bifida was as high as 7 per 1000 births in 1965 but has decreased dramatically in the last 35 years to 0.2–0.4 per 1000. The decreased birth prevalence of NTDs is most probably the result of several factors including the widespread adoption of folic acid supplementation to the diet and the inclusion of serologic and ultrasound screening for NTDs as integral part of prenatal care. NTDs are a recurrent condition. In USA the recurrence risk is 1.5–3% when one prior child has been affected and 4–6% when two prior children have been affected.

In the majority of cases, NTDs are the product of the interaction of environmental factors such as the amount of folic acid in the diet with genetic predisposition involving genes coding for enzymes regulating folic acid, cobalamin, and homocysteine metabolism. The importance of folic acid deficiency as an etiologic factor or key mediator in the mechanism of disease has been demonstrated by studies indicating that adequate amounts of folic acid in the diet can prevent between 70 and 85% of all cases of NTDs. Folic acid is a cofactor required for methylation reactions and its deficiency may affect the methylation of DNA at a critical point during embryologic development. With respect to genetic predisposition, it has been found that a deficiency in the enzymatic activity of MTHFR, usually due to a C677T mutation, is associated with NTDs. Deficient MTHFR activity causes a blockade in the transformation of homocysteine into methionine, resulting in the accumulation of homocysteine. High levels of homocysteine are associated with fetal NTDs. Also, there are observations suggesting that abnormal cobalamin metabolism and deficient methionine synthase activity may be additional factors responsible for the hyperhomocysteinemia associated with NTDs. Another environmental factor linked to NTDs is maternal hyperthermia and women using a hot tub or sauna during the first 8 weeks of gestation have a 2.9 relative risk of having a child with NTDs (Milunski et al., 1992).

Serologic screening for NTDs is performed by measuring MSAFP between 15 and 20 weeks of gestation. In most cases MSAFP is measured during second trimester screening with the triple or quad tests. In cases of open spine defects, the concentration of beta-hCG, estriol, and inhA are normal. In cases of anencephaly the concentration of estriol is low, usually around 0.2 MoM. The concentration of MSAFP is corrected for maternal weight (obese mothers have lower MSAFP levels than do patients with normal weight), diabetes (diabetic mothers have lower MSAFP levels than nondiabetics), and race (Black women have higher MSAFP levels than Caucasians). After corrections, the MSAFP concentration is compared with values obtained from a normal population for each day of gestation between 15 and 20 weeks and expressed as MoM. Values above 2.5 MoMs or below 0.5 MoMs are considered abnormal. Approximately 3.9% of pregnant women will have elevated MSAFP and 3.4% will have decreased MSAFP (Milunski et al., 1989b) and each of these situations need separate discussion.

Elevated MSAFP

MSAFP levels above 2.5 MoMs have a detection rate of 90.9% for open spina bifida and 100% for anencephaly with a false positive rate of 2–5%. The negative predictive value of a normal MSAFP is 99.9% for open spine and 100% for anencephaly. The positive predictive value of an abnormally elevated MSAFP is 1.9% for spina bifida and 1.7% for anencephaly (Milunski et al., 1989b). Elevated MSAFP may occur in the absence of an NTD in situations such as error in the estimation of gestational age, multifetal pregnancies, and fetal demise.

A common problem is an elevated MSAFP resulting from an error in the clinical estimation of the gestational age. For this reason it is recommended that a dating ultrasound examination should be always obtained before the performance of the triple or quad tests. MSAFP concentration increases with gestational age and an apparently high value may become normal when corrected because the gestational age was underestimated (Figure 2-5). Recognition of a dating error and reassignment to a more advanced gestational age will make further testing unnecessary in about 20–25% of all patients with elevated MSAFP levels. Also, approximately 15% of patients with elevated MSAFP levels have undiagnosed multifetal pregnancies. A third cause of an elevated MSAFP level is undiagnosed fetal demise that may be present in as many 5% of the patients with elevated MSAFP levels. In 2–3% of the cases, elevated MSAFP levels occur in fetuses with omphaloceles. Less frequently, elevated MSAFP may be secondary to B19 parvovirus infection. Other causes of elevated MSAFP include fetomaternal bleeding, congenital nephrosis, and major structural fetal defects.

The possibility of an NTD is directly related to the concentration of MSAFP. When the MSAFP is between 2.5

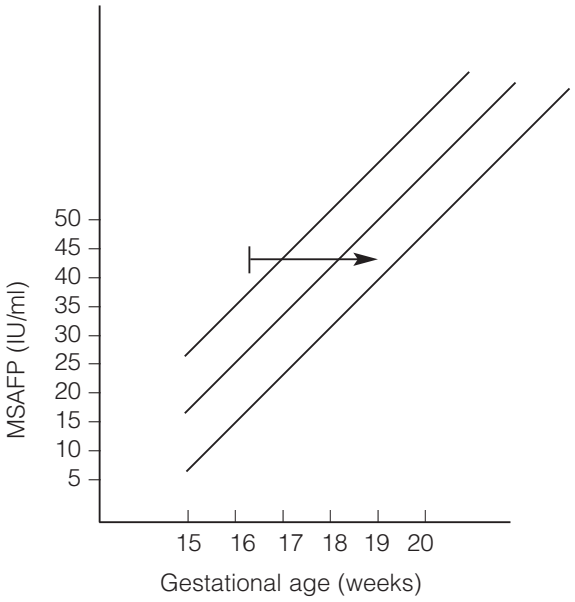

Figure 2-5. Effect of incorrect estimation of gestational age in the evaluation of MSAFP. Elevated MSAFP value becomes normal when underestimated gestational age is corrected.

and 2.9, MoM the risk of NTD is 1.4%. This risk increases to 3.3% when the MSAFP is between 3.0 and 3.9 MoM, to 4.9% if MSAFP is between 4.0 and 4.9 MoM, to 10.9% if the MSAFP is between 5.0 and 7.0 MoM, and to 13.4% if the MSFAFP is greater than 7.0 MoM. The possibility of causes different to NTD explaining elevated MSAFP values also increases with the concentration of MSAFP: abdominal wall defects are present in < 1, 1.6, 5.4, and 17.3% at MoM concentrations of 3.0–3.9, 4.0–4.9, 5.0–7.0, and > 7.0 MoM, respectively (Reichler et al., 1994).

Advances in ultrasound technology have raised the detection rate of NTD to figures similar to those obtained by amniotic fluid analysis for AFP and acetylcholinesterase and have made ultrasound the preferred follow-up for women with elevated MSAFP in the second trimester screening. However, it is important to emphasize that the ultrasound examination in cases of elevated MSAFP should be performed in units that specialize in fetal diagnosis. The detection of small defects and of lesions in the sacral area is difficult. Visualization of the spine may be suboptimal in obese women and in this or any other situation where the sonographer is not 100% confident in the accuracy and quality of the examination, the woman should be offered amniocentesis.

A complete examination of the fetal spine with ultrasound requires identification of three ossification centers in the coronal and transverse planes for each vertebra. In cases of spina bifida, a characteristic widening of these ossification centers will be seen. Also, there are findings in the cranial ultrasound that are strongly suggestive of the possibility of an open spine defect which results from the herniation of the cerebellum and brain stem through the foramen magnum (Arnold–Chiari malformation). These findings are obliteration of the cisterna magna and the banana sign that correspond to a marked posterior convexity shape of the cerebellum, and the lemon sign that corresponds to the shape of the frontal skull secondary to the changes in the posterior fossa.

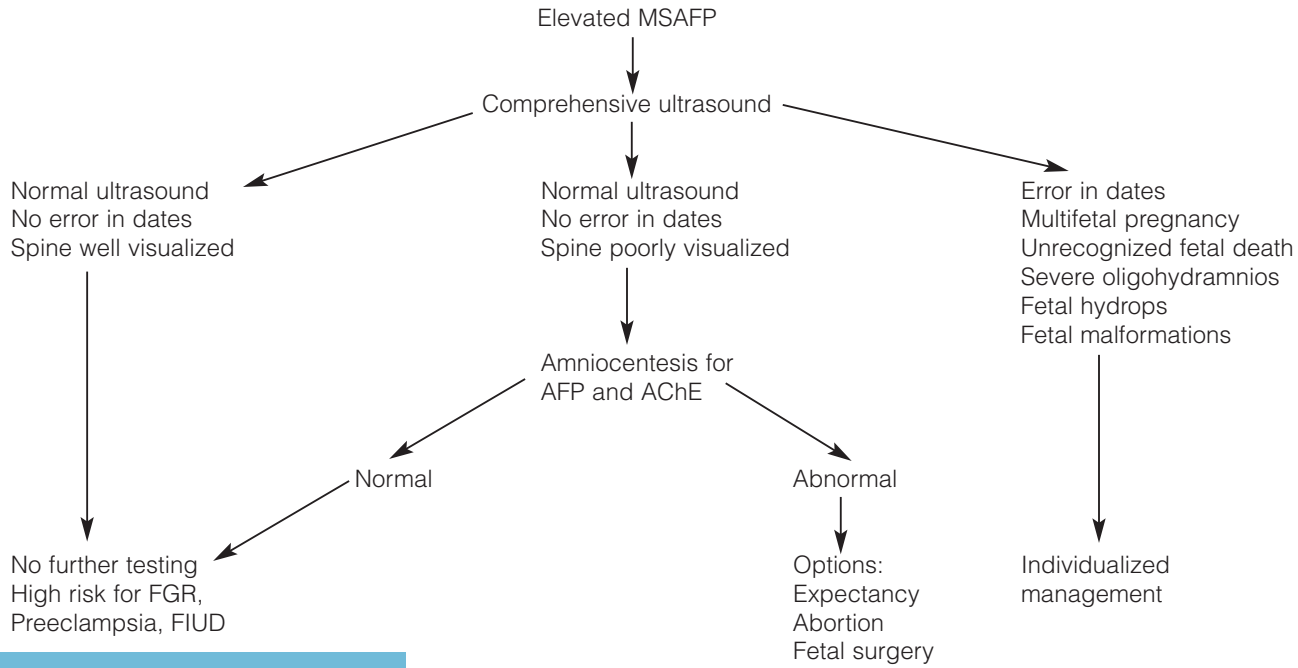

Figure 2-6. Management of elevated MSAFP.

Amniocentesis is the procedure of choice following the ultrasonic discovery of an open NTD and when it is not possible to adequately visualize the spine by ultrasound in women with elevated MSAFP. The objective of the amniocentesis when an open NTD has been recognized is to rule out the presence of a chromosome abnormality. Chromosome analysis is of value since a significant proportion of fetuses with NTDs also have chromosomal abnormalities. Also, knowledge of the existence of a normal or abnormal karyotype may be very important for parents considering termination of pregnancy. A chromosome analysis of the amniocytes is also necessary in women with elevated serum MSAFP level and inconclusive ultrasound examination. The objective of amniocentesis in these cases is to determine the concentration of AFP and acetyl cholinesterase in the amniotic fluid. Amniotic fluid AFP determination is a diagnostic test, in contrast to MSAFP determination, which is a screening test. If the amniotic fluid AFP concentration is normal for the gestational age of the fetus, an open NTD is highly unlikely, and there is no need for further testing. The patient must be informed, however, that unexplained elevations in MSAFP levels are associated with an increased risk of spontaneous abortion, stillbirth, prematurity, fetal growth retardation, and neonatal death (Milunski, 1989) and that the risk of complications is directly related to the magnitude of the MSAFP elevation (Nelson et al., 1987).

The recommended sequence of steps to follow for patients with elevated MSAFP is shown in Figure 2-6.

Decreased MSAFP

The discovery of an association between low MSAFP and autosomal trisomies was the initial event leading to the development of multiple serum analytes, making possible to extend the screening for chromosome defects to the overall obstetrical population. Before MSAFP screening, the only known association of autosomal trisomies was with maternal age and all women 35 years of age or older at the time of delivery were advised to undergo genetic amniocentesis. With the development of serologic screening, the search for autosomal trisomies has been extended to the overall obstetrical population and at the present time the potential exists to discover prenatally 90% or more of all autosomal trisomies. An MSAFP test may be falsely low if there is an error in the determination of the gestational age (Figure 2-5).

Prevention of NTDs

The value of folic acid supplementation in the prevention of NTD has been clearly established. Milunski et al. (1989a) looked retrospectively to the pregnancy outcome of 22,776 pregnancies and found a prevalence of NTD of 3.5 per 1000 among women who did not use multivitamins after conception and 0.9 per 1000 for women who used folic acid containing vitamins during the first 6 postconceptional weeks. A prospective, randomized double blind study by the United Kingdom Medical Research Council demonstrated a 72% protective effect of 4 mg of folic acid taken about the time of conception in the prevention of recurrence of NTDs (Medical Research Council Vitamin Study, 1991). Another prospective, randomized study using 0.4–0.8 mg of folic acid for 1 month before and 3 months after conception demonstrated clearly the protective effect of this vitamin in the prevention of NTDs (Czeizel and Duds, 1992).

Due to the evidence of effectiveness, the Center for Disease Control of USA recommended in 1992 that all women of childbearing age take 0.4 mg of folic acid daily and in 1996 the US Food and Drug administration recommended the fortification of grain products with 140 µg of folic acid for each 100 g of grain product. Several countries have followed the US lead, and are fortifying their grain products with folic acid. The effect of these efforts to increase the ingestion of folic acid is at least partially responsible for the dramatic decrease in the incidence of NTDs in several western countries.

The present recommendation of the US Public Health Service and the American College of Obstetricians and Gynecologists is that all women of reproductive age consume 400 µg of folic acid daily to reduce the risk of having a fetus with NTDs. Some experts recommend 800 µg or more for women trying to conceive. Women with a previous child with NTD, women who have taken anticonvulsants, and women with homozygous MTHFR deficiency should take 4 mg of folic acid per day before and after conception.

SCREENING FOR CYSTIC FIBROSIS

CF is characterized by pancreatic insufficiency, pulmonary abnormalities, and elevated sweat electrolyte levels. The fundamental biochemical defect is an alteration in the regulation of chloride transport. CF is a relatively common disorder among Caucasians, affecting approximately 1 out of 2000 newborns. An estimated 1 out of every 20 Caucasians is a carrier for the abnormal gene. The disease is transmitted as an autosomal recessive trait. The risk for Caucasian individuals of having a child with CF is shown in Table 2-6 (Bowman and Mangos, 1976). The disease is rare in Oriental and Blacks. Although the morbidity of patients with CF has improved significantly, more than 50% of these patients die before they reach 20 years of age. Individuals who have been exposed to the emotional trauma of seeing a family member suffering and dying of this disease frequently look for genetic counseling and antepartum screening.

The application of molecular genetic technology to the diagnosis of CF has been extremely productive.

Table 2-6. Risk of having a child with cystic fibrosis

One parent	Other parent	Risk of CF in each pregnancy
No CF history	No CF history	1:1600
No CF history	First degree relative with CF	1:240
No CF history	Sib with CF	1:120
No CF history	Has CF	1:40
Sib with CF	Sib with CF	1:9

From Bowman BH, Mangos JA. Current concepts in genetics. Cystic Fibrosis. N Engl J Med 1976; 294: 937–43.

Table 2-7. Risk of cystic fibrosis after several screening situations

Situation	European Caucasian
No screening	1/3300
Both partners negative	1/78,400
One partner negative, other untested	1/16,240
One partner positive, other negative	1/560
One partner positive, other untested	1/116
Both partners positive	1/4

Researchers found that the CF gene is located in the middle part of the long arm of chromosome 7 and extended over approximately 250-kb DNA. The protein coded by the CF gene contains 1480 amino acids, is named cystic fibrosis transmembrane regulator protein (CFTR) and acts as a chloride ion channel. Approximately 1000 mutations capable of producing CF have been identified. The most common mutation found in USA, affecting 70–75% of Caucasian carriers, has been named delta F508. This mutation corresponds to the loss of a trinucleotide codon (CTT) and results in the loss of a phenylalanine originally situated in position 508 in the CFTR protein. The amino acid substitution results in an abnormal CFTR protein which cannot transport chloride ions inside the cell, and the consequence is a predominance of intracellular absorption of sodium over chloride. Water follows sodium inside the cell, causing dehydration of the luminal surface of the respiratory cells.

The relative frequency of the mutations causing CF varies with the population being studied. In Hispanics the mutation delta F508 is found in only 50–55% of the cases. In Ashkenazi Jews the delta F508 mutation is present in only 30% of the CF cases. The most common mutation in Ashkenazi Jews is W1282X that consists of the substitution of a tryptophan by a stop codon at position 1282. The variation in the mutations causing CF means that a high number of carriers will be missed if the population is tested only for the delta F508. In 1997 an NIH consensus conference recommended screening of the population and subsequently a task force recommended a screening panel of 25 mutations. Two of those mutations were dropped in 2004, leaving the present screening recommendation at 23 mutations that include all those occurring as frequently as 1 per 1000 (0.1%) in the general population. Several laboratories offer panels that screen for more than the 23 recommended mutations as well as ethnic specific panels. The detection rates with these panels are only marginally better than with the 23 mutations' panel in individuals with a negative family history but definitely better when there is a positive family history. It is interesting that the recommendation of the NIH consensus conference was to *offer* screening to Caucasians of Ashkenazi Jewish or European descent and to be *made available* to other ethnic groups, but the distinction between offer and made available was not defined.

Since the panel of 23 mutations used for CF screening does not cover all the mutations capable of producing CF, a negative screening does not exclude the possibility of CF. Also, the possibility of CF will change if one of the partners is untested or if one or both test positive. Table 2-7 describes the risk of CF in various screening situations.

There are no specific recommendations about the advantages of screening one or both parents simultaneously. One approach is to test the mother first and only if the result is positive to test the husband. Testing both parents at the same time increases the carrier detection rate but, as shown in Table 2-7, the risk of an affected fetus when one partner is negative and the other untested is very low (1 in 16,240). When CF screening is negative for both parents or when one of the parents has a mutation but the other parent is negative, no further evaluation is necessary. However, the couple should know that a negative screening does not mean a 100% certainty that the condition will not be present. Chorionic villi analysis or amniocentesis are recommended to determine if the mutation is present in the fetus when one parent is positive and the other is not tested (risk 1 in 116), when both parents are carriers, and when a mother had a child with CF.

Determination of microvillar enzyme activity in the amniotic fluid is an indirect method for the prenatal diagnosis of CF that may be useful in situations where DNA analysis is not possible. The enzymes most commonly used for this assay are gamma-glutamyl transpeptidase, aminopeptidase-M, and alkaline phosphatase. In fetuses affected with CF, the activity of these enzymes is decreased. This method is approximately 90% reliable with a false positive rate of 1–4% and a false negative rate of 6–8% (Szabo et al., 1990).

INDIAN EXPERIENCE OF CHROMOSOMAL ABNORMALITIES

Practice of genetic evaluation by the obstetrician is a step further in preventive obstetrics. This not only improves the quality of life of the parents, but also helps to reduce the cost of emotional, social, and financial burden to the society. In future, the obstetrician will be called upon to play a crucial role in shaping the quality of life (Walvekar, 2006). The methods of fetal tissue sampling and prenatal diagnosis have been well established in dedicated centers for genetic studies in metropolitan towns in India. Kotwaliwale and Ketkar (2001) reported that triploidy was a frequent cause of early pregnancy wastage. Gogate (2006), accounting on an experience of over 10,000 cases of CVS, reported procedure success rate of 97.8% and pregnancy loss rate of 2.2%. There was no case of limb reduction deformity following CVS in this study. Gogate further quoted that in a multicentric study on amniocentesis for various indications (chromosomal studies, NTD screening, biochemical studies, metabolic diseases, microbiological immunological investigations to detect congenital infections, Rh isoimmunization, and fetal lung maturity testing), their success rate was 99.5% and the pregnancy loss rate was 0.8%. Clinical complications included amniotic fluid leakage, preterm labor, infection, fetomaternal transfusion, fetal trauma, and amniotic band syndrome. Gogate (2006) reported on a series of over 1000 cordocentesis with a success rate of 93% and pregnancy loss rate of 2.85%. However, cordocentesis entails a long learning curve and should be performed by experienced operators. Dhillon-Pai (2006) reported on the value of early pregnancy screening, triple markers and ultrasonography, and concluded that a screening test including four markers (triple test + AFP-L3) has a sensitivity of 81.5% with a false positive rate of 4.1% in women aged 35 years and a sensitivity of 83.3% and a false positive rate of 2.0% in women aged 40 years.

Genetic causes account for 50% abnormalities in spontaneous first trimester abortions and about 20% of spontaneous second trimester abortions. Aneuploidy and polyploidy have been implicated (Pai and Shah, 2006).

IMPORTANT POINTS

1. All pregnant women are at risk of carrying a fetus with genetic abnormalities. Screening for genetic abnormalities should be an integral part of the prenatal care.
2. The most frequent chromosome abnormalities are T21, T18, T13, Turner's syndrome, and sex chromosome abnormalities. The incidence of T21, T18, and T13 increases with maternal age and decreases with gestational age.
3. There is an association between T21, open spina bifida, and folic acid deficiency. All pregnant women should ingest 400 µg of folic acid daily. Women with a previous fetus with open spina bifida should ingest 4 mg of folic acid before conception and during pregnancy.
4. The recurrence risk for women with a previous fetus with nondisjunctional Down syndrome is 0.75% higher than the maternal age- and gestational age-related risk.
5. First trimester screening for aneuploidy consists in a combined assessment of the NT by ultrasound and the serum concentration of free beta-hCG and PAPP-A when the CRL is between 45 and 85 mm (10 weeks 4 days and 13 weeks 6 days of gestation). First trimester screening has a detection rate for Down syndrome of 87.5% with a false positive rate of 4.5% in women younger than 35 years and a detection rate of 92% with a false positive rate of 14.3% in women older than 35 years.
6. Second trimester screening for aneuploidy can be performed by the triple or the quad tests. The triple test measures the serum concentration of AFP, beta-hCG, and uE3. The quad test includes a fourth analyte, inhibin-A. The detection rate of the triple test is approximately 69% for a false positive rate of 5%. The detection rate of the quad test is 81% for a false positive rate of 7%.
7. An absent NB in the first trimester and an absent or hypoplastic NB in the second trimester are powerful predictors of aneuploidy. It has been calculated that if measurement of the NB is added to the first trimester screening, the detection rate will be 97% for a false positive rate of 5%.
8. Assessment of the NT and the NB requires adherence to rules that guarantee the reproducibility of the measurements and training and continuous surveillance of the individuals performing the ultrasound examination.
9. Genetic ultrasound in the second trimester is a comprehensive examination of the fetus that includes searching for "markers" of Down syndrome. Markers are ultrasound features that are found more frequently in fetuses with Down syndrome than in normal fetuses. The value of these markers is expressed as a likelihood ratio. When a marker is present, it increases the likelihood that the fetus has Down syndrome (positive LR). When a marker is absent, the likelihood of Down syndrome decreases (negative LR).
10. The likelihood ratio resulting from the presence or absence of ultrasound markers of Down syndrome is multiplied by the background risk to obtain a new or posterior risk. The background risk is that

corresponding to the maternal age and the gestational age at the time of the examination.

11. There is no adequate information to recommend genetic ultrasound as a primary screening method for aneuploidy. This method is recommended only for women older than 35 years who decline amniocentesis and for younger women who decline first or second trimester screening. The absence of ultrasound markers of Down syndrome has a negative likelihood ratio between 0.4 and 0.1 depending on the quality of the examination.
12. A negative genetic ultrasound will avoid approximately 75% of the amniocentesis presently recommended for women older than 35 years.
13. The markers with larger positive likelihood ratio are absent such as hypoplastic NB in Caucasian individuals, increased NFT, cardiac or major anatomic defect, short humerus, short digits, and echogenic bowel. Other markers with smaller positive likelihood ratio are short femur, bilateral pyelectasis, and intracardiac echogenic foci.
14. A normal genetic ultrasound decreases the risk of Down syndrome resulting from an abnormal triple test screening. When the genetic ultrasound is normal, the triple test risk needs to be 1 in 40 or greater in order for the posterior risk to reach a level of 1 in 270, which is the threshold presently used to recommend amniocentesis.
15. The screening test for open NTDs is the concentration of MSAFP between 15 and 20 weeks of gestation. This test is one of the components of the triple or quadruple second trimester screening. The negative predictive value of this test is 99.9% for open spine and 100% for anencephaly. The positive predictive value is disappointingly low, 1.9% for open spine and 1.7% for anencephaly.
16. There are multiple reasons for a falsely elevated MSAFP. The most common are error in the dating of the pregnancy, multifetal pregnancy, fetal demise, severe oligohydramnios, fetomaternal bleeding, abdominal wall defects, and parvovirus infection.
17. In the majority of cases of elevated MSAFP, a comprehensive ultrasound examination can rule out the presence of anencephaly or open spina bifida with 99% negative predictive value. In some cases the fetal spine cannot be adequately visualized and amniocentesis is recommended.
18. The American College of Obstetricians and Gynecologists recommends genetic screening for CF in Caucasian individuals, sickle cell disease in African-American, alpha-thalassemia in Southeast Asians, beta-thalassemia in Mediterraneans, Tay-Sachs and Canavan disease in Ashkenazi Jews.
19. Approximately 1000 mutations capable of producing CF have been identified. The most common mutation found in approximately 70–75% of the Caucasian carriers in the USA is the delta F508.
20. The present recommendation is to offer screening to the Caucasian population with a panel of 23 mutations that include all those occurring as frequently as 1 per 1000 in the general population. Several laboratories offer panels that screen for many more than the recommended 23 mutations, but the detection rate with these extended panels is only marginally better.
21. Since the panels used for CF screening do not include all the mutations capable of producing the disease, a negative screening does not exclude the possibility of being a CF carrier. Also, the possibility of fetal CF will be different if one of the parents is untested or if one or both test positive.
22. The screening test for sickle cell carriers is hemoglobin electrophoresis.
23. The risk of pregnancy loss following genetic amniocentesis varies and is approximately 0.5% (1 per 200 procedures). This risk changes with the gestational age at the time of the procedure, the concomitant or preprocedure use of ultrasound, the needle size, the number of needle insertions, the characteristics of the amniotic fluid, and the experience of the individual performing the procedure.
24. Leakage of amniotic fluid following amniocentesis occurs in 1–2% of the cases. Approximately one-third of these cases will end in pregnancy loss.
25. CVS is performed between 8 and 12 weeks. The chorionic villi can be obtained under ultrasound guidance following transabdominal, transcervical, and transvaginal approaches. The method used will depend on the placental location, the position of the uterus, and the presence of complicating factors. Approximately 80% of all CVS are transabdominal.
26. The risk of pregnancy loss following CVS is higher than that after amniocentesis at 16 weeks. The reason is the nonprocedure-related loss that normally occurs between 11 and 16 weeks. If the normal attrition is discounted, the pregnancy loss after CVS is similar to that following amniocentesis.
27. Mosaicism occurs in approximately 1.5% of CVS specimens. The majority of mosaics are present in the direct preparation and are not confirmed in mesenchymal and fetal cell cultures.
28. The most common indication for cordocentesis is rapid karyotype in fetuses with abnormalities found in ultrasound examination.
29. The pregnancy loss rate following cordocentesis is about 1%.

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3

Fetal Dysmorphology

CHAPTER OUTLINE

Approximately 2% of newborn infants in USA have a major congenital malformation (Peller et al., 2004), making this the leading cause of infant mortality in this country. Survivors are usually afflicted by lifelong disabilities, resulting in the need for frequent hospital admissions and long-term care. Advances in ultrasound technology have made possible the prenatal identification of an increasingly large number of fetal congenital malformations and abnormalities of the placenta and amniotic fluid volume. For this reason the practicing obstetrician needs to be proficient in the diagnosis, prognosis, and treatment of these abnormalities. In this chapter we will describe the fetal and amniotic fluid abnormalities most commonly found with the use of office ultrasound.

MIDTRIMESTER COMPREHENSIVE ULTRASOUND EXAMINATION

The current method for the detection of fetal congenital abnormalities is a comprehensive ultrasound examination or fetal anatomical survey performed between 18 and 22 weeks of gestation. It is possible that with advances in ultrasound technology and with specialized training of the individuals performing the examination, the optimal gestational age for this examination can be reduced to 11–14 weeks of gestation (Timor-Tritsch et al., 2004). Fetal anatomical surveys require extensive training, experience, and certification of the personnel performing the examination. Studies have demonstrated significant differences in the accuracy of the exams when performed in private practices versus academic centers (Ewigman et al., 1993).

A good scanning technique is a fundamental prerequisite for a proper prenatal ultrasound examination. Also, since it is possible to recognize only what one knows, knowledge regarding fetal anatomy and fetal abnormalities is a fundamental component of a proper examination. Experience is also valuable but the ability to make correct deductions from the ultrasound findings and theoretical knowledge about an abnormality could be an adequate substitute for experience.

In USA there is a decreasing debate concerning the value of the routine use of ultrasound in obstetrics. Opposition to the routine use of ultrasound is based on the results of the RADIUS study (Ewigman et al., 1993) that failed to show a significant difference in perinatal outcome between women allocated to routine ultrasound screening and women in a control group. Further investigation and analysis of the RADIUS trial results have made apparent that many of the conclusions of the study are questionable (Goncalves et al., 2001). Furthermore, meta-analysis of several randomized trials have demonstrated that routine ultrasound screening leads to a higher detection of growth abnormalities, multifetal pregnancies, and severe malformations than when the ultrasound is performed only for specific indications (Bucher and Schmidt, 1993). The current majority opinion is that a properly performed ultrasound examination is an integral part of routine prenatal care and that probably three ultrasound exams (one at the end of the first trimester to establish dates—rule out multiple gestation and perform first trimester screening for aneuploidy; a second between 18 and 22 weeks to screen for abnormalities; and a third to assess fetal growth after 32 weeks) are necessary for adequate pregnancy surveillance.

The American Institute of Ultrasound in Medicine (AIUM) has indicated the following areas of assessment as essential elements of a standard examination of the fetal anatomy:

1. Head and neck: Cerebellum, choroids plexus, cisterna magna, lateral cerebral ventricles, midline falx, and cavum septum pellucidum
2. Chest: Four-chamber view of the fetal heart and, if technically feasible, evaluation of the outflow tracts
3. Abdomen: Stomach (presence, site, and situs), kidneys, bladder, umbilical insertion site into the fetal abdomen, umbilical cord vessel number
4. Spine: Cervical, thoracic, lumbar, and sacral spine
5. Extremities: Legs and arms (presence or absence)
6. Gender: Indicated in low-risk pregnancies only for the evaluation of multiple gestations

The Fetal Medicine Foundation has more astringent requirements for the fetal anatomical survey:

1. Skull: Examination of integrity and normal shape, and measurement of biparietal diameter, and head circumference
2. Brain: Examination of cerebral ventricles, choroid plexus, midbrain, posterior fossa (cerebellum and cisterna magna) and measurements of the anterior and posterior horns of the lateral ventricles
3. Face: Examination of the profile, orbits, and upper lip
4. Neck: Measurement of the nuchal fold thickness
5. Spine: Examination both longitudinally and transversely
6. Heart: Examination of rate and rhythm, four-chamber view, and outflow tracts
7. Thorax: Examination of the shape of the thorax, the lungs, and diaphragm
8. Abdomen: Examination of the stomach, liver, kidneys, bladder, abdominal wall, and umbilicus and measurement of the abdominal circumference
9. Limbs: Examination of the femur, tibia and fibula, humerus, radius and ulna, hands and feet (including shape and echogenicity of long bones and movement of joints), and measurement of femur length.

ABNORMALITIES OF THE CENTRAL NERVOUS SYSTEM

An adequate ultrasound examination of the fetal central nervous system (CNS) requires visualization of the cerebellum and the cisterna magna, the lateral ventricles and the choroids plexus, the thalami, the third ventricle, the cavum septum pellucidum, and the falx cerebri. Most of this information can be obtained with a transverse scan at the level of the septum pellucidum, a coronal view perpendicular to the transverse scan, and a suboccipitobregmatic view. Examination of the spine requires sagittal and coronal views. The CNS abnormalities most frequently found during the 18–22 weeks' sonographic examination are anencephaly, spina bifida, ventriculomegaly, holoprosencephaly, Dandy–Walker malformation, and choroids plexus cysts.

Anencephaly

Anencephaly is the absence of the cranial vault and the cerebral hemispheres. It is the most frequent of the open neural tube defects (NTDs)—a group of abnormalities caused by a failure of the embryonic neural tube to close—that include spina bifida, encephalocele, cranioschisis, and iniencephaly. The incidence of open NTDs is approximately 1:1000 births in USA but in Ireland and Wales reaches 5:1000. The incidence has been estimated to be five times greater in abortion material than at birth. Females are affected more frequently than males, with a ratio of 4:1. The risk of recurrence is 5% after one affected child and 13% after two affected children. Because of this high risk of recurrence, patients who have had a previous anencephalic child should be screened with ultrasound early in the second trimester.

The exact etiology of anencephaly is unknown. The defect is secondary to a failure in the closure of the rostral neuropore at an early embryonic stage. Pathologically, anencephaly is characterized by the absence of the structures derived from the forebrain and skull. The forebrain and midbrain are absent or replaced by rudimentary fibrovascular tissue and scattered islands of neural elements covering the crown of the head, or area cerebrovasculosa. The cerebellum and the midbrain are less involved or are completely spared. The base of the skull and the facial bones are not affected, but the supraorbital region of the frontal bone and the parietal occipital squama of the temporal bone are absent. Other features that characterize these fetuses are bulging eyes, short neck, and a large tongue.

Anencephaly was the first fetal anomaly detected in utero by sonography. The diagnosis is made by demonstrating an absent skull vault and brain (Figure 3-1). The diagnosis may be suspected in the first trimester during examination with endovaginal probes but is usually not certain until after 14 weeks. In the first trimester the skull is absent but some of the brain is present giving to the head the resemblance of a Mickey Mouse-shaped head (Nishi and Nakano, 1994). The accuracy of the sonographic diagnosis is 100% in experienced hands. The differential diagnosis includes large encephaloceles, microcephaly, and anencephaly secondary to amniotic bands syndrome. Acrania and exencephaly are early forms of anencephaly when some brain segments are still present. A significant number of cases of anencephaly are discovered as a result of first or second trimester screening for chromosomal abnormalities. The screening procedures do not differentiate anencephaly from other causes of elevated maternal serum alpha-fetoprotein (MSAFP). As explained in Chapter 2, an elevated MSAFP demands follow-up with ultrasound examination to rule out the possibility of anencephaly, spina bifida, or abdominal wall defects.

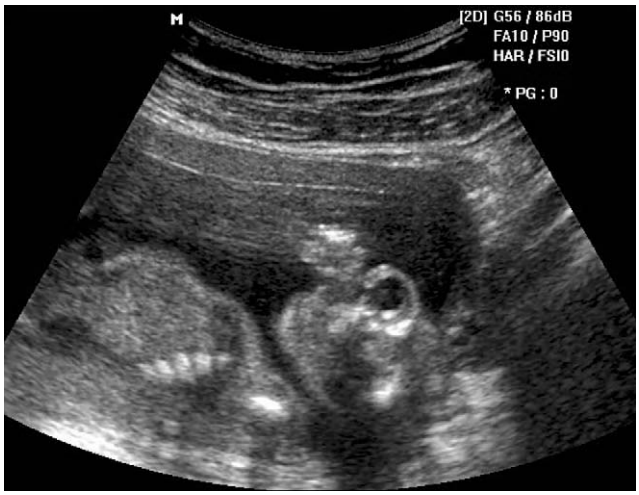


Figure 3-1. Anencephaly. Prominent eyes and absence of the cranial vault are apparent.

The incidence of associated anomalies in anencephaly is approximately 30% and half of them are spinal defects. The most frequent is spina bifida, which may be found in 27% of the cases. Other less common anomalies are hydronephrosis in 16%, cleft lip in 10%, omphalocele in 6%, and cardiac anomalies in 4% of the cases. Polyhydramnios is present in approximately 35% of the cases. The reason for the excessive amount of amniotic fluid is not completely understood and diminished fetal swallowing, secretion of cerebrospinal fluid directly into the amniotic cavity, and excessive micturition have been implicated as possible etiologic factors.

Anencephaly is a lethal condition. Most fetuses deliver prematurely, although post-term pregnancy can be present in 15% of cases. Approximately 30% of the fetuses are born alive and die within the first hours of life. However, rare cases of survival for several months have been reported. Since anencephaly has a lethal prognosis and its sonographic diagnosis is highly reliable, it is a generally accepted indication for pregnancy termination. The use of anencephalic fetuses for organ transplantation is surrounded by ethical questions and is not accepted in many institutions.

Inadequate intake of folic acid before and during pregnancy is strongly associated with the occurrence of anencephaly and spina bifida. The mechanism underlying the association between maternal folic acid status and NTDs has not been clarified but defective DNA methylation and increased concentrations of homocysteine are two metabolic pathways compromised in cases of folic acid deficiency which could be implicated in the production of these defects. Randomized clinical trials have demonstrated that maternal supplementation with folic acid reduces the risk of anencephaly and spina bifida by up to 70% (Medical Research Council, 1991; Berry et al., 1999).

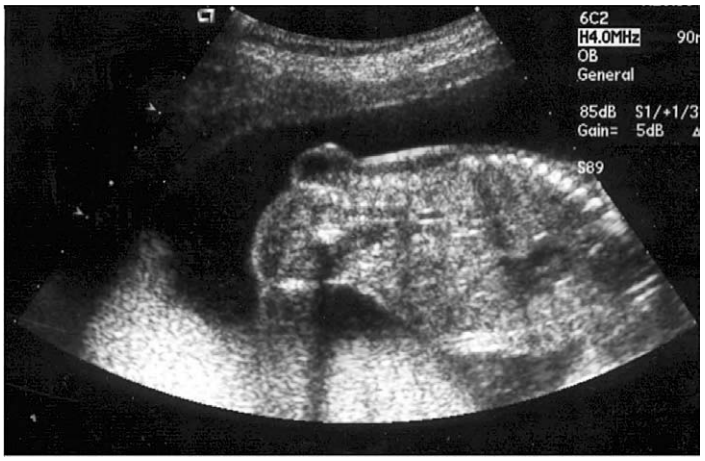
Spina Bifida

Spina bifida is a midline defect of the spine resulting in exposure of the contents of the neural channel. The incidence of spina bifida in USA is approximately 1–2 per 1000 births. Caucasians apparently are at higher risk. The incidence is higher in England although a significant decline in the prevalence of NTDs has been observed during the last 20 years. The reason for this trend is unknown and only a part of this tendency may be attributed to antenatal testing. Other explanations include environmental factors, vitamin supplementation, and better nutrition. The recurrence rate in England is 5 per 100 after 1 affected child and 9 per 100 after 2 affected children. In USA, the recurrence risk is 2–3 per 100 after the first affected child and 5.7 per 100 after 2 affected children.

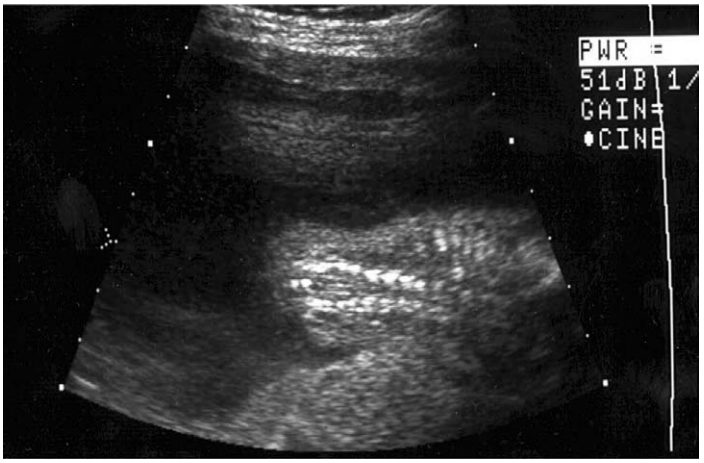
The majority of cases of spina bifida are multifactorial in origin. However, the incidence of aneuploidy, particularly trisomy 18 reaches 13% (Babcook et al., 2000). Since the recurrence risk and the decision to continue an affected pregnancy are affected by the presence or absence of a chromosomal abnormality, it is important in these cases to perform amniocentesis for determination of the fetal karyotype. Approximately 90% of fetuses with open spina bifida are born to women who have no predisposing factors. However, malformations that follow a Mendelian pattern of inheritance, trisomies 18 and 13, triploidy, exposure to valproic acid, thalidomide, or aminopterin, and maternal diabetes are etiologically related factors.

The term spina bifida encompasses several types of spinal abnormalities. Classically, spina bifida has been divided into "aperta" (open) or "occulta" (closed). The latter represents approximately 20% of the cases of spina bifida. Spina bifida occulta is usually a small, clinically asymptomatic defect, covered by skin, which can be diagnosed through radiographic examination. In rare cases the lesion may be apparent by the presence of a subcutaneous lipoma. In open spina bifida the defect is usually covered by a thin meningeal membrane, giving the appearance of a cystic tumor. If the mass contains spinal fluid and meningeal tissue, it is known as meningocele. If it contains spinal fluid and neural tissue, it is referred as myelomeningocele. Spina bifida affects the lumbosacral region of the spine in over 63% of the cases. Ventral defects of the spine are extremely rare.

A CNS lesion frequently associated with spina bifida is hydrocephalus secondary to the presence of an Arnold–Chiari malformation. In this anomaly, the cerebellar vermis is herniated through the foramen magnum, displacing the fourth ventricle inside the neural canal and causing obstructive hydrocephalus. Other associated CNS malformations include holoprosencephaly, agenesis of the corpus callosum, and polymicrogyria. Limb deformities include clubfoot and dislocation of the hip. The pathogenesis of limb defects is related to the unopposed action of muscle groups due to a defect in the peripheral nerve corresponding to the involved myotomes. Other abnormalities seen less frequently affect the gastrointestinal and renal systems.



A



B

Figure 3-2. Meningomyelocele. A, A sacral myelomeningocele is clearly apparent in this longitudinal view of the spine. B, Sagittal view of the lumbar spine. The lower lumbar vertebrae are abnormally separated.

The ultrasound diagnosis of spina bifida requires the sonographer to be completely familiar with the normal appearance of the fetal spine. The spine can be visualized in any of three main planes of examination: coronal, transverse, or sagittal. For the diagnosis of spina bifida, the ideal visualization is in the transverse plane. In this plane the three bony structures of the spinal axis are clearly seen. They are the two lateral processes of the vertebra and the midline vertebral body. In cases of spina bifida, there is typically an absence of the posterior laminae and the lateral vertebral processes are set apart (Figure 3-2).

There are sonographic findings in the fetal brain, useful in the diagnosis of spina bifida. They are the "lemon"

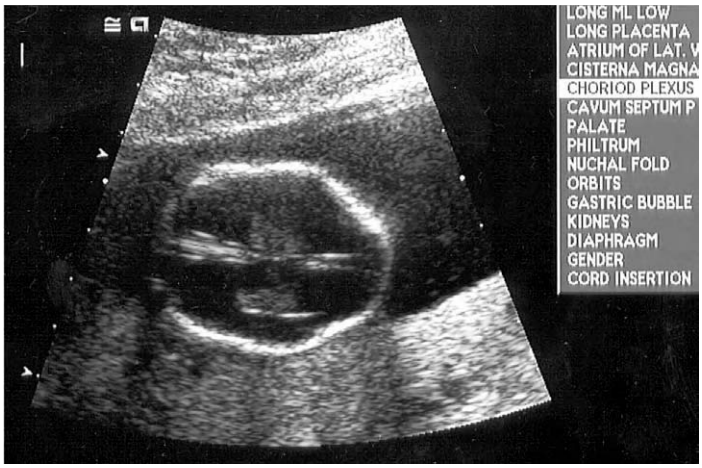


Figure 3-3. Lemon sign.

sign and the "banana" sign. The lemon sign is a scalloping deformity of the frontal calvarium, best seen when scanning in the ventricular plane. It is so called, because the cranium resembles the shape of a lemon (Figure 3-3). In a study of 130 cases of spina bifida, the lemon sign was found in 98% of fetuses with a gestational age of 24 weeks or less (Van den Hoff et al., 1990). However, 1% of normal patients may present the lemon sign. This sign disappears spontaneously prior to 34 weeks. The banana sign describes the curved shape of the cerebellar hemispheres wrapped around the posterior midbrain that is compressed into the posterior fossa due to an Arnold–Chiari malformation. The demonstration of an obliterated cisterna magna complements the diagnosis. In one study the predominant cerebellum abnormality found in fetuses at 24 weeks or less was the banana sign (72%), while after this gestational age a sonographic "absence" of cerebellum was found in 81% of the patients (Nicolaides et al., 1986). In another study the banana sign had a sensitivity of 96% and a negative predictive value of 100% for the diagnosis of spina bifida (Benacerraf et al., 1989). Other useful sonographic signs are the presence of clubfoot and hydrocephalus. The latter has been reported in as high as 90% of cases of spina bifida, but only in 75% before 24 weeks. The accuracy of ultrasound to diagnose spina bifida depends on the experience of the ultrasonographer, the population studied (low or high risk), and the resolution of the equipment used, but overall the sensitivity and specificity of sonography in diagnosing open spina bifida and abdominal wall defects is close to 100% (Lennon and Gray, 1999). Women at risk for a fetus with spina bifida can be identified by second trimester screening with MSAFP, which is one of the components of the triple and the quadruple screening tests. This topic is extensively discussed in Chapter 2.

The prognosis of spina bifida depends on the fetal karyotype, the localization of the lesion, its extent, and its association with hydrocephalus or other abnormalities.

Table 3-1. Neonatal prognosis for spina bifida according to the level of the lesion

Complication	C1–L2 (%)	L3–L5 (%)	L5–S (%)
Hydrocephaly	100	100	91
Arnold–Chiari	15	6	12
Kyphoscoliosis	89	45	20
Shunt	100	97	91
Locomotion without aids	0	7	57
Wheelchair	90	45	17
Urinary continence	0	0	17
Bowel continence	80	68	100
Learning disability	17	27	25

From Cochrane DD, Wilson RD, Steinbok P, et al. Prenatal spinal evaluation and functional outcome of patients born with myelomeningocele: information for improved prenatal counseling and outcome prediction. Fetal Diagn Ther 1996; 11: 159–68.

As shown in Table 3-1, lesions localized high in the spine have the worst prognosis, and inability to walk, bladder and rectal incontinency, and need for shunting are the rule for lesions at L3 level or above (Cochrane et al., 1996). For lesions below L3 the prognosis following neonatal surgery has improved modestly in the last 10 years (Bruner and Tulipan, 2004) but still remains dismal perhaps with the exception of newborns with small sacral defects. Since the prognosis is closely related to the localization of the defect, the accuracy in determining the upper level of the lesion is important. However, only 29% of community physicians were successful in assigning the upper level of the lesion in the study of Brunner et al. (2004). Three-dimensional ultrasound has made a precise identification of the limits and extent of the spinal lesion possible.

Termination of the pregnancy is an option when the diagnosis of spina bifida is made early in gestation. Management of viable fetuses concerns mainly the timing and the mode of delivery. These fetuses should be delivered at term, with the exception of those developing a rapidly progressive hydrocephalus. However, even in these fetuses, lung maturity should be ensured before delivery. The mode of delivery is controversial. One study of 72 infants with spina bifida, followed for 1-year postdelivery, failed to demonstrate any benefit of abdominal over vaginal delivery (Bensen et al., 1988). Other studies indicate that cesarean section before the onset of labor may result in better subsequent motor function than that with vaginal delivery (Luthy et al., 1991). Delivery should take place in a tertiary center, where a team of neurosurgeons, pediatricians, and rehabilitation therapists is available for immediate evaluation.

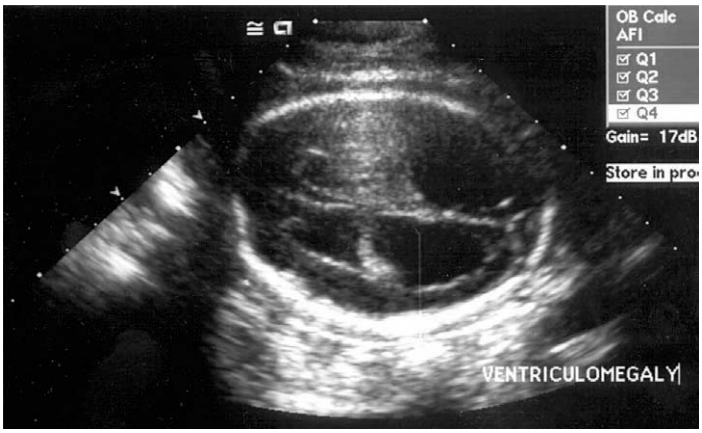
Correction of the open spine defect is usually carried out within 48 hours of birth, and a shunt is placed if ventriculomegaly is present. In the last few years, attempts

have been made to close the lesion while the fetus is still "in utero" to avoid the potential neurologic deterioration that may occur during gestation as a result of exposure of the neural tissue to amniotic fluid. The initial experience with fetal surgery indicates a reduction in the frequency of hindbrain herniation (Sutton et al., 1999; Tulipan et al., 1999) and decreased need for shunting. Short-term observations suggest that bladder function and motor function of the lower limbs are not different following intrauterine or neonatal treatment. A randomized controlled trial comparing outcomes of surgery before and after birth is in progress.

Ventriculomegaly and Hydrocephaly

The literature in this topic is confusing because the terms ventriculomegaly and hydrocephaly are frequently used interchangeably. The fundamental characteristic of hydrocephaly is an abnormally large size of the head. With advances in imaging technology, mild degrees of ventricular dilatation without alteration in the head size are visualized and designated as ventriculomegaly or ventricular dilatation. Both hydrocephaly and ventriculomegaly are terms generic in nature and include several different conditions. However, some investigators define ventriculomegaly as dilatation of the fetal lateral cerebral ventricles with normal intraventricular pressure and hydrocephaly as dilatation of the fetal ventricular system not secondary to brain atrophy associated with increased intraventricular pressure. Since ventriculomegaly includes all the cases of hydrocephaly, this term will be used in this chapter to refer to all the cases of dilated brain ventricles diagnosed in the antenatal period and hydrocephaly will be used to refer to severe cases of ventriculomegaly causing enlargement of the head. The most common conditions causing fetal ventriculomegaly are aqueductal stenosis, Arnold–Chiari malformation secondary to spina bifida, Dandy–Walker malformation, and holoprosencephaly. Aqueductal stenosis is responsible for approximately 60% of the cases and the other 40% are the result of Arnold-Chiari malformation. Dandy–Walker and holoprosencephaly correspond to less than 1% of the cases.

The cerebrospinal fluid is formed in the choroid plexus and cerebral capillaries of the ventricular system. It flows in a unidirectional fashion from the lateral ventricles into the third ventricle across the foramen of Monro, and from the third to the fourth ventricle through the aqueduct of Sylvius. From the fourth ventricle it moves through the foramina of Luschka into the basal cisterns and reaches the subarachnoid space by moving across the foramen of Magendie. The fluid is then reabsorbed by the granulations of Pacchioni which are distributed along the superior sagittal sinus. In most patients with ventriculomegaly, there is an alteration in cerebrospinal fluid dynamics, usually the result of an obstructive process, causing an



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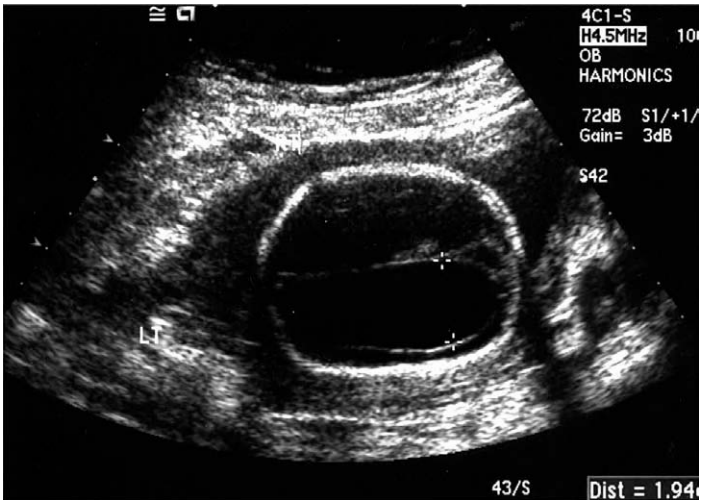


B

Figure 3-4. Ventriculomegaly. Two examples of abnormal ventricular dilatation. A, Atrial dilatation, with displacement of the choroid plexus. B, Marked enlargement of the posterior horn of the lateral ventricles.

increase in intraventricular pressure. The etiology and the site of the obstruction are the most important features in the pathogenesis of this condition although the amount of fluid produced and its rate of flow and absorption are also important factors determining the severity of the dilatation. Some conditions such as destructive brain processes or developmental anomalies in which the affected tissue areas are replaced by fluid have increased cerebrospinal fluid and normal intraventricular pressure.

The prenatal diagnosis of ventricular dilatation is made by measuring the width of the ventricular atrium of the cerebral hemisphere farthest away from the transducer in an axial plane through the thalamus near the plane used for measuring the biparietal diameter (Cardoza et al., 1988). The cerebellum should not be seen in the correct plane for the atrial measurement (Figure 3-4). The mean atrial width is 7.6 mm (SD 0.6), a value that remains stable during the second and third trimesters of pregnancy. A 10 mm value is widely accepted as the upper limit of normal.

The mean atrial width is slightly greater in males than in females, but this difference has no clinical significance (Nadel and Benacerraf, 1995). The incidence of ventricular dilatation diagnosed "in utero" by ultrasound examination is approximately 1 in 100. The incidence of severe ventricular dilatation or hydrocephaly is much less, approximately 2 per 1000.

In cases where it is difficult to obtain an adequate transverse plane for measuring the ventricular atria, the diagnosis of ventriculomegaly can be made using the ventricular to hemisphere width ratio (LVW/HW) in the coronal plane. This ratio is approximately 0.71 at 15 weeks and decreases to 0.37 at 24 weeks. These figures reflect the normal decrease in the ventricular to brain ratio that occurs as the fetus develops. Any value of the LVW/HW ratio over 0.5 after 24 weeks should be considered abnormal. Other morphologic criteria such as the separation of the choroid plexus from the medial wall of the lateral ventricle and the size and configuration of the horns may be useful in the early diagnosis of ventricular dilatation.

An accurate diagnosis and classification of fetal ventricular dilatation requires a systematic sonographic evaluation of the posterior fossa, the third and fourth ventricles, the subarachnoid space, the bony calvaria, and a careful examination of the fetal spine. A detailed fetal anatomic survey is also necessary in these cases because the incidence of abnormalities in other systems may be as high as 63%. These include hydronephrosis, dysplastic kidneys, ventricular septal defects (VSDs), tetralogy of Fallot, and hypoplastic left heart syndrome (HLHS). Gastrointestinal malformations are less common and include omphalocele, gastroschisis, tracheoesophageal fistula, and malrotation of the bowel. Finally, chromosomal abnormalities are seen in 11% of these patients. These include Down's syndrome, trisomies 13 and 18, balanced translocations, and mosaicisms.

Aqueductal Stenosis

Aqueductal stenosis is the most common cause of ventricular dilatation and hydrocephalus accounting for 40–60% of the cases. It is more common in females. The condition results from the narrowing of the aqueduct of Sylvius, resulting in dilated third and lateral ventricles and a normal fourth ventricle. The cerebellum and the cisterna magna are usually normal but in cases of severe ventricular dilatation, the cisterna and even the cerebellum may not be seen. The most frequent differential diagnosis is Arnold–Chiari malformation but in these cases examination of the spine will reveal the open spine defect. Aqueductal stenosis may be produced by diverse agents but infection and inflammation account for approximately 50% of the cases. In about 5% of the cases aqueductal stenosis may be inherited as an X-linked recessive trait, and in these cases the prognosis is poor and profound mental retardation is common. Infectious processes related to the disease include syphilis, toxoplasmosis, Cytomegalovirus (CMV), and influenza virus. The role of teratogenic factors is unknown.

Ventriculomegaly secondary to aqueductal stenosis may be mild (atrial width between 10 and 15 mm) or severe (atrial width > 15 mm) but the prognosis has a relatively weak association with the degree of ventricular dilatation and is more heavily dependent on the presence of associated structural or chromosomal abnormalities. Similarly, the thickness of the cortical mantle in prenatal ultrasound examinations has limited prognostic value because the mantle will regain close to normal thickness, once a shunt is placed in the neonatal period. In cases of aqueductal stenosis without associated abnormalities, the overall prognosis is good and approximately 50% of the cases will have normal neurodevelopmental outcome. The prognosis is better in cases of mild ventricular dilatation and 85% of them will have normal neurologic function and require no shunting.

Theoretically, ventricular dilatation secondary to aqueductal stenosis is an ideal situation for fetal surgery. However, in utero shunting procedures had disappointing results, even in fetuses with early and progressive hydrocephalus too immature for delivery. In a study of 44 cases, the intraoperative mortality was 10% and the overall procedure-related mortality was 17%. Only 35% of the treated fetuses were normal on serial postoperative testing, while 65% had varying degrees of neurologic and systemic defects. The incidence of false negative sonographic examination for associated malformations was a discouraging 22%.

Dandy–Walker Malformation

The Dandy–Walker syndrome (Figure 3-5) includes three classic features: hydrocephalus, posterior fossa cyst, and a

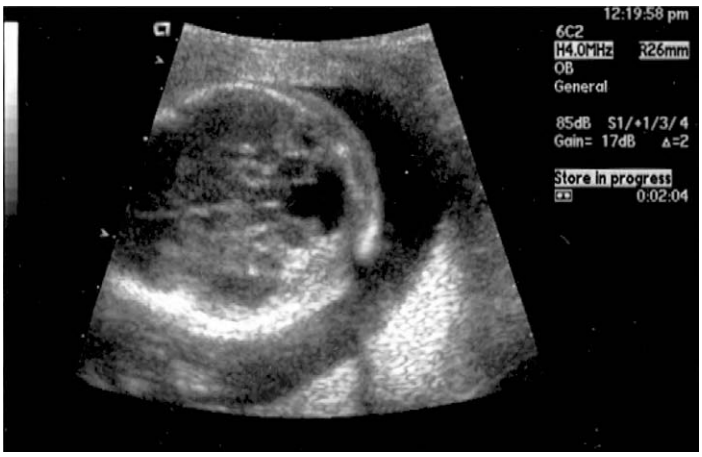


Figure 3-5. Dandy–Walker malformation. Note the absence of cerebellar vermis, enlarged cisterna magna, and lateral displacement of cerebellar hemispheres.

defect in the cerebellar vermis. It accounts for approximately 5–10% of cases of hydrocephalus. Its etiology is unknown, although it has been associated with Mendelian disorders, chromosomal abnormalities, infectious processes such as CMV, toxoplasmosis, and rubella, and exposure to Coumadin and alcohol. Approximately 80% of patients with Dandy–Walker malformations present with ventriculomegaly. However, the degree of ventricular dilatation varies, and some cases with open foramina of Luschka and Magendie may never develop ventricular dilatation in utero. The malformation should be suspected when there is a marked increase in the diameter of the cisterna magna (more than 10 mm from the cerebellar vermis to the inner border of the skull) and an absence of the cerebellar vermis with or without associated ventricular dilatation. The differential diagnosis includes subtentorial arachnoid cyst and dilatation of the cisterna magna as seen in cases of trisomy 18.

The incidence of associated cerebral defects is as high as 68%. A common associated defect is the absence of the corpus callosum which is evidenced by an inability to visualize the cavum septum pellucidum. Chromosomal abnormalities are present in approximately 20% of the cases and include trisomies 13, 18, and 21.

The prognosis of fetuses diagnosed with Dandy–Walker malformation is poor. Approximately 30% of them will die in utero or in the immediate neonatal period. The outcome of survivors depends on the presence of associated anatomic or chromosome abnormalities. When the defect is isolated and there is no hydrocephaly, expectancy is the usual treatment. Most neonates with ventricular dilatation require ventriculoperitoneal shunting.

Holoprosencephaly

Holoprosencephaly is a term to describe a spectrum of brain malformations resulting from an arrest in the cleavage of the forebrain. In the most severe form, alobar prosencephaly, there is a monoventricular cavity with no cortical mantle and complete fusion of the thalami (Figure 3-6). In the semilobar type, there is partial posterior closure of the brain hemispheres and incomplete fusion of the thalami with the singular ventricular cavity having a horse-shoe shape. In lobar prosencephaly there is almost complete division of the brain into two hemispheres but there is an anterior central ventricle interrupting the falx. The cavum pellucidum is absent, indicating agenesis of the corpus callosum. Occasionally the third ventricle can be seen separated from the central ventricle by a small echogenic area. Facial deformities occur quite often in lobar and semilobar holoprosencephaly. They include hypotelorism or a single orbit (cyclops deformity), absent nose, midline cleft, and a midline proboscis above the level of the eyes.

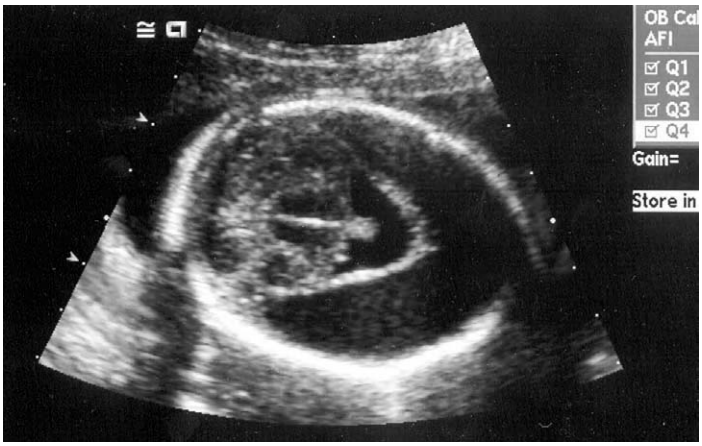


Figure 3-6. Alobar prosencephaly.

Chromosomal abnormalities, particularly trisomy 13 and 18 occur in about 30% of the cases of holoprosencephaly. Associated extracranial malformations are equally common. All forms of holoprosencephaly have a poor prognosis.

ABNORMALITIES OF THE NECK

Cystic Hygroma

Cystic hygroma is a malformation characterized by the presence of single or multiloculated fluid-filled cavities in the fetal posterior cervical region. Cystic hygromas result from a defect in the drainage of the fetal lymphatic system. In the normal fetus, the lympathic vessels drain into two sacs lateral to the jugular veins. At approximately 40 days of gestation, these sacs develop communications with the venous system and become the terminal portions of the right lymphatic duct and the thoracic duct. Failure to develop these communications leads to an accumulation of lymph in cystic structures localized in the posterior triangles of the neck and in other tissues. This series of events and their resulting phenotypic features comprise the so-called jugular lymphatic-obstruction sequence. Theoretically this sequence can be reversed by the formation of alternative routes of lymph drainage. The incidence of cystic hygroma is poorly defined and probably ranges between 5 and 15 per 1000 live births.

Chromosomal abnormalities are present in more than 60% of fetuses with cystic hygroma. The most common chromosomal abnormality is Turner's syndrome. Other conditions are trisomy 21, trisomy 18, and several forms of mosaicism. Malformation syndromes, such as Noonan's syndrome, Robert's syndrome, fetal-alcohol syndrome, and familial pterygium colli are also related. In utero exposure to aminopterin and trimethadione has also been reported in relation with cystic hygroma.

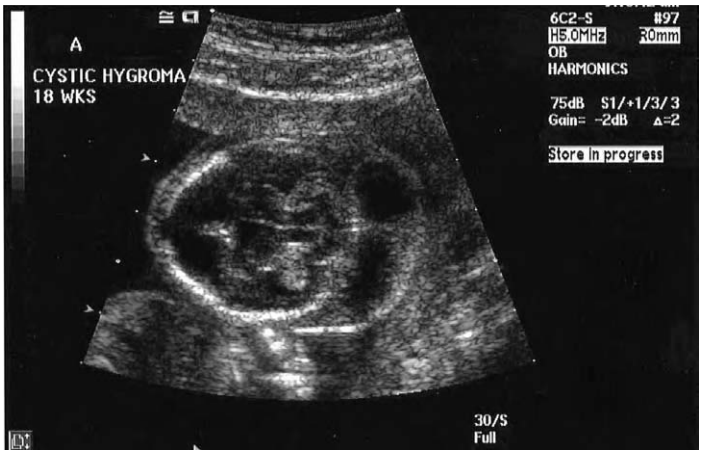


Figure 3-7. Cystic hygroma. A cystic mass is present in the posterior aspect of the fetal head. Karyotype revealed trisomy 21.

The diagnosis of cystic hygroma can be made with high reliability through ultrasound examination. Characteristically, there is a large cystic mass occupying the posterolateral aspect of the fetal neck (Figure 3-7). Sometimes the cystic contents are interrupted by septa that occasionally can be incomplete. Large, septated, multilocular hygromas seem to a have a worse prognosis than nonseptated ones. The differential diagnosis includes occipital encephalocele, cervical meningocele, and cystic teratoma of the neck.

Two types of cystic hygromas have been described, each with a different prognosis. In one type the diagnosis is usually made after 30 weeks. It consists of a localized lymphatic defect without associated fetal hydrops or other abnormalities. This condition has a fairly good prognosis, and surgical repair may be performed at any time during the neonatal period. They are the cystic hygromas familial to the pediatricians. The second type of cystic hygroma is diagnosed early in pregnancy. In the first trimester the lesion has the sonographic appearance of a nuchal membrane and is associated with chromosome abnormalities in approximately 60% of the cases. The majority of fetuses with normal chromosomes have spontaneous resolution of the lesion before 20 weeks. In the second trimester the lesion has the typical sonographic characteristics of a cystic hygroma and may be associated with nonimmune hydrops. The cystic lesion may be multiloculated and the frequency of chromosome abnormalities is greater than 80%. Fetal death usually occurs shortly after diagnosis. The cause of death has been related to chronic fetal hypoxemia secondary to compression of the thoracic structures by the generalized edema. The association with hydrops fetalis is the most important prognostic factor. When hydrops is present the fetal mortality rate is near 100%.

Following the diagnosis of cystic hygroma, it is necessary to perform a detailed ultrasound evaluation for cardiac anomalies, abdominal pleural or pericardial effusions, and skin edema. The fetal karyotype should be obtained and expectancy for spontaneous resolution should follow a normal result. If the karyotype is abnormal, the prognosis is extremely poor and the large majority of these fetuses will die or be aborted.

There is no available in utero treatment for cystic hygroma. Do to its extremely poor prognosis, termination of pregnancy should be an option when the diagnosis is made before viability and the chromosomes are abnormal. In cases of late diagnosis without associated hydrops, expectant management is indicated. Intrapartum management should be conservative. Large cystic masses may cause dystocia, and if present in a nonhydropic fetus, a cesarean section should be performed. Webbing of the neck and puffiness of the extremities are characteristic postnatal features in these cases. The risk of recurrence of cystic hygroma associated with chromosomal abnormalities is around 1%. However, if the etiology is related to an autosomal-related condition the risk may be as high as 25%.

CARDIAC ABNORMALITIES

Cardiac anomalies are one of the most common congenital defects affecting almost 1% of all pregnancies and causing 20–30% of all perinatal deaths. The true incidence of congenital cardiac anomalies may be five times higher than the newborn incidence because many affected fetuses will die in utero or are aborted early in gestation. Box 3-1 shows the relative frequency of various congenital cardiac anomalies.

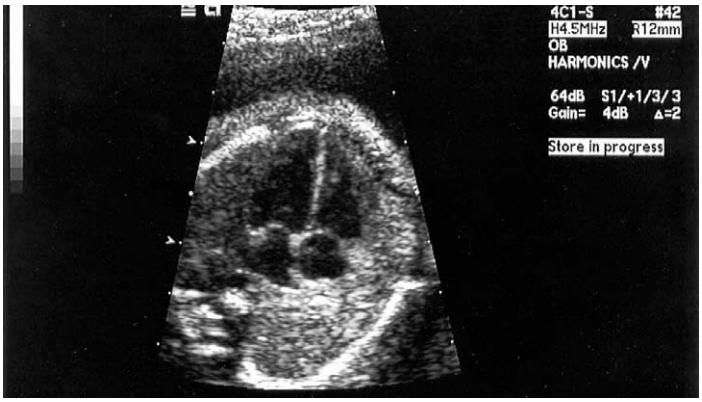
The large majority of congenital cardiac anomalies can potentially be detected by a careful ultrasound examination of the fetal heart although there is a wide difference in the detection rate among different laboratories. The

BOX 3-1

Frequency of congenital heart lesions

Ventricular septal defects	35.7.0%
Coarctation of the aorta	8.9%
Atrial septal defects	8.2%
Atrioventricular septal defect	6.7%
Tetralogy of Fallot	6.2%
Univentricular heart	4.8%
Truncus arteriosus	4.8%
Hypoplasia of the left ventricle	4.6%
Transposition of the great arteries	4.3%
Double-outlet right ventricle	2.4%
Hypoplasia of the right ventricle	2.4%
Other lesions	13.0%

From Hoffman JIE. Incidence of congenital heart disease: II. prenatal incidence. Pediatr Cardiol 1995; 16: 155–65.



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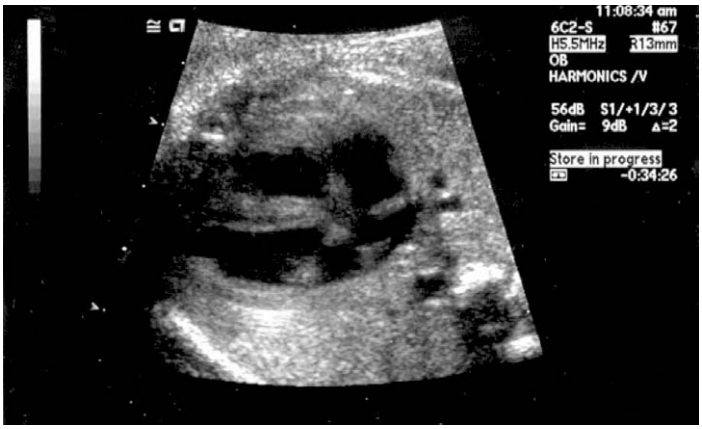


B

Figure 3-8. Four-chamber views of the fetal heart. A, Apical; B, transverse.

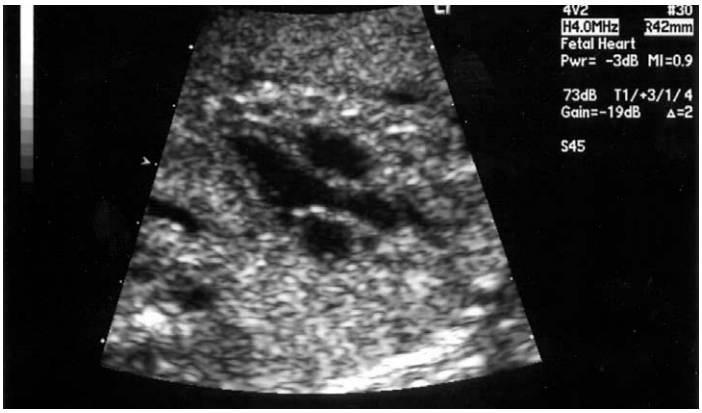


Figure 3-9. Left outflow tract: long axis view of the aorta.

best detection rates occur in examinations that include apical and subcostal four-chamber views and left and right outflow tract views as a part of the routine examination of the fetus at 18–22 weeks' gestation. The four-chamber view (Figure 3-8) is of great importance and has a 92% sensitivity, a 99.7% specificity, a 95.8% positive, and a 99.4% negative predictive value in the detection of congenital heart disease (Copel et al., 1987). A more detailed examination of the fetal heart requires additional

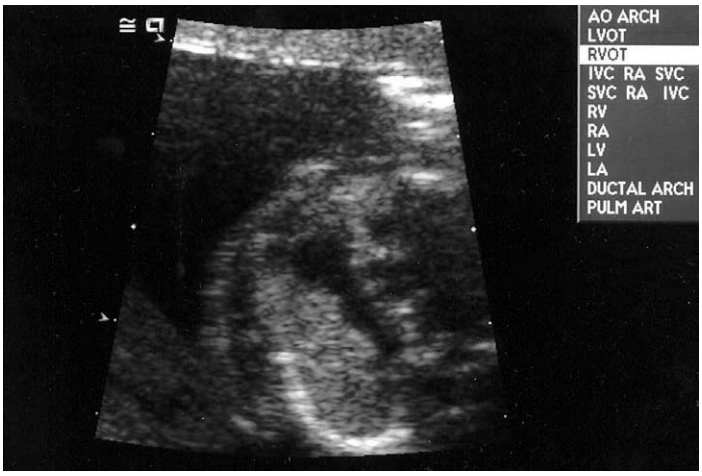
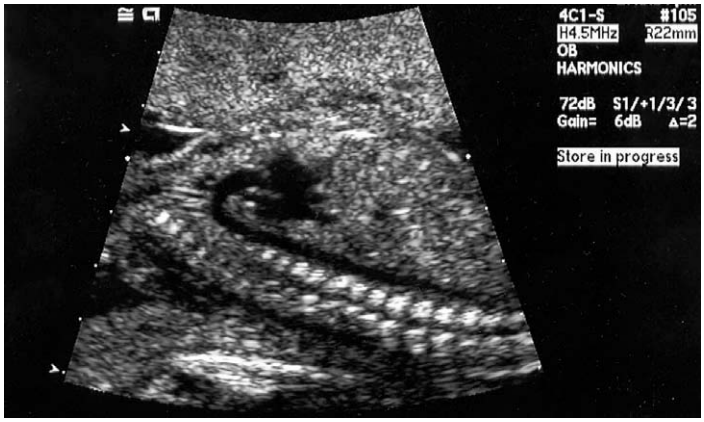


Figure 3-10. Right ventricle outflow tract: long axis view of the pulmonary artery.



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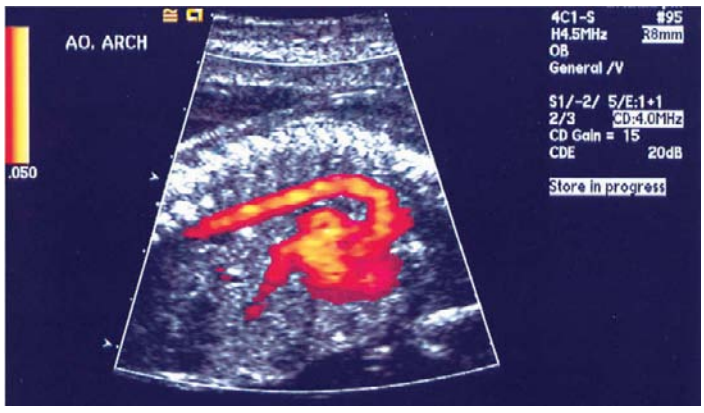


B

Figure 3-11. A, Aortic arch. B, Color Doppler view of the aortic arch.

long axis views of the ventricular outflow tracts (Figures 3-9 and 3-10), views of the aortic (Figure 3-11) and ductal (Figure 3-12) archs, short-axis views of the ventricles (Figure 3-13) and the great vessels (Figure 3-14), a view of the superior and inferior vena cava entering the right atrium (Figure 3-15), and a three-vessel view.

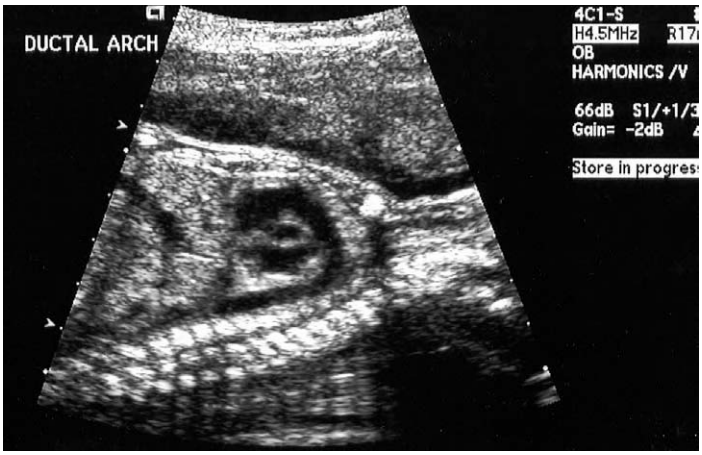


Figure 3-12. Ductal arch.

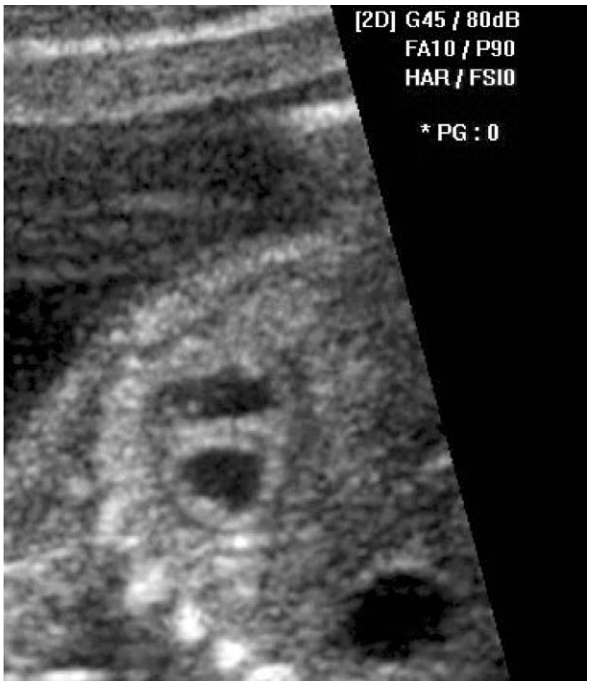


Figure 3-13. Short axis view of the ventricles.

The incidence of chromosomal abnormalities is approximately 35% in fetuses with congenital heart anomalies and genetic amniocentesis is strongly recommended. Approximately 50% of fetuses with Down's syndrome and almost 100% of fetuses with trisomy 13 and 18 exhibit cardiac abnormalities. The incidence of congenital heart disease is increased fivefold in women with insulin-dependent diabetes.

Ventricular Septal Defects

VSDs are the most common congenital heart abnormalities affecting 1–2% of all newborns and accounting for approximately 35% of all cardiac defects in the newborns. The intraventricular septum contains two distinct regions: the membranous and the muscular. The muscular

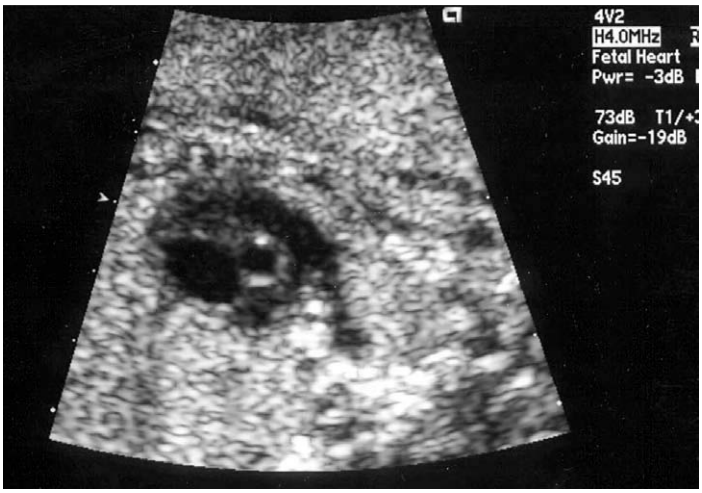


Figure 3-14. Short axis view of the great vessels.

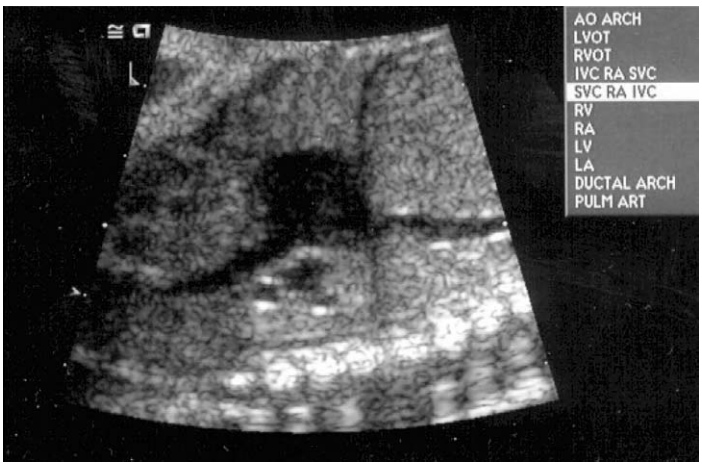
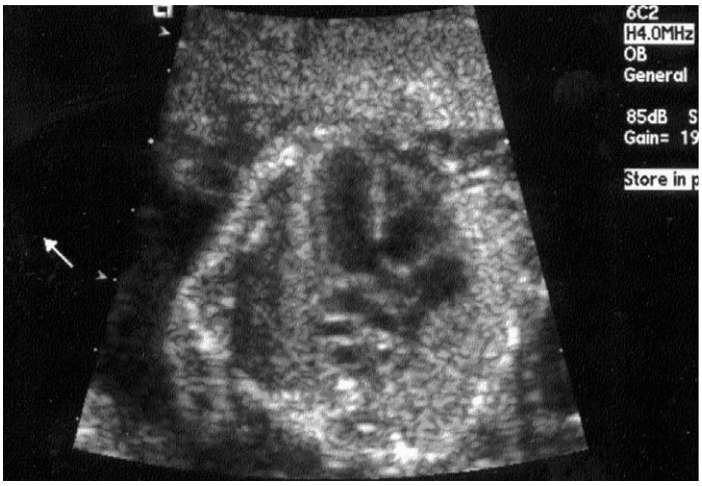


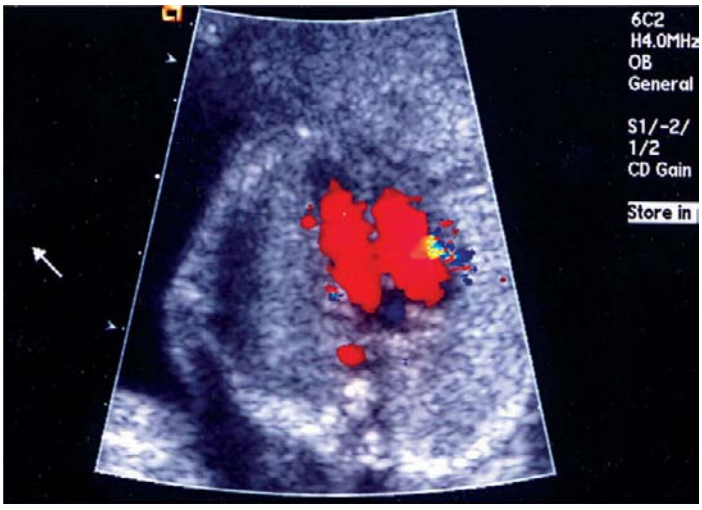
Figure 3-15. Right atrium and superior and inferior vena cava.

part of the intraventricular septum is formed by the apposition and fusion of the medial walls of the two primitive ventricles at about the 7th week of gestation. The membranous part of the septum is a small area near the base of the heart that results from the fusion of the septum dividing the conus cordis with the muscular portion of the intraventricular septum. Defects in the membranous area of the septum make up 80% of all VSDs and since most of them involve a portion of the muscular area they are described as perimembranous defects. Muscular defects account for the other 20% of VSDs and frequently are multiple. Up to 75% of all VSDs diagnosed during fetal life disappear spontaneously before birth and another 75% will close during the 1st year of life with the tendency to close being greater in muscular than in membranous defects.

The best approach to the ultrasound diagnosis of VSD is to take advantage of the improved axial resolution of ultrasound and apply the ultrasound beam perpendicular to the long axis of the septum to obtain a subcostal four-chamber view, a long axis view of the left



A



B

Figure 3-16. A, Ventricular septal defect. B, Color Doppler image of ventricular septal defect.

ventricular outflow tract, and a view of the short axis of the ventricles. The VSD will present as an anechoic area in the septum that can be demonstrated in more than one plane (Figure 3-16). Frequently it is possible to see an area of increased echogenicity in the tip of the intact portion of the septum. Frame by frame analysis of color Doppler through the area will identify unidirectional or bidirectional shunting and turbulence due to the shunting.

Prenatal diagnosis of VSD is inaccurate and has high false positive and false negative rates. The diagnosis early in gestation is more inaccurate and since a large number of these defects will close spontaneously, all early diagnosis should be followed by repeated assessment late in gestation. Isolated VSD in utero does not cause fetal morbidity and mortality and there is no indication for close fetal surveillance. Persistent defects require careful evaluation in the newborn period.

Atrial Septal Defects

Atrial septal defects (ASDs) involving the portion of the atrial septum below the foramen ovale (septum primum) are a component of atrioventricular septal defects (AVSDs). Septal defects above the foramen ovale (septum secundum) are relatively common and correspond to about 10% of all cardiac congenital abnormalities but their prenatal diagnosis is extremely difficult and probably unnecessary, since they do not cause abnormalities of the fetal heart function.

Atrioventricular Septal Defects

AVSDs are a spectrum of cardiac anomalies that include abnormal development of the atrial and ventricular septa and the mitral and tricuspid valves. They are also known as endocardial cushion defects or atrioventricular canal defects. They are classified as complete, partial, and intermediate. In the complete form, there is a large septal defect involving both the atrial and ventricular septa and a single atrioventricular valve composed of five leaflets. In the partial form of AVSD, the mitral and tricuspid orifices are separate, ASDs and VSDs are present, and the mitral annulus is displaced apically so that the mitral and tricuspid valves appear inserted at the same septal level. The intermediate type of AVSD is infrequent and similar to the complete form but the common atrioventricular valve is divided into separate mitral and tricuspid components. AVSDs are found in approximately 40% of fetuses with Down's syndrome.

The embryologic development of the atrioventricular

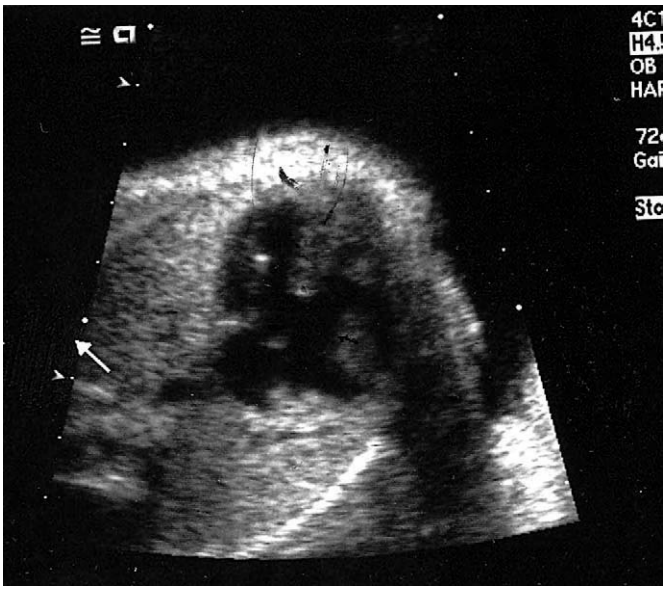


Figure 3-17. Atrioventricular canal: large ventricular and atrial septal defects. A common atrium is present. The ventricles and the atria are separated by two large floppy valves. There is an echogenic focus in the left ventricle.

canal depends on the proliferation of four endocardial cushions and the conus cushion that occurs between the 27th and 37th days of gestation. By day 33, two of the endocardial cushions fuse resulting in a mitral and a tricuspid orifice. Closure of the atrial and ventricular septa and formation of the mitral and tricuspid leaflets complete the process.

Most AVSDs are large defects and can be easily recognized from an apical or subcostal four-chamber view. Typically they appear like a single large atrial cavity separated from the ventricles by a large single valve (Figure 3-17). A large interventricular septal defect is readily apparent particularly in the subcostal view. Color Doppler will demonstrate the communication between the four chambers and regurgitation of the common valve.

Most complete AVSDs require surgical treatment within 1–2 years of age. The repair includes closure of the interatrial and interventricular communications using a single or a double patch and construction of two separate atrioventricular valves. Long-term survival after surgery is 80% at 10 years.

Hypoplastic Left Heart

HLHS is a condition characterized by underdevelopment of the left side of the heart. It encloses several degrees of hypoplasia of the aorta, aortic valve, mitral valve, left atrium, and left ventricle. The incidence of this anomaly is estimated to be 10–15% of all congenital cardiac anomalies. The etiology is unknown. Its risk of recurrence is only 0.5%. However, some investigators have suggested the possibility of an autosomal recessive inheritance in some cases, with a recurrence risk of approximately 25%.

In fetuses with HLHS the ascending aorta is usually hypoplastic, and in as many as 80% of the cases aortic coarctation is present. When the aorta is hypoplastic, there is a diminished right to left shunt at the level of the atria, the left heart is nonfunctional, and the right heart maintains the systemic circulation through the ductus arteriosus. Therefore the onset of cardiac decompensation in newborns with HLHS is delayed until several hours after birth when the ductus starts to close.

The prenatal diagnosis of HLHS relies on ultrasound, Doppler, color flow mapping, and M-mode echocardiography. HLHS alters the normal appearance of the four-chamber view of the heart (Figure 3-18). The demonstration of a dilated and hypertrophic right ventricle, atrium, and tricuspid valve, associated with hypoplasia of left heart structures and of the aortic arch, makes the diagnosis. In many occasions the left heart structures and the ascending aorta are hard to identify and the precise diagnosis of HLHS is not feasible. Adequate visualization of the cardiac structures is sometimes difficult after 30 weeks when increased amounts of bone calcium produce rib and vertebral shadowing. Hydrops is not a constant feature in fetuses with HLHS. Its presence should raise the suspicion of an additional obstructive or regurgitant lesion in the right heart.

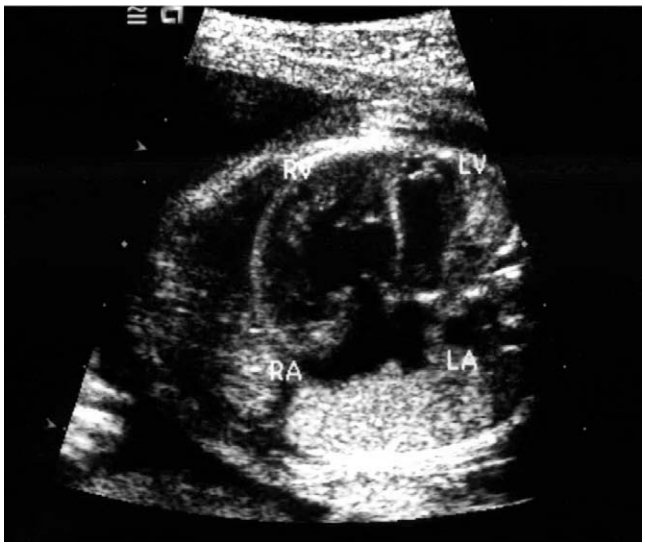


Figure 3-18. Hypoplastic left heart. Four-chamber view shows disproportion in ventricular size with the left ventricle smaller than the right in a fetus with hypoplastic left ventricle.

If the fetus with HLHS is delivered in a hospital without adequate resources for neonatal cardiac surgery, prostaglandin E1 should be used to prevent closure of the ductus until the infant is transferred. Palliative procedures include atrial septectomy and banding of the pulmonary artery with the creation of an aortopulmonary shunt. Surgical postnatal treatment of these neonates with the Norwood procedure or with cardiac transplantation has elevated mortality (Morris et al., 1990).

Hypoplasia of the Right Ventricle

Most cases of hypoplastic right heart result from the combination of pulmonary atresia with an intact interventricular septum—a condition that severely restricts the blood flow to the right ventricle and affects its ability to develop properly. In these cases the pulmonary artery is small and the pulmonary blood flow is maintained through the ductus arteriosus. The tricuspid valve is small and its leaflets are dysplastic, resulting in various degrees of regurgitation and right atrial enlargement. The left ventricle is often enlarged due to the increased blood volume reaching the left side of the heart through the foramen ovale. Hypoplastic right heart may also result from atresia of the tricuspid valve, resulting in lack of communication between the right atrium and ventricle.

The most important ultrasound finding in hypoplastic right heart is the presence of a disproportion between the right and left ventricular size due to the presence of a

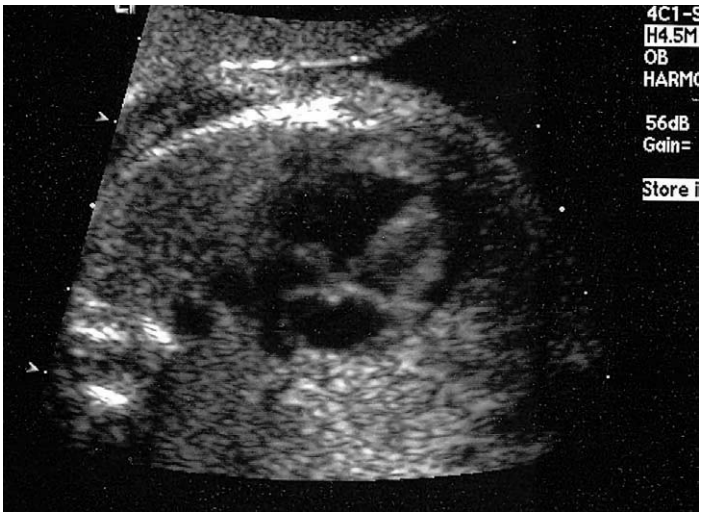


Figure 3-19. Hypoplastic right heart. Disproportion in ventricular size with the right ventricle smaller than the left ventricle in this patient with pulmonic stenosis and hypoplastic right heart.

small right ventricle (Figure 3-19). This is readily apparent in apical or subcostal four-chamber views of the fetal heart. Sometimes the right ventricle is so small that it is difficult to identify and the condition may be confused with a univentricular heart. Color Doppler is useful in this situation to visualize the small right ventricular chamber. Once the small right ventricle is identified, the next step is the study of the pulmonary artery and the tricuspid valve. The differentiation between pulmonary atresia with intact septum and tricuspid atresia as cause of the hypoplastic right heart is based on the absence of blood flow through the tricuspid valve in cases of atresia, but the two entities share many similar features and are difficult to differentiate in utero.

In hypoplastic right heart the pulmonary circulation is maintained by the ductus arteriosus and neonatal treatment with prostaglandin E1 is necessary to keep the ductus open until surgery is performed. Different types of surgery are available depending on the characteristics of the abnormality. The surgical results are continuously improving but long-term survival still remains relatively low.

Aortic Coarctation

Coarctation of the aorta is a narrowing of the aortic lumen that varies in severity from a slight narrowing to complete interruption of the aortic arch. This condition is found in approximately 6% of all fetuses with congenital heart disease and in one-third of the cases it is an isolated abnormality. In the other two-thirds of cases it is associated with other cardiovascular anomalies, particularly bicuspid aortic valve, or with gastrointestinal defects.

The prenatal diagnosis of aortic coarctation is difficult because in most cases the ultrasound appearance of the aortic arch is normal. The most common finding is a discrepancy in the size of the ventricles, with the right ventricle appearing slightly larger than the left. Another clue to the presence of coarctation is a pulmonary artery width larger than the ascending aorta. In the study of Hornberger et al. (1994), the mean right-to-left ventricular diameter ratio was 1.69 ± 0.16 compared to 1.19 ± 0.08 in normal fetuses and the pulmonary artery to ascending aorta diameter ratio was 1.61 ± 0.35 in cases of coarctation compared to 1.18 ± 0.06 in normal fetuses. The same investigators found that the ratio of the descending to the ascending aorta diameter was greater than normal due to the relatively small size of the ascending aorta and to poststenotic dilatation of the descending aorta. The best views to appreciate the discrepancy in ventricular size and the difference in size of the great vessels are the four-chamber view and the short-axis view of the ventricles and the great vessels. To compare the diameter of ascending and descending aorta, the best view is a sagittal view of the aortic arch. Color Doppler may be useful to visualize high-velocity areas of turbulence before or after the coarctation.

Prenatal diagnosis of aortic coarctation is important because it will make possible early institution of medical or surgical treatment that could be lifesaving for infants with severe forms of this condition. Unfortunately, prenatal diagnosis is not easy and requires a high index of suspicion.

Transposition of the Great Arteries

Transposition of the great arteries is a malformation in which the aorta originates in the right ventricle and the pulmonary artery originates in the left ventricle. Transposition is one of the so-called conotruncal abnormalities that are the leading cause of cyanotic heart disease in the newborn. It can occur with or without intact ventricular septum and with or without pulmonary stenosis. There are two types of transposition: complete or d-transposition that occurs in 80% of the cases and congenitally corrected or l-transposition that occurs in the other 20%. In both types the aorta is connected to the right ventricle and the pulmonary artery is connected to the left ventricle but in the congenitally corrected transposition, the left ventricle is in the right side and connected to the right atrium and the right ventricle is in the left side and connected to the left atrium. Transposition of the great vessels occurs in approximately 8% of all newborns with congenital heart disease.

Transposition of the great vessels is a lesion difficult to detect in utero and the key to its diagnosis is the presence of parallel great vessels that do not cross (Figure 3-20). A long-axis view of the left ventricle outflow tract will reveal that the vessel coming out of the left ventricle divides in two branches rather than becoming the ascending aorta.

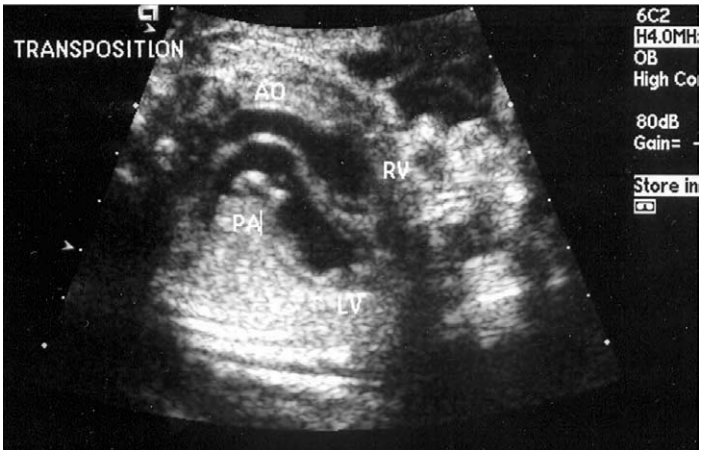


Figure 3-20. Transposition of the great vessels.

In the newborns with complete transposition the pulmonary and systemic circulations are parallel and mixing of arterial and venous blood will occur only if the ductus arteriosus remains open or a VSD is present. Newborns with congenitally corrected transposition are not cyanotic and are free of hemodynamic problems except for those resulting from associated malformations.

Tetralogy of Fallot

Tetralogy of Fallot is a complex malformation characterized by the presence of interventricular septal defect, overriding aorta, pulmonary stenosis, and right ventricular hypertrophy. The last feature is usually not present in the fetus because of the shunting provided by the ductus arteriosus and the foramen ovale and because some of the blood flow goes into the overriding aorta particularly if the pulmonary stenosis is severe. Tetralogy of Fallot is present in approximately 10% of all cases of neonatal congenital heart disease.

Tetralogy of Fallot is associated with chromosome abnormalities in approximately 25% of the cases, making determination of the fetal karyotype mandatory when this abnormality is detected. In particular, a 22q microdeletion is present in 11–34% of fetuses with tetralogy of Fallot. The abnormality is also a frequent component of genetic syndromes. Noncardiac-associated defects are present in 16% of the cases. The recurrence rate of tetralogy of Fallot is 2.5% if one sibling is affected and 8% if two are affected. If the mother is affected the risk for the offspring is 2.5%. If the father is affected the risk for his children is 1.5%.

The first ultrasound finding suggestive of the presence of tetralogy of Fallot is a left-side deviation of the axis of the heart (levorotation). This finding should be followed by a search for the three features of the Fallot's anomaly that are present during the fetal life, all of which can be detected in a careful ultrasound examination of the heart. The VSD is in the membranous area and can be seen in a subcostal four-chamber view and corroborated by color Doppler. From this view, a slight cephalad angulation of the ultrasound transducer will allow a clear definition of the overriding aorta. The degree of overriding is important and in cases of tetralogy of Fallot, more than 50% of the aorta should be above the left ventricle. If more than 50% of the aorta is above the right ventricle, there is strong possibility that the correct diagnosis is double-outlet right ventricle. Once the VSD and the overriding aorta have been seen, the next step is the study of the right outflow tract in both long- and short-axis views to determine the presence and severity of the pulmonary stenosis. Another frequent ultrasound finding in tetralogy of Fallot is dilatation of the aortic root. Normally the pulmonary artery is larger than the aorta but in fetuses with Fallot's tetralogy the aorta is larger than the pulmonary artery.

Surgical repair of the tetralogy of Fallot usually has excellent results. Depending on the characteristics of the lesion, complete repairs are performed when the newborns are between 2 and 6 months of age but in other cases the initial treatment is a systemic to pulmonary shunt followed by complete repair at 18–24 months of age. The prognosis of these patients depends mainly on the severity of the pulmonary stenosis and the excellent survival rate decreases markedly when pulmonary atresia or hypoplastic pulmonary artery branches are present.

Ebstein's Anomaly

Ebstein's anomaly is characterized by the apical displacement of the septal and posterior leaflets of the tricuspid valve, resulting in reduction in the size of the right ventricle and "atrialization" of the upper part of the right ventricle that behaves functionally as a part of the right atrium. These patients have severe tricuspid insufficiency which contributes to the enlargement of the right atria. Ebstein's abnormality is a rare congenital defect occurring in 1 in 20,000 live births. The recurrence risk of Ebstein's abnormality is 1% when one sibling is affected and 3% when two siblings are affected. The association of Ebstein's anomaly with chromosome abnormalities is not as strong as it is for other congenital cardiac abnormalities. Associated cardiac abnormalities include mainly pulmonary stenosis or atresia, ASD, and VSD. Noncardiac abnormalities are uncommon.

The ultrasound feature characteristic of Ebstein's anomaly is the presence of an enlarged right atrium (Figure 3-21). This finding must lead to a comparison of the level of the insertion of the septal leaflet of the tricuspid and mitral valves and appreciation of the apical displacement of the tricuspid valve. Fetuses with Ebstein's anomaly frequently have associated pulmonary artery valvular stenosis or atresia and exhibit signs of cardiac

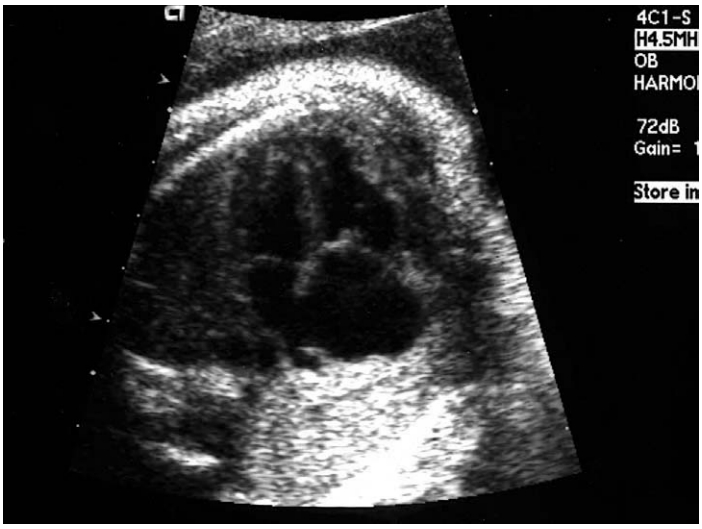


Figure 3-21. Ebstein abnormality.

dysfunction and rhythm abnormalities. Cardiomegaly and fetal hydrops are not uncommon, making the fetal prognosis extremely poor. However, once fetuses with Ebstein's anomaly are born, the drop in pulmonary vascular resistance causes a dramatic improvement in cardiac function with disappearance of the signs of congestive heart failure, making the neonatal prognosis better than the fetal.

Fetal Cardiomyopathies

Primary disorders of the heart muscle account for approximately 2% of congenital heart disease in newborns. The most common presentation is hypertrophic cardiomyopathy that in the majority of cases occurs in fetuses of diabetic mothers. A second form is dilated cardiomyopathy that is usually secondary to high-output failure due to severe fetal anemia (Rh alloimmunization) or volume overload (twin–twin transfusion, acardiac twin). A rare form of fetal cardiomyopathy is endocardial fibroelastosis that can be primary or secondary to obstructive lesions of the left side of the heart.

Hypertrophic cardiomyopathy in maternal insulin-dependent diabetes is usually apparent in the third trimester of pregnancy and occurs more frequently in macrosomic infants. The overall frequency varies and has been reported to complicate 33–84% of diabetic mothers. The characteristic feature of this condition is the marked hypertrophy of the interventricular septum that can be easily appreciated in a subcostal four-chamber view or by means of M-mode ultrasound. The cause of the asymmetric septal hypertrophy is not known, but it is suspected that it may result from the anabolic effect of excessive fetal insulin. The ventricular walls are usually thickened but not at the same extent as the interventricular septum. Hypertrophic cardiomyopathy is usually asymptomatic in the fetus of diabetic mothers but the stroke volume may be reduced, decreasing the fetal capacity to respond to situations requiring an increase in cardiac output. After birth the cardiomyopathy usually resolves spontaneously between 3 and 6 months of age. In approximately 10% of the cases, hypertrophic cardiomyopathy is familial and inherited in an autosomal dominant pattern. In a few cases the etiology is a chromosomal defect. In other few cases, the condition is a component of the Noonan's syndrome.

Septal or ventricular wall thickening is not a feature of dilated myocardiopathy secondary to fetal anemia or to volume overload. In these cases the chambers are mildly to moderately dilated and poor contractility of the heart is apparent. Similarly, ventricular wall thickening is not present when cardiomyopathy is secondary to myocardial damage such as in cases of fetal infection or in myocardial ischemia secondary to supraventricular tachycardia (SVT). Poor contractility of the heart can be appreciated qualitatively but it can be quantified by measuring the ventricular-shortening fraction by means of M-mode ultrasound. An M-mode tracing through the ventricles in short-axis view is used to measure the end-diastolic (EDD) and end-systolic (ESD) dimensions of the ventricles. Shortening fraction is the result of (EDD–ESD)/EDD and the normal values for the left and right ventricles are 0.3 and 0.25, respectively.

Endocardial fibroelastosis is a rare form of dilated cardiomyopathy caused by a abnormal deposition of elastic tissue in the endocardium. Characteristically, ultrasound examination demonstrates increased endocardial echogenicity. The heart is dilated, particularly the left ventricle, and hydrops fetalis is present.

The ultrasound diagnosis of fetal dilated cardiomyopathy requires accurate measurements of the thoracic circumference (TC) and the thoracic area (TA) to avoid the erroneous diagnosis of a dilated heart in situations where the heart is of normal size but the thorax is small. If the chest circumference is within normal limits for the gestational age, the next step is to measure the cardiac circumference (CC) and the cardiac area (CA) and calculate the CC/TC and CA/TA ratios which should be approximately 0.5 and 0.33, respectively. Values greater than 0.6 and 0.4 are suggestive of dilated cardiomyopathy. The next step will be to measure the thickness of the septum and the ventricular walls and compare the results with tables of norms for gestational age.

Fetal Arrhythmias

Fetal arrhythmias are irregularities of the cardiac rhythm not associated with uterine activity. Fetal arrhythmias are diagnosed in approximately 1–2% of all pregnancies. Sometimes the diagnosis is made incidentally during electronic monitoring or ultrasound examination of the fetus,

but the large majority of cases are discovered at the time of auscultation of the fetal heart during routine prenatal visits. Fortunately only about 5% of fetal arrhythmias are hemodynamically significant (Copel et al., 2000). Not all fetal arrhythmias are fetal in origin and there are maternal conditions that have to be considered when fetal arrhythmia is present. They are tachycardia, fever, intake of caffeine, and abnormal thyroid function.

The heart begins to beat in a synchronized fashion at about 21–22 days of intrauterine life. At this early gestational age, the heart contracts without any identifiable conducting system and the initial pacemaker is in the sinus venosus. After day 24, when the interatrial and interventricular septa are formed the cardiac rate increases, and it is primarily directed by the sinus node through the newly formed conductive system. The sinus node is identifiable by the 6th week and the atrioventricular node is formed by the 10th week. By the 16th week of gestational age, the conductive system of the heart is functionally mature.

Fetal arrhythmias should be investigated by fetal echocardiography. One of the components of this examination the M-mode ultrasound can establish the type of arrhythmia, identify pericardial effusions, and measure wall thickness, chamber size, and fractional shortening. Doppler is another part of the fetal echocardiogram that is useful to assess the adequacy of flow across the chambers and outflow tracts and to determine the degree of heart block.

Several classifications have been proposed for fetal arrhythmias but essentially the fetal heart rate (FHR) may be abnormally fast (tachycardia), abnormally slow (bradycardia), or irregular. The relative frequency of presentation of these abnormalities during a 10-year period was 255 cases (75.8%) of irregular rhythms, 46 cases (13.6%) of tachycardia, and 35 cases (10.4%) of bradycardia in the series of Copel et al. (2000).

Irregular rhythms originate in ectopic beats of atrial, nodal, or ventricular origin, occurring more than once in every 10 beats. In more than 80% of the cases the irregular fetal heart rhythm is due to atrial premature beats or premature atrial contractions (PACs). In the majority of cases, PACs resolve spontaneously during pregnancy or disappear during labor or after delivery. Structural cardiac abnormalities are found only in 3 of each 1000 fetuses with irregular heart rhythms. Less than 1% of fetuses with PACs develop SVT. Irregular rhythms due to the presence of PACs should be managed expectantly. They are benign and the possibility of developing a rapid rhythm is less than 1%. The majority of benign PACs disappear before labor.

Fetal tachycardia is diagnosed when there are recurrent episodes of rapid heart beat frequency greater than 200 beats per minute (bpm) lasting more than 10 seconds, detected on at least in two occasions, no more than 1 day apart. Tachycardia affects 0.4–0.6% of all pregnancies and corresponds to approximately 10% of all fetal arrhythmias. Most tachycardias are supraventricular in origin and include SVT, sinus tachycardia, Wolff–Parkinson–White syndrome, atrial fibrillation, and atrial flutter. Anatomic abnormalities, including cardiac tumors and Ebstein's malformation are present in approximately 5–10% of the cases. Ventricular tachycardia is rare. SVT is by far the most common fetal rapid arrhythmia and the one that has more clinical importance because persistent SVT can lead to heart failure and nonimmune hydrops fetalis (NIHF).

An adequate diagnosis and management of fetal tachycardia demands knowledge of the frequency of atrial and ventricular contractions. The best way to simultaneously determine the atrial and ventricular contraction rate is using M-mode in an apical four-chamber view, placing the transducer in a plane perpendicular to both chambers. If the ventricle and atrial contractions have a 1:1 ratio, the diagnosis is SVT. If the atrial rate is greater than the ventricular rate, the diagnosis is atrial flutter (atrial rate between 300 and 360 bpm) or atrial fibrillation (atrial rate between 400 and 500 bpm). If the ventricular rate is greater than the atrial rate, the diagnosis is ventricular tachycardia. The most frequent of these abnormalities is SVT. Atrial flutter and fibrillation are rare and ventricular tachycardia is seen exceptionally.

The management of SVT is complex and requires understanding of the electrophysiology of the abnormal rhythm and the fetal and maternal pharmacokinetics of the antiarrhythmic agents. The most common cause of SVTs is accessory pathways that bring back to the atrium electrical impulses that under normal circumstances are generated in the atrium and propagated through the atrioventricular node and the ventricle. This creates a circular movement of electrical energy between the atrium and the ventricle (re-entrant tachycardia). In approximately 5% of the cases, the cause of SVT is an ectopic atrial focus that takes over the pacemaker activity from the sinus node. It is not possible to distinguish between re-entrant and ectopic focus fetal tachycardia. In both cases, the FHR frequency is about 240 bpm with little or no variability and the runs of tachycardia vary in length from a few seconds to several hours. However, ectopic focus tachycardia should be suspected in cases of SVT unresponsive to pharmacologic therapy.

There are several management alternatives in cases of SVT depending on the characteristics of each case (Copel et al., 1997). If SVT is associated with hydrops, the condition must be considered a serious threat to the fetus and since the hydropic fetus usually has a poor response to the administration of antiarrhythmic drugs to the mother, the best option may be delivery by cesarean section if the fetus

is 34 weeks or more. If the fetus is less than 34 weeks, administration of antiarrhythmic drugs to the mother should be initiated promptly. If the immature fetus responds poorly to the administration of drugs to the mother, consideration should be given to direct intravascular administration of drugs to the fetus.

Treatment of the fetus with SVT in the absence of hydrops depends initially on the gestational age. If the fetus is at term, delivery is the best option. Cesarean section may be the procedure of choice in view of the inability to adequately monitor the fetal condition during labor. If the fetus is preterm, continuous monitoring of the FHR to assess the frequency and duration of the episodes of SVT is mandatory. If the fetus remains in SVT more than 50% of the time, administration of an antiarrhythmic drug to the mother should be initiated. If the episodes of SVT occupy less than 50% of the time, there are no signs of hydrops, the FHR is reassuring in the intervals without SVT, and expectant management is adequate.

There are a large number of antiarrhythmic agents useful in the treatment of SVT. The first drug of choice is digoxin which acts in the atrioventricular node by depressing conduction and prolonging the refractory period. Relatively high doses are used trying to maintain the maternal serum digoxin level between 2.0 and 2.5 ng/ml. Treatment may be started with IV digoxin using a 1.0 mg loading dose split in three doses of 0.5, 0.25, and 0.25 mg at 6-hour intervals. This is followed by oral maintenance, and frequently doses between 0.5 and 1.0 mg/day are required to maintain the serum concentration at an optimum level. Since digoxin absorption during pregnancy is erratic and the placental transfer is only about 40%, the maternal serum level should be tested periodically. Also, checking the maternal EKG for evidence of toxicity is warranted. If no fetal response is seen after achieving and maintaining high maternal serum levels of digoxin, it is necessary to add another drug to the treatment and perhaps the best choice is flecainide. This medication is a powerful inhibitor of the sodium channel which markedly inhibits intraventricular conduction. The initial dose of flecainide is 50 mg orally every 12 hours. If the response is inadequate, it may be increased to 100 mg orally every 12 hours. Other drugs useful in the treatment of SVT include procainamide, propanolol, quinidine, and amiodarone. The use of multiple agents is discouraged because their interactions and the complexity of their cardiac effects make their combined effect unpredictable and potentially dangerous. In our opinion, if the arrhythmia persists and hydrops worsens despite a well-controlled medical treatment with digoxin and flecainide, the patient should be delivered. Fetal administration of medications through cordocentesis has been reported. However, the risk involved in repeated procedures makes this approach less than ideal.

Fetal bradycardia is a rhythm of less than 100 bpm sustained for a period of at least 10 seconds. Most episodes of bradycardia in fetuses at term or close to term are transient and due to umbilical cord compression secondary to oligohydramnios, funic presentation, or abnormal positions of the cord. More prolonged episodes of fetal bradycardia are seen as a terminal episode in fetuses with profound hypoxia. Persistent bradycardia in women not in labor and otherwise having an uncomplicated pregnancy is usually an alarming finding during a prenatal office visit. Fortunately, this type of arrhythmia is present in only 1 out of 20,000 live-borns and only 5% of fetal arrhythmias are classified as bradycardia. The first step in the evaluation and management of these patients is to avoid rushing them to the operating room for an emergency cesarean delivery. They need a careful ultrasound examination of the heart because approximately 40% of these fetuses have anatomic malformations, the most common being atrioventricular canal defects and outflow vessel abnormalities. These fetuses usually develop hydrops and die in utero or shortly after birth. If the heart is anatomically normal, M mode should be used to obtain a simultaneous registry of the frequency of atrial and ventricular contractions because the most common cause of persistent fetal bradycardia is a congenital heart block secondary to maternal Sjogren's disease. In these cases maternal antibodies (SSA and SSB) destroy the fetal cardiac conductive system and the frequency of atrial contractions will be normal but a second- or third-degree atrioventricular block is present, resulting in a slower ventricular rate. The prognosis is better for fetuses with a heart rate of 50 bpm or above. Experiences with in utero treatment have been disappointing. Expectancy is the treatment of choice, and a good outcome is the most common result.

THORACIC ABNORMALITIES

Pleural Effusions

Pleural effusions in the fetus may be primary or a component of generalized fetal hydrops. Primary pleural effusion is a relatively rare prenatal finding with a frequency of 1 in 10,000 births. It was first described as an isolated ultrasonic abnormality in 1978 and its association with pulmonary hypoplasia was first reported in 1981. The etiology includes chylothorax, intrauterine viral infections, congenital pulmonary lymphangiectasia, and Turner's and Down's syndrome. Congenital chylothorax is by far the most common cause. This abnormality is associated with a high mortality rate estimated between 15 and 57% (Castillo et al., 1987, Adams et al., 1988).

The most important ultrasonic sign of pleural effusion is the finding of an echo-free area between the lungs, chest

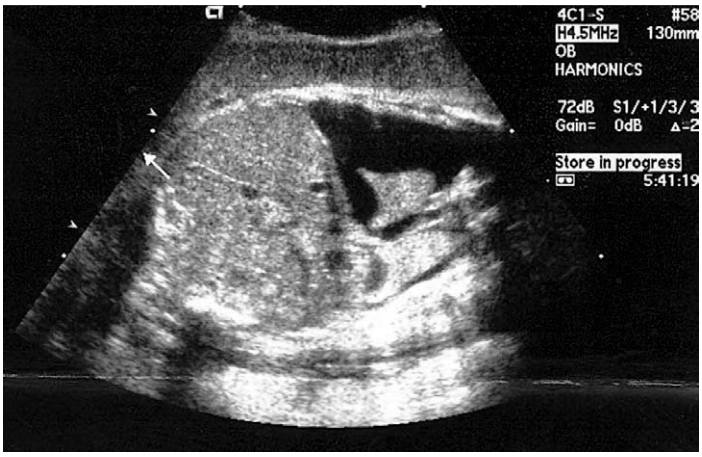


Figure 3-22. Pleural effusion.

wall, and diaphragm. Other findings include mediastinal shift and polyhydramnios. Approximately 67% of the cases are initially diagnosed in the third trimester of pregnancy. Male infants are affected more than twice as often as females. Right-sided effusions are more common than left, and a small number are bilateral (Figure 3-22). Chylothorax, the most common cause of pleural effusion, can be diagnosed before birth if fetal thoracentesis demonstrates a predominance of lymphocytes on the differential cell count of the fluid. In the newborn it can be diagnosed by demonstrating chylomicrons in the pleural fluid after feeding the baby. The most important differential diagnosis is with hydrops fetalis. In hydrops there are invariably other ultrasonic features including cutaneous edema, ascites, pericardial effusion, and placental enlargement. Because of the recognized association between congenital pleural effusion and Down's syndrome, amniocentesis should be performed to rule out chromosomal abnormalities.

Intrauterine thoracentesis for decompression is impractical, other than immediately before delivery, because the fluid reaccumulates in the fetus within 6–48 hours after aspiration. A better treatment is long-term drainage using pleuroamniotic shunts during the second trimester, in fetuses with normal chromosomes and no associated life-threatening abnormalities (Rodeck et al., 1988). This procedure has been successful and has prevented the development of pulmonary hypoplasia. In cases diagnosed late in pregnancy, expectant management is the best approach when the hydrothorax is small and unilateral. When the effusion is large and its duration unknown, it may be preferable to place a pleuroamniotic shunt and decompress the lungs for several days before delivery. In patients in early labor, drainage of the pleural infusion will facilitate neonatal resuscitation. Delivery should take place in a tertiary center where aggressive neonatal support can be offered.

The prognosis depends on the etiology, associated anomalies, and evolution of the lesion. Overall mortality is about 15% but the prognosis is worse when there is generalized hydrops. Survival of fetuses treated with thoracoamniotic shunts is much better and reaches 90% in those with isolated pleural effusions. Serial ultrasound should be performed to define persistence, resolution, or worsening of the lesion. Several studies have demonstrated spontaneous resolution of pleural effusion in utero. The presence of pulmonary hypoplasia and associated abnormalities are major adverse prognostic factors. Unilaterality and absence of hydrops are good prognostic signs.

Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a herniation of the abdominal contents into the fetal thorax through a diaphragmatic defect. CDH occurs in approximately 1 of every 2000–5000 births. It is a sporadic malformation with a risk of recurrence of 2%. A familial recurrence has also been reported. These familial cases have a higher male to female ratio, a high incidence of bilateral defects, and a lower incidence of associated life-threatening malformations than sporadic cases (Harrison et al., 1986). The etiology of CDH is unknown. Maternal ingestion of thalidomide, quinine, and antiepileptic drugs has been associated with sporadic cases.

The development of the diaphragm begins at approximately 3 weeks of intrauterine life and is mostly complete by the 9th week, when a well-defined septum dividing the thorax and abdomen can be identified. The formation of the diaphragm is achieved by the fusion of four developmental compartments: the ventral or septum transversus, the lateral aspects formed from muscular components of the body wall, the dorsal esophageal mesentery, and the pleuroperitoneal membrane. Diaphragmatic defects may result from a delayed fusion of the four compartments or from a primary diaphragmatic malformation. In either case, the diaphragmatic defect permits the migration of the abdominal contents into the thoracic cavity. The negative pressure created by fetal breathing movements will contribute to this process.

From a pathologic point of view, CDH includes five different types of defects: hernia of Bochdalek, hernia of the foramen of Morgagni, diaphragmatic eventration, agenesis of the diaphragm, and esophageal hiatal hernia. The prenatal diagnosis of CHD includes only the first three categories. Diaphragmatic agenesis and esophageal hiatal eventrations are rare entities with little relevance in prenatal diagnosis. Bochdalek hernias account for as many as 90% of the fetal diaphragmatic anomalies. They are secondary to a defect in the closure of the pleuroperitoneal membranes. They usually appear as a posterolateral defect, affecting the left hemithorax in 80% of the cases. The small bowel is involved in 90% of the cases, the stomach in

60%, the colon in 56% , and the spleen in 54%. The pancreas, liver, and kidneys may also be involved, but to a lesser extent. Hernias of the foramen of Morgagni account for approximately 2% of all diaphragmatic defects. They appear in the anteromedial retrosternal portion of the diaphragm, most commonly in the right hemithorax, and often lack a peritoneal covering. They are usually secondary to a maldevelopment of the septum transversus. The most common herniated organ is the liver, followed by the colon, the stomach, and the small bowel. Herniation into the pericardial sac also has been reported. Eventrations of the diaphragm correspond to about 5% of all cases of CDH. They are a sac of herniated viscera covered by abdominal peritoneum that elevates a weak aponeurotic diaphragm. Usually they involve the whole hemidiaphragm and are more common in the right side than in the left, although bilateral cases have also been reported.

Displacement of intra-abdominal contents into the thoracic compartment alters the normal development of the lungs. Fetal lung development is an active process that begins around 5–6 weeks and continues throughout gestation and after birth. In the normal fetus, the bronchial tree is completely developed and a full number of airways established by 16 weeks. The alveoli develop through a canalicular phase that ends at approximately 24 weeks and then go through a terminal sac period until the fetus reaches term. The alveolar development continues in the postnatal period until approximately 8 years of age. Normal expansion of the pulmonary tissue and fetal breathing movements are necessary to ensure normal lung growth.

The severity of pulmonary developmental abnormalities depends on when and to what extent viscera herniate into the chest. If the herniation occurs before the 16th week of intrauterine life, the number of bronchial divisions will be reduced. If the compression is persistent, the airway size will be diminished and the number and size of saccule, alveoli, and preacinar and intra-acinar vessels will be decreased. The potential for further growth and development after surgical decompression will depend on the time at which the insult was initiated.

Excluding lung hypoplasia and gut malrotation that are part of the pathophysiological sequence of the disease, CDH is associated to other abnormalities in 16–57% of the cases. Classically CDH has been associated with NTDs, omphalocele, and oral cleft. Other anomalies include the cardiac, gastrointestinal, skeletal, and genitourinary systems. Cardiac defects are present in 23% of patients. The most common malformations are tetralogy of Fallot and interventricular septal defects. Chromosomal abnormalities such as trisomies 13, 21, and 18 also occur in association with CDH. The Morgagni type of CDH has been associated with trisomy 21 in several reports. Familial cases of CDH have a lower incidence of associated malformations.

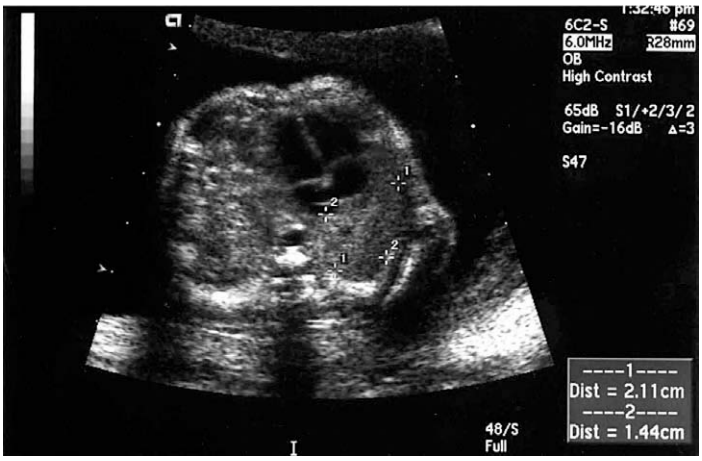


Figure 3-23. Diaphragmatic hernia. The heart is displaced toward the right side. Several loops of bowel can be identified on the left hemithorax.

The first clue in the ultrasound diagnosis of diaphragmatic hernia is an alteration in the position of the fetal heart that is deviated toward the right in left-side hernias and toward the left in right-side hernias. Left-sided CDH are easier to diagnose (Figure 3-23); the echo-free fluid stomach and small bowel contrast with the more echogenic lung tissue, and peristalsis may be observed. When the stomach is pushed toward the back, usually the liver is herniated. Liver herniation can be confirmed using color Doppler and seeing the portal vessels following an anomalous vertical path toward the chest. The stomach is not visualized in the abdomen and the abdominal circumference is smaller in relation to the head circumference and the femur length. The herniated bowel is easy to confuse with the lung but occasionally peristalsis can be seen. In a right-side hernia the liver is in the chest and the heart is deviated toward the left hemithorax. The portal vessels can be seen with color Doppler in the right hemithorax. The stomach is usually deviated toward the right and assumes a horizontal rather than a vertical position. CDH is a dynamic process and the abdominal herniated viscera move in and out of the fetal chest. In most cases the amniotic fluid is normal. The presence of polyhydramnios suggests the presence of gastrointestinal tract obstruction and has a strong association with pulmonary hypoplasia and poor neonatal prognosis.

The prenatal differential diagnosis between the three types of CDH is difficult. Diaphragmatic eventration has the same features as a Bochdalek hernia, but the abdominal circumference is usually normal. Morgagni hernias are anteriorly located and may be accompanied by pericardial and pleural effusions. The differential diagnosis of CDH includes other intrathoracic masses such as congenital cystic malformation of the lung, bronchogenic and enteric cysts, mediastinal cystic teratoma, pulmonary sequestration, bronchial atresia, and unilateral agenesis of the lung.

The prognosis of CDH is poor and has not changed much in the last years, despite advances in perinatal and postnatal care. The presence of associated anomalies is the most important prognostic factor. The association of CNS and cardiac anomalies has the worst prognosis. The presence of chromosomal abnormalities also compromises the prognosis and management. The mortality rate is also related to respiratory insufficiency due to varying degrees of lung hypoplasia. The reported survival rate varies widely. Some estimates are as low as 10.5%. Others report 50% survival for fetuses that survive beyond delivery. The increased survival rate seen in the last decade is probably due to better treatment of pulmonary hypoplasia using high-frequency oscillatory ventilation and extracorporeal membrane oxygenation (ECMO). More recently "gentle ventilation" limiting peak inflation pressures with permissive hypercapnia have increased survival rates up to 80% (Smith et al., 2005).

The most important prognostic index of pulmonary hypoplasia is the lung to head (L/H) ratio of the contralateral lung. In a left-side hernia the two largest anteroposterior and transverse diameters of the right lung posterior to the heart are multiplied and the product divided by the head circumference. The lung volume of the left lung will be used in cases of right diaphragmatic hernias. An L/H ratio of 1.4 or greater is associated with excellent neonatal prognosis and a ratio of 0.6 or below is usually associated with neonatal death.

Once the diagnosis of CDH has been made, a careful search for associated anomalies and a cytogenetic study are warranted. If the diagnosis is made before viability, termination of pregnancy may be offered to the parents. In viable fetuses, the best approach is expectant management. The timing and mode of delivery must not be altered. The delivery must take place in a tertiary center where a team of pediatric surgeons and neonatologists can offer immediate assistance. High-frequency ventilation has been found to show marked improvement versus conventional ventilation in these infants. Ideally they should be delivered in a facility with capability for ECMO. This technology has made the survival of newborns with severe forms of CDH possible. ECMO is not free of complications and the main problem associated with its use in the setting of CDH is intracranial bleeding with injury to the CNS.

Fetal surgery for CDH is evolving quickly. The initial attempts using open surgical techniques with hysterotomy and direct correction of the defect have been abandoned due to significant complications including preterm labor, premature rupture of the membranes (PROM), chorioamnionitis, and fetal death. The new techniques are endoscopic and consist of the placement of a device for the temporary occlusion of the fetal trachea. This procedure results in expansion of the lung tissue with displacement of the herniated viscera into the abdomen. The procedure is experimental and further evaluation of the risks versus the prognosis of a conservative approach will take place over the next few years.

Congenital Cystic Adenomatoid Malformation of the Lung

Congenital cystic adenomatoid malformation (CCAM) of the lungs is a histologically benign tumor of the fetal lung characterized by overgrowth of the terminal bronchioles. They are usually unilateral and are classified into macrocystic (type I), mixed (type II), and microcystic (type III). The macrocystic type appears in ultrasound examination as one or more intrathoracic cystic masses while in the microcystic variety the tumor appears solid and with markedly increased echogenicity (Figure 3-24). In the mixed type, small cystic areas are surrounded by echogenic tissue. Polyhydramnios is frequently present and abnormal displacement of the heart is often the first indication of the presence of the tumor.

As many as 20% of microcystic CCAM lesions regress spontaneously in utero. A few are complicated by the development of fetal hydrops and when this occurs the prognosis is poor. Maternal preeclampsia is a frequent complication when the fetus is hydropic (mirror syndrome). When the lesion is a single, large cyst the best approach is the placement of a thoracoamniotic shunt. Most CCAM lesions can be surgically resected in the neonatal period with excellent outcomes.

Newborns with CCAM are at significant risk for air entrapment in the tumor and sudden deterioration after delivery. Due to the risk for maternal and fetal complications, mothers having fetuses with CCAM should be under the care of maternal–fetal medicine specialists and delivered in tertiary centers with a neonatal intensive care unit, pediatric surgeons, and, ideally, ECMO facilities.

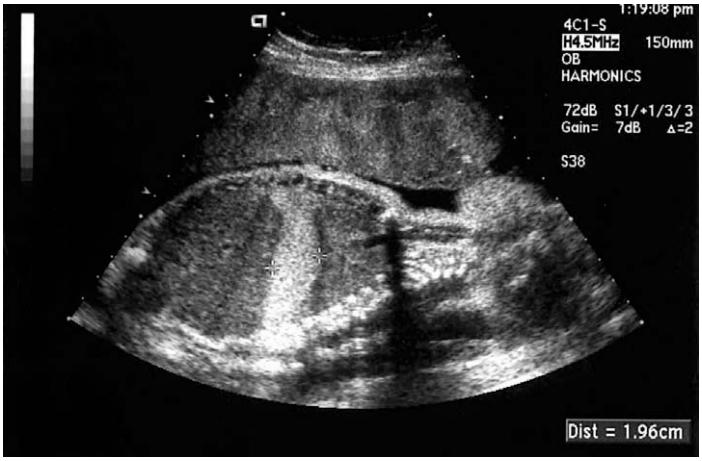


Figure 3-24. Congenital cystic adenomatoid malformation of the lungs.

Pulmonary Sequestration

Pulmonary sequestrations are masses of lung tissue that do not communicate with the bronchial tree and have a vascular supply originating in the thoracic or abdominal part of the descending aorta. Most pulmonary sequestrations are intralobar. About 25% of them are extralobar and have their own pleural membrane. Intralobar sequestrations are equally distributed between the two hemithoraxes while the less common extralobar sequestrations are mostly on the left side of the chest. Sequestrations are frequently associated with cardiac abnormalities, tracheoesophageal fistulas, diaphragmatic hernias, aneuploidy, and fetal hydrops.

The differential diagnosis between microcystic CCAM and pulmonary sequestration is difficult and can be made only by identification of the vascular supply of the sequestration by means of color Doppler. Both lesions are densely echogenic intrathoracic masses and both can cause alteration in the position of the heart.

The prognosis of pulmonary sequestration is good as long as fetal hydrops and marked changes in the position of the heart are not present. Many of them disappear spontaneously during pregnancy. Placement of a thoracoamniotic shunt may be indicated if the fetus develops pleural effusion. In the neonatal period, the main prognostic variable is the degree of pulmonary hypoplasia that may be severe and may require high-frequency oscillatory ventilation and ECMO. Once the newborn has been stabilized, thoracotomy and resection of the sequestration are accomplished. Because of the sophisticated neonatal care required, fetuses with pulmonary sequestration need to be delivered in tertiary care centers.

ABDOMINAL ABNORMALITIES

Gastroschisis

Gastroschisis is a herniation of the abdominal viscera through a paraumbilical defect of the anterior abdominal wall. The defect is usually located at the right side of the cord insertion and compromises the full thickness of the abdominal wall. There is no sac or membrane covering the herniated organs. The incidence of gastroschisis is approximately 1 per 12,000 live births. Gastroschisis appears to be a sporadic event with no genetic association or recurrence risks.

The herniated organ is usually the bowel and very rarely other structures are involved. Since there is no membrane covering the defect, the herniated bowel is continuously exposed to the irritating effect of the amniotic fluid which produces thickening and edema of the intestinal wall and at delivery the bowel may appear covered by an inflammatory exudates or "peel."

The pathophysiology of gastroschisis is controversial. The defect seems to result from an ischemic event at an early embryonic stage, either due to a disruption of the right omphalomesenteric artery or due to an alteration in the normal involution of the right umbilical vein. In contrast to omphalocele, gastroschisis is rarely associated with other congenital abnormalities. The most frequent associated anomalies are gastrointestinal in origin and are related to the same vascular embryologic problem that originates the gastroschisis. Intestinal atresia or stenosis are found in 7–30% of the cases. Cardiac malformations are found in 8% of the cases and sporadic cases of diaphragmatic hernia have been reported in fetuses with gastroschisis. Gastroschisis is also associated with IUGR (intrauterine growth restriction) and preterm labor.

The sonographic diagnosis of gastroschisis is usually made incidentally during a routine sonographic study, or in women referred because of a high alpha-fetoprotein titer. The diagnosis is based on the presence of a mass adjacent to the anterior abdominal wall (Figure 3-25). A differential diagnosis with omphalocele can be made in over 75% of the cases. This is important, since omphalocele has a much greater incidence of associated chromosomal and cardiac abnormalities and a worse prognosis. The findings that help to make a differential diagnosis with omphalocele are the presence of a normal cord insertion, the position of the defect on the right side of the cord insertion, the absence of a membrane covering the defect with the herniated organs floating in the amniotic fluid, and the presence of thickened loops of bowel that are matted together.

Other features that may help in the diagnosis of gastroschisis are the presence of polyhydramnios, which is not a constant finding, and the absence of multiple herniated organs. The sonographic appearance of the herniated bowel has been proposed as a prognostic factor.

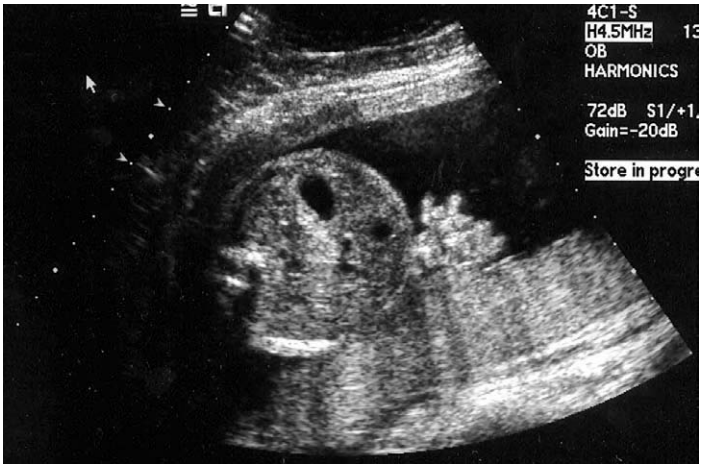


Figure 3-25. Gastroschisis. Loops of bowel are floating freely in the amniotic fluid in this transverse view of the fetal abdomen.

Thickening of the intestinal wall and small bowel dilatation are considered by some as indicators of poor neonatal outcome. However, other studies have shown no clinical advantage in the use of these sonographic signs. After the diagnosis of gastroschisis has been made, it is necessary to perform a comprehensive ultrasound examination to rule out the presence of other anomalies. A fetal echocardiogram and fetal karyotyping should also be performed.

In the management of gastroschisis, termination of pregnancy is an option that should be discussed when the diagnosis is made before viability. In the viable fetus, after the initial work-up, serial sonographic studies are indicated for the detection of complications such as fetal growth restriction, bowel obstruction, or polyhydramnios. Delivery should be performed once pulmonary maturity is confirmed to decrease the duration of exposure of the bowel to the extra-abdominal environment.

The mode of delivery for these fetuses has been a controversial issue over the past few years. Cesarean section was initially proposed as the ideal mode of delivery, because it was thought to decrease the risk of bowel trauma and contamination. However, several recent studies have failed to demonstrate any advantage of cesarean section over vaginal delivery. Therefore, cesarean section should be reserved for obstetrical indications. Most newborns with gastroschisis are operated on immediately after birth.

Omphalocele

Omphalocele is a midline defect of the anterior abdominal wall, characterized by herniation of the abdominal viscera into the base of the umbilical cord. Omphalocele is a defect of the umbilical ring, which results from a failure of the two lateral abdominal wall folds to migrate and fuse normally in the midline around the 3rd or 4th week of intrauterine life. The defect is characteristically located at the base of the umbilical cord, and may contain abdominal and sometimes thoracic structures. The herniated viscera are included in a sac, which is formed internally by the peritoneum and externally by Wharton's jelly and the amnion. The protruding organs are typically covered by a thin amnioperitoneal membrane. The incidence of omphalocele is approximately 1 in 4000 to 1 in 5000 live births. It occurs more frequently in males than in females with a ratio of 3:1. The recurrence risk for isolated omphalocele is less than 1%. The etiology of omphalocele is unknown. Most cases are sporadic. Chromosomal abnormalities, such as trisomy 13 and 18, are commonly associated with this defect. A familial occurrence with a sex X-linked or autosomal pattern of inheritance has also been reported.

Some investigators give physiopathologic significance to the presence or absence of hepatic tissue in the sac. For them, an omphalocele that only contains bowel represents a persistence of the primitive body stalk beyond 12 weeks of gestational age. In contrast, an omphalocele that contains liver suggests a primary failure of the body wall closure because the liver is never found outside the abdominal cavity throughout the embryonic development.

There are two genetic syndromes that classically have been associated with omphalocele. They are the pentalogy of Cantrell, which includes midline supraumbilical abdominal defects, a defect of the lower sternum, anomalies of the diaphragmatic pericardium and the anterior diaphragm, and cardiac anomalies, and the Beckwith–Wiedemann syndrome, which is characterized by macrosomia, macroglossia, visceromegaly, pancreatic hyperplasia, diaphragmatic hernia, and several degrees of omphalocele.

Associated anomalies are detected in 50–88% of the cases. The most common ones include cardiac malformations such as ectopia cordis, transposition of the great vessels, and VSDs; skeletal malformations, mainly scoliosis and xyphosis; gastrointestinal anomalies, including diaphragmatic hernia and ascites; genitourinary anomalies, such as renal dysplasia; and CNS anomalies, including holoprosencephaly, encephalocele, and cerebellar hypoplasia. Chromosomal abnormalities have been reported in as many as 43% of fetuses with omphalocele, the most common being trisomies 13, 18, 21, and Turner's syndrome. An abnormal karyotype has been strongly related to the presence of polyhydramnios or oligohydramnios and to the absence of liver in the herniated sac. Omphalocele has a strong association with high levels of maternal serum alpha-fetoprotein.

The ultrasonic diagnosis of omphalocele is made by the visualization of a mass in close proximity to the anterior abdominal wall (Figure 3-26). The defect may vary in size and has several characteristic features such as a central location, umbilical cord inserted into the sac, and presence of a membrane limiting the herniated contents. These findings are useful in making a differential diagnosis with gastroschisis. Spontaneous in utero rupture of an omphalocele has been reported and in these cases, a differential diagnosis with gastroschisis is difficult. Polyhydramnios is a frequent finding in patients with omphalocele.

The most important prognostic factor in omphalocele is the presence of associated anomalies. When they are present the mortality may be as high as 80%. Mortality is almost 100% in the presence of major cardiovascular malformations. Fetuses without associated malformations have a mortality of around 10%. The size of the omphalocele or the presence of ascites is not of prognostic importance. The presence of liver in the sac has been associated with normal fetal karyotype, while the absence of hepatic tissue has been associated with abnormal karyotype. However, the information concerning the prognosis of fetuses with or without liver in the omphalocele sac varies widely and is controversial.

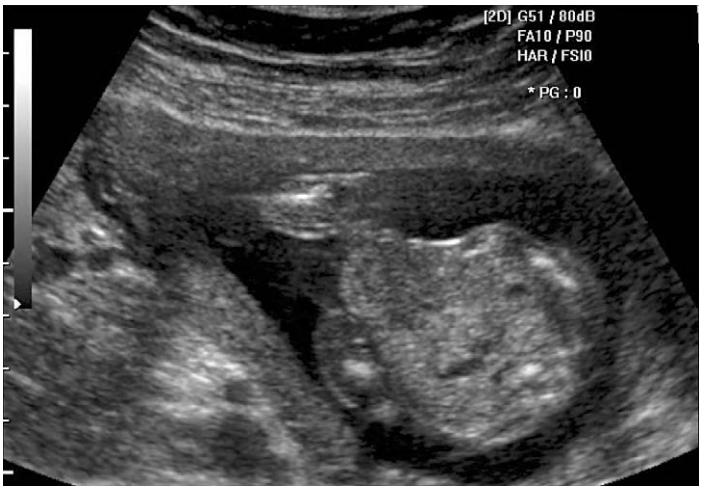


Figure 3-26. Omphalocele. A part of the fetal intestine has herniated through an anterior abdominal wall defect. A membrane covers the herniated organs. The umbilical vessels come out from the hernial sac.

Once the diagnosis of omphalocele is made, a comprehensive ultrasound should be performed in search of associated anomalies and the fetal karyotype should be determined. Since cardiac anomalies are the most frequent associated abnormalities, and possess a high prognostic value, an echocardiogram should always be performed on these fetuses.

With respect to antenatal management, termination of pregnancy is an option that should be discussed with the parents when the diagnosis is made before fetal viability. If the fetal karyotype is normal and no life-threatening associated abnormalities are seen, expectant management is indicated. Delivery should be in a tertiary care center and the pediatric surgeon and neonatologists should be notified and be ready for immediate postpartum evaluation and treatment.

The mode of delivery of these fetuses should not be altered by the presence of the defect. Several studies have demonstrated that vaginal delivery does not alter the prognosis. Therefore, cesarean section should only be performed for obstetrical reasons or in fetuses with herniated liver that may be damaged during vaginal delivery.

ABNORMALITIES OF THE URINARY TRACT

Structural abnormalities of the urinary tract are a common finding in the ultrasound examination of the fetus. They encompass a group of entities with varied clinical, sonographic, and pathological manifestations. The disorders most commonly found are as follows:

1. Fetal hydronephrosis
2. Obstructive uropathy
3. Unilateral or bilateral multicystic kidney dysplasia.
4. Infantile polycystic kidney disease
5. Adult polycystic kidneys.

Fetal Hydronephrosis

Fetal hydronephrosis is an abnormal distention of the urinary collecting system that may be unilateral or bilateral. This term includes conditions causing partial or incomplete obstruction of the urine flow and more severe lesions causing complete urinary obstruction. The fundamental distinction between complete and partial urinary obstruction is the amniotic fluid volume. Complete obstructions are characterized by severe oligohydramnios while partial obstructions are associated with normal fluid volume.

Unilateral or bilateral dilatation of the urinary tract is a common finding during a fetal ultrasound. A review of the ultrasound records of 20,049 women (Feldman et al., 2001) revealed 393 cases of hydronephrosis (1.9%) that was unilateral in approximately two-thirds of the cases. A similar incidence (2%) was found by Odibo et al. (2004) in a review of 7416 women. The relatively large frequency of this ultrasound finding makes it a common source of parental anxiety and a frequent cause of excessive utilization of medical resources.

The traditional method to evaluate the severity of fetal hydronephrosis is the measurement of the anteroposterior diameter of the renal pelves. Unfortunately, there are differences in the thresholds used by different investigators. A commonly used classification is by Mandell (1991) and is based on gestational age and AP diameter of the pelvis. Between 15 and 20 weeks, hydronephrosis may be mild (between 4 and 7 mm), moderate (between 7 and 10 mm), or severe (more than 10 mm). Between 20 and 30 weeks, hydronephrosis may be mild (5–8 mm), moderate (9–15 mm), or severe (>15 mm). After 30 weeks, hydronephrosis may be mild (7–9 mm), moderate (10–15 mm), or severe (>16 mm). The Society for Fetal Urology has adopted a definition that includes, in addition to the size of the renal pelvis, the presence of caliceal dilatation and the thickening of the renal parenchyma. Grade I is renal pelvis dilatation only, grade II renal pelvis dilatation and caliceal dilatation of a few, not all, calices, grade III renal pelvis dilatation and dilatation of all calices, and grade IV caliceal dilatation with renal parenchymal thinning (Fernbach et al., 1993).

The causes of fetal hydronephrosis differ with the severity of the problem. Mild pelvic dilatations may be physiological and due to the effect of maternal hormones on the smooth muscle of the collecting system or to vesicoureteral reflux (VUR) while ureteropelvic junction (UPJ) obstruction, vesicoureteral junction obstruction, prune belly syndrome, double collection system, VUR,

BOX 3-2

Causes of fetal pyelectasis

Ureteropelvic junction obstruction	89%
Ureterovesical junction obstruction	12.7%
Posterior urethral valves	8.5%
Vesicoureteral reflux	6.3%
Prune belly syndrome	6.3%
Other causes	4.2%

ureterocele, and renal duplication are the prevalent causes when the dilatation is severe (Box 3-2).

With respect to neonatal prognosis, the work of Odibo et al. (2004) indicates that a renal pelvis anteroposterior diameter of less than 7 mm after 32 weeks is highly predictive (sensitivity and specificity of 87 and 85%, respectively) of normal neonatal renal function (Gloor et al., 2002). The implication of this work is that when mild pyelectasis (less than 7 mm) is found early in pregnancy the neonatal prognosis will be determined by the size of the renal pelvis in repeated ultrasound examination after 32 weeks. If the renal pelves diameter remain under 7 mm the prognosis is uniformly good. Cases with a diameter above 7 mm would benefit from pediatric urology consult and careful follow-up.

UPJ obstruction is the most common congenital malformation of the urinary tract, representing approximately 40% of all obstructive uropathies, and 20–50% of all urologic congenital anomalies are detected in utero. Its incidence has been estimated at 1 in 1258 liveborns. In the large majority of cases, this condition affects males and is unilateral. UPJ obstruction usually results from a partial mechanical interruption of the urinary tract at the junction of the renal pelvis and the ureter. Anatomical abnormalities such as adhesions, valves, and aberrant vessels have been described as causes of the obstruction. A peristaltic alteration of the ureter, secondary to an abnormality in the arrangement of the longitudinal muscular layers, has also been proposed as an etiologic factor.

UPJ is a unilateral defect in 70% of the cases, usually presenting on the left side. Severe bilateral involvement is rare, and even in those cases the compromise is asymmetric and not necessarily fatal. Characteristically the fetus with UPJ obstruction presents with pelvic and caliceal dilatation without megacystis and with normal amniotic fluid volume. The degree of pelvic and caliceal dilatation is variable but cases with clinical neonatal significance are usually those with an AP diameter of the pelvis > 1.0 cm and concurrent caliceal dilatation. Irreversible renal parenchymal damage is very unusual and, in general, this entity has a good outcome. Prenatal identification may benefit the neonate by the adoption of measures to avoid the development of recurrent urinary infection.

Associated anomalies of the urinary tract are seen in 27% of the cases of UPJ obstruction. These include VUR, ureteral duplication, meatal stenosis, hypospadia, contralateral renal agenesis, and lower urethral obstruction. Anomalies outside of the urinary system are seen in 19% of the cases and include Hirschsprung's disease, cardiovascular anomalies, NTDs, esophageal atresia, and congenital hip dislocation.

The most important factor in the follow-up of these patients is the amount of amniotic fluid. Oligohydramnios is a poor prognostic sign and suggests the possibility of contralateral renal agenesis or dysplasia. Bilateral UPJ is quite rare.

Ureterovesical joint (UVJ) obstruction is the second most common cause of obstructive uropathy accounting for about 23% of the cases. It is usually secondary to the presence of a megaureter, an ureterocele, or to a physiological dysfunction of the distal ureter. UVJ obstruction is usually unilateral and affects more males than females. The large majority of ureteroceles are associated with duplication of the urinary collecting system.

The sonographic diagnosis of UVJ requires the demonstration of a dilated ureter or megaureter. Normal ureters are rarely seen through ultrasound. However, when dilated, they may be visualized as tortuous, fluid-filled hypoechogenic structures that can be traced to the renal pelvis. This visualization is not always easy to make, and often it is incomplete. The typical sonographic findings are dilated renal pelves and calices, dilated ureter, normal size bladder, and normal amount of amniotic fluid. The lower part of the ureter is usually larger than the upper part and in cases of ureteroceles, there is a thin circular membrane ballooning inside the bladder. Usually a normal size bladder is visualized in cases of UVJ with megaureter.

Unilateral UVJ does not require any specific prenatal therapy. In bilateral UVJ frequent monitoring of the amniotic fluid volume is warranted and cases with normal amount of fluid should be managed expectantly. The development of oligohydramnios indicates that the obstruction has become complete and delivery or intervention will be necessary.

There is a mild association between unilateral or bilateral pyelectasis and aneuploidy (Benacerraf et al., 1990) particularly with Down's syndrome and for that reason pyelectasis is one of the markers of aneuploidy in the second trimester genetic ultrasound. The predictive value for Down's syndrome of isolated renal pyelectasis is low. The reader will find information about the positive and negative likelihood ratios for this marker in Chapter 2.

VUR is a common cause of mild and moderate fetal hydronephrosis. VUR occurs more frequently in female fetuses. The condition is familial in nature and frequently mother and siblings share the lesion. Under normal conditions, reflux from the bladder to the ureter is prevented

by a flap mechanism that is dependent on the length of the intravesical portion of the ureter. Alterations in this mechanism permit the reflux of urine from the bladder to the ureter, transmission of the bladder pressure to the kidneys, and maintenance of a residual volume in the bladder. Children with VUR are prone to develop urinary tract infections and when reflux is combined with infection, the possibility of infection and damage to the kidneys is significant. For this reason VUR is the most common etiology of end-stage renal disease and hypertension in children and young adults. It follows that antenatal diagnosis of fetal hydronephrosis is of significant importance because many of these fetuses will have VUR, and prophylactic antibiotic treatment to avoid infection and renal damage may be initiated in the neonatal period.

There are no characteristic features that allow the sonographic diagnosis of VUR. However, the diagnosis is possible using color Doppler and vesicocentesis to determine the presence of retrograde flow of urine into the ureter (Quintero et al., 1995b).

Obstructive Uropathy

The term obstructive uropathy refers to a group of conditions affecting the lower part of the urinary tract, causing complete obstruction of the urine flow, progressive retrograde dilatation of the anatomical structures above the obstruction, and irreversible renal damage. The most common conditions causing obstructive uropathy are posterior urethral valves (PUVs), urethral stricture, urethral agenesis, persistent cloaca with associated urethral agenesis or stenosis, and megacystis-microcolon-hypoperistalsis syndrome.

PUVs are a sporadic disorder that affects only male fetuses. They are membranous folds located in the posterior wall of the urethra that are classified as types I–III according to their localization and to their gross anatomic characteristics. Only types I and III have clinical relevance, type I being the most frequent. The obstruction of the lower urinary tract caused by PUV is followed by a progressive retrograde dilatation of the urinary tract. Depending on the severity and time of initiation of the obstruction megacystis, megaureter, hydronephrosis, and eventually renal dysplasia may develop. Associated anomalies of the urinary tract include duplication of the urethra, megalourethra, cryptorquidia, and hypospadias. The most common associated anomalies outside of the urinary tract are cardiovascular, scoliosis, skeletal anomalies of the lower extremities, and chromosomal abnormalities.

The sonographic diagnosis of PUV should be suspected in the presence of dilated bladder with a "key hole" which corresponds to a dilated proximal urethra, megaureter, hydronephrosis, bladder wall hypertrophy, and oligohydramnios (Figure 3-27). The prognosis for these fetuses depends on a series of factors: timing of the obstruction, severity of the process, associated anomalies, karyotype, and the most important, presence or absence of oligohydramnios. Abnormal karyotype has been found in 15–40% of fetuses with obstructive uropathy.

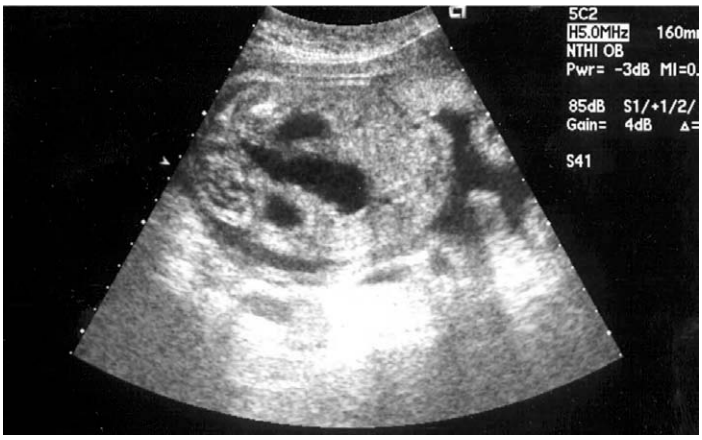


Figure 3-27. Obstructive uropathy due to posterior urethral valves. The "key hole" sign is apparent in the lower part of the bladder.

Prenatal surgical treatment should be reserved for cases with progressive and persistent oligohydramnios, preserved renal function, gestational age less than 30–32 weeks, normal karyotype, no sonographic evidence of renal dysplasia, and no associated life-threatening abnormalities. To evaluate renal function, urine aspiration by ultrasound-guided transabdominal vesicocentesis should be performed on three consecutive days to obtain fresh fetal urine and determine if renal function is adequate as evidenced by urinary sodium < 100 mmol/L, chloride < 90 mmol/L, calcium < 8 mg/dl, osmolarity < 200 mOsm/L, and beta-2 microglobulin < 6 mg/L.

The procedure most commonly used for the treatment of fetal PUV is the placement of a vesicoamniotic catheter under ultrasound guidance. Before shunt placement it is necessary to perform amnioinfusion to improve visualization and search for associated abnormalities. Cordocentesis is required to study the fetal karyotype since oligohydramnios precludes the utilization of amniotic fluid for this purpose. The device most commonly used is the Harrison's double pig-tail catheter. In cases with good renal function, shunting of the bladder will be associated with a significant decrease in neonatal mortality and in the incidence of renal failure during childhood and adolescence. However, shunt placement and function are not free of complications and shunt displacement, urinary ascites, premature rupture of membranes, and chorioamnionitis are relatively frequent complications.

One impressive advancement in endoscopic fetal surgery has been the development of percutaneous fetal cystoscopy with visualization of the inside of the bladder, identification of the PUV, and fulguration of the valves

with a laser beam (Quintero et al., 1995a). This procedure avoids the complications resulting from malfunctioning and migration of vesicoamniotic shunts, provides definite treatment for the condition, and should be the procedure of choice in most cases selected for surgical intervention.

Prune belly syndrome is another cause of fetal obstructive uropathy that is predominant in males (male to female ratio 18:1). These fetuses have marked distention of the bladder early in gestation, but postnatal evaluations show no evidence of urinary obstruction. Characteristically they have redundant wrinkled abdominal skin and absent or atrophic anterior abdominal muscles. A feature that helps in the differentiation with PUV is that the amniotic fluid may be decreased but is never completely absent as it is in fetus with PUV.

Obstructive uropathy in female fetuses usually has a poor prognosis. The most common causes are *urethral atresia, cloacal malformation,* and *megacystis-microcolon-hypoperistalsis syndrome*. Urethral atresia may also occur in males and is sonographically indistinguishable from PUV. The only way to make this differential diagnosis is by means of fetal cystoscopy. Cloacal malformation is the presence of a single outflow system for the genital, intestinal, and urinary tracts. It is a rare malformation that may mimic the ultrasound appearance of PUV and should be suspected when obstructive uropathy is found in a female fetus. The amniotic fluid volume may be decreased but is usually not completely absent. Fetal cystoscopy will demonstrate the presence of fat in the urine. Megacystis-microcolon-hypoperistalsis syndrome is an autosomal recessive condition more common in females (1:4 ratio). Similar to cloacal malformation the amniotic fluid volume is preserved. Fetal cystoscopy will reveal no apparent obstruction of the urethra. If the endoscope is moved from the bladder into the abdominal cavity, it will be possible to visualize the abnormal appearance of the fetal colon and make the prenatal diagnosis.

Multicystic Dysplastic Kidneys

Multicystic dysplastic kidneys (MDK), also known as Potter's II, is a condition characterized by the presence of renal cysts secondary to dilatation of the collecting tubules. It is considered to be the most common neonatal renal mass. The disorder is usually unilateral, but it can be bilateral or segmental. The approximate incidence is 1 per 10,000 live births but many believe that this figure is an underestimation and that the real incidence is around 1 in 1000. MDK may represent as much as 10% of all fetal uropathies. MDK usually is a sporadic condition but it may also be a part of a large number of genetic syndromes. The most common anomalies associated with MDK are malformations of the cardiovascular system, CNS, and gastrointestinal tract, and chromosomal aberrations. In contrast with Potter's type I and III, MDK is not associated with cystic changes in other organs. In some studies MDK has been associated with maternal diabetes mellitus.

The main alteration in MDK seems to be a disturbance in the differentiation of the nephrogenic tissue. Developmental failure of the mesonephric blastema to form nephrons and early obstructive uropathy are the two types of insults that may initiate this process. Some authors believe that all developmental failures are secondary to an obstructive process. A classification of MDK has been proposed on the basis of obstruction as the primary etiology and taking into consideration the macroscopic appearance of the kidneys. Two groups of patients are recognized:

1. Patients with classical Potter's type II. This abnormality is the result of pelvoinfundibular atresia and atresia of the proximal third of the ureter. The obstructive process occurs before 8–10 weeks. In these cases the cysts are randomly distributed and noncommunicating and grossly alter the normal architecture of the organ.
2. Hydronephrotic variety. This results from an obstructive event occurring after 10 weeks and leading to the same cystic changes observed in the Potter's type II form of disease, but with preservation of a normal renal pelvis and infundibulum. A differential diagnosis with obstructive uropathy is difficult to establish because the dilated renal pelvis communicates with the peripheral cysts, and the normal shape of the kidney is preserved. Determination of the concentration of urinary phosphates may be useful in these cases. In hydronephrosis urinary PO_4 is low (0.41–0.98 mg/dl) while it is higher (1.87–2.64 mg/dl) in MDK.

The sonographic diagnosis of MDK has been made as early as 18 weeks. The typical sonographic appearance is that of a paraspinal mass with cystic changes. Characteristically the cysts are noncommunicating, have different sizes and shapes, and are randomly distributed, resembling a "bunch of grapes" (Figure 3-28).

The prognosis depends on the severity of the process. When it is unilateral the prognosis depends on the functional integrity of the contralateral kidney and the presence of associated malformations (Eckoldt et al., 2004). Oligohydramnios is an important prognostic factor and its presence is associated with a poor prognosis. Up to 50% of cases of unilateral disease have associated anomalies of the urinary tract in the opposite side (Feldenberg and Siegel, 2000). The contralateral kidney may be affected by multicystic kidney disease (MKD) in 19%, renal agenesis in 11%, and UPJ obstruction in 7% of the cases. The condition is lethal when complicated with the first two of these defects.

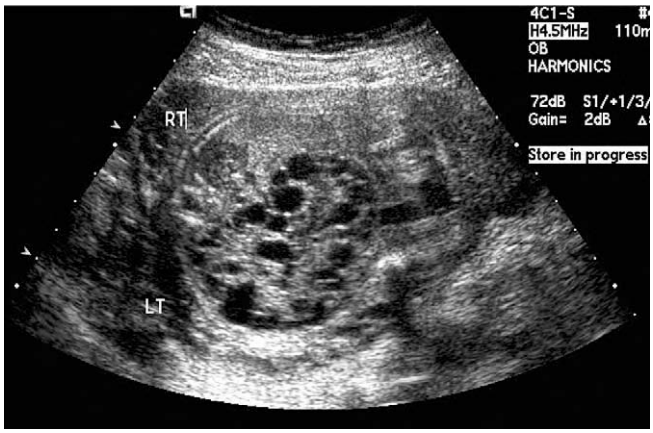


Figure 3-28. Multicystic dysplastic left kidney. Atrophic right kidney.

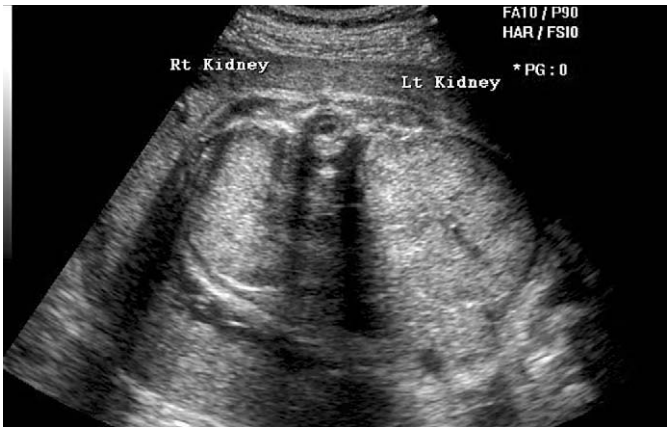


Figure 3-29. Infantile polycystic kidney disease.

After the diagnosis is made, a complete work-up including genetic diagnosis and level II ultrasound must be made. If bilateral MKD is diagnosed prior to viability, termination of pregnancy should be offered. If viability has been reached when the initial diagnosis is first made, a conservative approach should be followed. In cases of unilateral disease with absence of other congenital anomalies and a normal karyotype, standard obstetrical management should not be changed. In cases where MKD is associated with a contralateral obstructive process, delivery should take place as soon as lung maturity is confirmed.

Infantile Polycystic Kidney Disease

Infantile polycystic kidney disease (IPKD), also known as Potter's I or more recently as autosomal recessive polycystic kidney disease, is a condition characterized by dramatic symmetric and bilateral enlargement of the kidneys secondary to a primary defect in the collecting tubules. The incidence of this problem is 1 in 6000 to 1 in 60,000 births. IPKD is an autosomal recessive condition with a 25% recurrence risk. The disease is caused by mutations in the PKHD1 gene coding for fibrocystin, a 447-kD protein with a long extracellular portion, a transmembrane domain, and a short intracellular portion. Fibrocystin is abundant in the collecting ducts of the fetal kidneys and acts as a membrane receptor that most probably elicits intracellular responses essential to the normal formation and function of the renal tubules (Wilson, 2004). Alterations in fibrocystin structure and function are responsible for the formation of innumerable 1–2 mm cysts that are radially arranged, extending from the renal cortex to the calices. There is no proliferation of connective tissue, and the calices, papillae, and renal pelves are normal. Macroscopically the kidneys are enlarged but maintain their reniform configuration. Cystic changes are also present in the liver and there is portal and interlobular fibrosis with variable degrees of biliary duct hyperplasia. Fetuses with IPKD do not have an increased risk for other associated malformations. IPKD has been classified into perinatal, neonatal, infantile, and juvenile depending on the time of diagnosis. The most common presentation is the perinatal variety, which unfortunately has a high mortality rate secondary to pulmonary hypoplasia.

The sonographic diagnosis of IPKD has been made as early as 16 weeks of gestation. The diagnosis relies on the visualization of bilateral enlarged hyperechogenic kidneys that retain their reniform shape (Figure 3-29). The innumerable tubules provide a multitude of reflective interfaces that explain this characteristic sonographic appearance. Other sonographic diagnostic features include increase in the kidney to abdomen circumference ratio, oligohydramnios, and inability to visualize the bladder. Although several studies report early diagnosis, IPKD is usually first apparent late in gestation. Hence, fetuses at risk for the disease should be examined periodically throughout pregnancy. When a fetus is first diagnosed, sonographic renal examination of the parents and other members of the family is warranted.

The prognosis depends on the clinical variety of IPKD. As mentioned before, the most common presentation is the perinatal variety which guards a poor prognosis because it usually leads to stillbirth or to early neonatal death due to pulmonary hypoplasia. Other presentations lead to variable forms of renal insufficiency, with different prognosis. Termination of pregnancy is an option to be considered when the diagnosis of IPKD is made before fetal viability. When the diagnosis is made late in gestation the best course of action is expectant management. Rarely, enlarged kidneys can be a cause of dystocia.

Adult Polycystic Kidneys

Adult polycystic kidney disease (APKD), also known as Potter's III, or autosomal dominant polycystic kidney disease, is the most common form of polycystic kidney disease

and is a relatively frequent cause for hemodialysis in the adult life. The incidence is around 1 per each 1000 live-borns but it may be as high as 1 in 500 in autopsy material. There are two types. Type I accounts for approximately 90% of the cases and is caused by mutations in the PKD1 gene while type II is due to mutations in the PKD2 gene, and these are responsible for the production of two transmembrane proteins polycystine-1 and polycystine-2. These proteins have a key role in the regulation of the morphogenesis of the renal tubules and alterations in their structure cause severe disruption in this process (Wilson, 2004). The gene has a penetrance of 100% but its expressivity varies widely and the disease may manifest as a lethal neonatal condition or can be an incidental finding during the autopsy of an adult. The characteristic feature of APKD is the coexistence of cysts and normal tissue. The cystic structures correspond to dilated collecting tubules and to other portions of the nephron. The renal compromise is almost always bilateral, with cystic structures of different size. Liver compromise in the form of periportal fibrosis occurs, but less frequently than in IPKD. APKD also has been associated with cystic lesions in the pancreas, lungs, spleen, and testes.

APKD is the third most common cause of adult chronic renal failure. The disease is generally first diagnosed during the fourth decade of life and neonatal and infantile presentations are rare. It is also rarely seen during fetal life. The sonographical diagnosis of APKD has been made as early as 23 weeks. The most important diagnostic features include unilateral or bilateral kidney enlargement, seen in as much as 85% of the cases, increased renal echogenicity, and normal amounts of amniotic fluid.

There are no adequate prognostic guidelines when the disease is diagnosed in utero because APKD is a chronic disease that can become symptomatic over a wide range of time and has varied degrees of renal involvement. When the diagnosis is made before fetal viability, termination of pregnancy is an option that may be considered. If it is made after viability, the diagnosis of APKD should not alter standard obstetrical management.

SKELETAL ABNORMALITIES

Skeletal abnormalities are rare and many obstetricians will never see one during their professional lives. Achondroplasia and osteogenesis imperfecta (OI) are the most prevalent among these rare conditions.

Achondroplasia

Achondroplasia is the most common of the inherited short stature conditions. It is characterized by abnormal bone growth that results in rhizomelic shortening of arms and legs and by a large head with characteristic facial features. The intelligence and the life span of achondroplastic individuals is normal but they are at high risk for compression of the spinal cord, obesity, and sleep apnea.

In most cases, the ultrasound features of achondroplasia are apparent during the second trimester and are clearly seen in the third trimester. The long bones of arms and legs are very short, below the 5th percentile, the chest circumference is small, the abdomen is large, the third and fourth fingers are divergent (trident hand), and there is frontal bossing. Polyhydramnios is common. The diagnosis cannot be made before 22 weeks. When features consistent with achondroplasia are seen in the routine comprehensive ultrasound examination performed at 18–20 weeks' gestation, the most likely diagnosis is thanatophoric dwarfism.

Approximately 98% of individuals with achondroplasia have a G to A mutation at nucleotide 1138 in the fibroblast growth factor receptor 3 gene (FGFR3). FGFR3 is a transmembrane tyrosine kinase receptor that binds FGF and exerts a negative control on bone growth. The genetic defect results in the synthesis of activated FGFR3 and inhibition of bone growth. The genetic mutation responsible for achondroplasia is inherited in an autosomal dominant manner. However, in more than 80% of the cases of achondroplasia, the parents are of normal stature and the condition is the result of a de novo mutation. Most sporadic cases are exclusively inherited from the father and are associated with advanced paternal age.

The risk of having another child with achondroplasia is minimal if the parents are of normal stature. If one of the parents has the condition, the risk of having a child with achondroplasia is 50%. If both parents have the condition, the risk of having a child with heterozygous achondroplasia is 50% and the risk of having a child with homozygous achondroplasia, which is a lethal condition, is 50%. There is also a 25% probability that the child will be unaffected.

Prenatal diagnosis for cases in which one of both parents have achondroplasia is possible using fetal cells obtained by chorionic villus sampling (CVS) or by amniocentesis. A prerequisite for prenatal diagnosis is the identification of the genetic mutation in the affected parent or parents. Prenatal diagnosis can be strongly suggested by third trimester ultrasound and confirmed by DNA analysis of fetal cells.

No change in prenatal care is necessary for mothers carrying a fetus with achondroplasia. However, delivery by cesarean section is preferred since spinal cord compression may occur with manipulation of the neck at the time of delivery and the possibility of dystocia is high due to the large fetal head size.

Osteogenesis Imperfecta

The term osteogenesis imperfecta, or OI, encompasses a heterogeneous group of inheritable connective tissue disorders. Although fractures and bone deformation are the main clinical landmarks of the disease, OI is a generalized metabolic disorder associated with multiple systemic manifestations such as blue sclerae, impaired hearing, dentinogenesis imperfecta, hypermetabolism, platelet dysfunction, loose joints, and shortened limbs. The overall incidence of OI has been estimated at 1 in 20,000 to 1 in 60,000 live-born. There is no preferential distribution of OI by gender, race, or ethnic group.

OI is a disorder in the production of type I procollagen. OI was originally classified into four types, according to type of inheritance, radiographic findings, and clinical criteria. However, with advances in the understanding of the molecular basis of the disease, it is possible to recognize seven types. About 90% of individuals with OI types I, II, III, and IV have an identifiable mutation in either the COL1A1 or COL1A2 genes while these mutations are not present in individuals with OI types V, VI, and VII. The COL1A1 and COL1A2 genes encode the pro α1(I) and pro α2(I) chains of type I procollagen. Normally type I collagen has two pro α1(I) chains and a single α2 chain. The mutations responsible for OI types V and VI have not been identified. OI type VII is caused by a mutation in the short arm of chromosome 3. Fortunately, the two mildest forms, OI type I and OI type IV, account for the majority of cases of OI.

OI type I is the mildest and probably the most common type of the disease. It is inherited as an autosomal dominant trait and is characterized by the presence of blue sclerae, progressive presenile deafness, easy bruising, and skeleton fragility that may lead to deformity. Fractures decrease in frequency after puberty and increase again later on after age 50 in males and after menopause in females. It has been further subdivided into types IA and IB according to the absence or presence of dentinogenesis imperfecta, respectively. OI type II is the most severe form of the disease, being uniformly lethal for the fetus and the neonate. It is inherited in an autosomal dominant manner. The condition is readily identifiable at birth. These children are small for gestational age and have very poor bone mineralization which results in eggshell bone fragility and multiple in utero fractures. The skull is usually large for the body size and soft to palpation, the ribs are continuously beaded, and the long bones are short, bowed, and deformed by fractures. Approximately 60% of these infants die in the first day of life and survival beyond 1 year is extremely rare. OI type III is a severe form of the disease, although compatible with a full life span. It is characterized by progressive deformity of the long bones and spine that leads to a deformed phenotype. At birth the presence of multiple fractures is common. The face is characteristic, with a triangular appearance, and a skull relatively large for the trunk size. Growth deficiency is also a common feature. The blue sclerae of infancy, characteristic of the disease, become progressively pale with age. Growth is seriously impaired and adults are very short with adult stature that in many cases fails to reach 1 m. Intellect is normal. OI type IV is the most rare presentation of OI. It is inherited as an autosomal dominant disorder. Its clinical features include normal sclerae, bowing of long bones, joint hyperextensibility, and moderate short stature. Dentinogenesis imperfecta is common but is usually mild. Patients have variable ages at onset of fractures and occasionally may show spontaneous improvement with adolescence.

Initially patients with OI V, VI, and VII were classified as type III or type IV. They are characterized by short stature and fractures and absence of COL1A1 or COL1A2 mutations. Their sclerae are usually white. Type V exhibits hypertrophic callus formation at the site of fractures and calcification of the interosseous membrane between the ulna and the radius. Type VI is clinically similar to type IV but without the mutations and type VII exhibits rhizomelic shortening of the limbs.

The most characteristic finding in the ultrasound diagnosis of OI is the presence of one or several fractured or deformed long bones. The only type that can be diagnosed with accuracy by ultrasound before birth is type II because of the combination of deformed long bones and abnormal skull. The other types exhibit similar ultrasound features. Type II can be diagnosed as early as 15–17 weeks of gestation, and a normal sonogram at 18–20 weeks excludes the diagnosis of this lethal condition. The sonographic diagnosis relies on the demonstration of deformed long bones with poor echogenic properties and a compressible thin skull with high sonographic transparency. Other common ultrasonographic features include bone fractures, angulations, shortening, and localized thickening. Bowing of the limbs and hypoechogenicity of the skeleton are often not evident until after 24–32 weeks. Radiographic fetal studies may be helpful in a more precise evaluation of fetal limb growth and structure. Prenatal diagnosis of other types of OI has been reported although rarely. The differential diagnosis of OI includes hypophosphatasia as well as other forms of dwarfism.

There is no treatment for the fetus with OI. If the diagnosis is made before viability, termination of pregnancy is an alternative that may be considered. If detection is done after viability, the only specific obstetrical management issue is the mode of delivery. Cesarean section has been proposed as the ideal mode of delivery to avoid the risk for skull and/or body fractures.

Sacrococcygeal Teratoma

Sacrococcygeal teratoma (ST) is a fetal tumor arising from totipotential ectodermal, mesodermal, and endodermal embryonic cells of the coccyx. Fetal teratomas are the most common congenital neoplasms, and ST is their most common form. ST is rare. Its incidence is approximately 1 in 40,000 live births. Although the majority of these tumors occur sporadically, a familial occurrence has been reported in association with an autosomal dominant mode of transmission. Females are affected three to four times more than males.

ST originates from an area in the caudal edge of the bilaminar embryonic disk known as the primitive or Hensen's knot. Pathologically three grades have been described: benign, immature, and malignant. The first two are the most common varieties accounting for 87–93% of all cases of ST. The malignant variety is rarely seen prenatally. It has only been reported in 7–13% of cases of ST. Benign forms are usually derived from all three germ layers, neuroglia being the most common element.

The malignancy of the tumor has been related to the age at which the diagnosis is made. While a prenatal diagnosis ensures a low malignancy risk, a late postnatal diagnosis has a high correlation with the presence of malignant elements. The size and extension of the tumor has been also used as a form to classify ST. The disease has been divided into four types according to the internal or external components. Type I refers to an entirely external presentation of the tumor, while in type IV the tumor is entirely internal. In type II, there is an intrapelvic component and in type III an intra-abdominal extension.

The sonographic diagnosis of ST (Figure 3-30) is usually made when a patient is referred on the basis of a large-for-date uterus. The increased uterine size is secondary to the size of the mass or to the association with polyhydramnios that exists in 70% of the cases. The etiology of polyhydramnios is unclear, but its presence is not by itself a bad prognostic sign. The sonographic appearance of ST is that of a mass attached to the fetal rump with alternating cystic and solid components. Fragments of bone or other hyperechogenic images corresponding to dystrophic calcifications are also visualized. The identification of intrapelvic or intra-abdominal components of the teratoma is usually obvious in the sonographic study. Other less frequent sonographic findings are oligohydramnios and hydrops fetalis. The association with chromosomal abnormalities or other life-threatening congenital anomalies is rare. The differential diagnosis of ST must be made with chordoma, neurogenic tumor, lipoma, hemangioma, and malignant melanoma if the mass is predominantly solid. If the main component is cystic, myelomeningocele must be specifically excluded. Prognostic factors associated with a good outcome are external presentation of the mass, discovery after 30 weeks, and absence of placentomegaly, oligohydramnios, and hydrops.

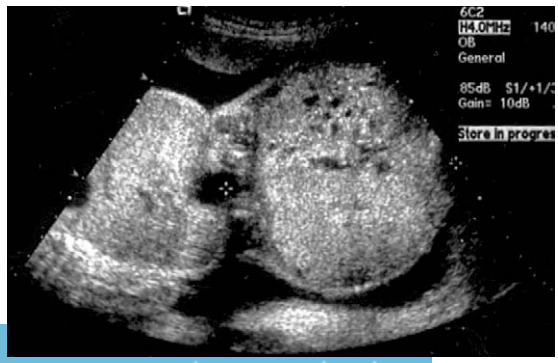


Figure 3-30. Sacrococcygeal teratoma.

The main risk to the fetus with ST is high-output heart failure. This problem is closely linked to the need to perfuse this large mass of tissue. Therefore, when the diagnosis is made before 32 weeks and there are signs of hemodynamic decompensation, it is necessary to consider the possibility of fetal surgery. The main purpose of the surgery is to interrupt the blood supply to the tumor to decrease the hemodynamic demands on the fetal heart. However, the procedure of choice has not been clearly defined. Interruption of the vascular supply to the tumor using laser photocoagulation or alcohol injection is one of the therapeutical possibilities. Attempts to reduce the tumor mass using radiofrequency ablation is another therapeutical option but involves substantial risk of thermal damage to pelvic structures. Because of the risk of avulsion with fatal fetal hemorrhage and/or dystocia, a cesarean section should be performed in cases with proven fetal lung maturity and a mass larger than 5 cm. Predominantly cystic masses may be aspirated, to facilitate delivery.

The delivery must take place in a tertiary center where a multidisciplinary team of a neonatologist and a pediatric surgeon are available for immediate evaluation. Neonatal surgical excision of the tumor is usually successful but stool and urinary incontinence are long-term disabilities that may affect as many as 25% of survivors.

MISCELLANEOUS SONOGRAPHIC ABNORMALITIES

Polyhydramnios

One of the abnormalities most commonly found during routine office ultrasound is polyhydramnios. It affects approximately 0.4–1.5% of all pregnancies. An amniotic fluid volume greater than 2000 ml is polyhydramnios, but since quantitative evaluation of the fluid volume is impractical the most commonly used definitions are by

ultrasound assessment. Clinically, the diagnosis may be suspected by finding a uterine size larger than expected for the gestational age, easy ballottement of the fetus, difficulty in defining fetal parts, and faded heart tones. The clinical diagnosis of polyhydramnios should always be confirmed by ultrasound. One definition is the finding of a pocket of fluid measuring 8 cm or more in vertical diameter. Another definition is an amniotic fluid index greater than 25 cm. Polyhydramnios is classified as acute when it occurs before 24 weeks, and chronic when the diagnosis is made in the third trimester.

The amniotic fluid volume depends on fetal and maternal factors. The alteration of any factor that regulates the fetomaternal equilibrium may induce an abnormal increase in fluid volume. The factors involved in this regulation are fetal swallowing, micturition, respiratory movements, uteroplacental blood flow, and the function of the maternal-membrane interface.

The conditions associated with polyhydramnios are multiple (Box 3-3). In approximately 65% of the cases polyhydramnios is idiopathic. In a study of 102 cases of polyhydramnios an etiology was found in only 16% of the mild cases, defined as a vertical amniotic fluid pocket greater than 8 cm but less than 12 cm. In severe cases, defined as a vertical pocket greater than 16 cm, an etiologic factor was identifiable in 91% of the cases (Carlson et al., 1990).

Maternal diabetes is the cause of approximately 14% of all cases of polyhydramnios. The etiology of polyhydramnios in diabetic patients is unknown. Fetal hyperglycemia with polyuria and increased osmolarity of the amniotic fluid secondary to high glucose concentration have been proposed.

BOX 3-3

Causes of polyhydramnios

Maternal	15%
■ Rh isoimmunization	
■ Diabetes	
Placental	<1%
■ Placental chorioangioma	
■ Circumvallate placenta syndrome	
Fetal	18%
■ Multiple pregnancy	
■ Fetal anomalies	
• CNS abnormalities	
• GI abnormalities	
• GU abnormalities	
• Skeletal malformations	
• Fetal tumors	
• Cardiac anomalies	
• Chromosomal defects	
• Genetic syndromes	
• Hematologic disorders	
• Fetal infections	
• Miscellaneous	
Idiopathic	65%

Fetal anomalies are responsible for approximately 12.0% of all the cases of polyhydramnios and that is the reason why this diagnosis demands a careful fetal anatomic survey with ultrasound. The most common lesions are defects of the CNS, gastrointestinal obstruction, skeletal malformations, fetal tumors, severe congenital heart disease, and persistent cardiac arrhythmias, chromosomal abnormalities and genetic syndromes, hematologic disorders, fetal infections, and nonimmune hydrops fetalis.

Multiple pregnancies account for approximately 5.0% of all cases of polyhydramnios. One special situation is when polyhydramnios results from the occurrence of twin–twin transfusion. In these cases the amniotic sac of the recipient twin has one or more fluid pockets measuring more than 8 cm in diameter while the donor sac has oligohydramnios with the largest pocket diameter being less than 2 cm. This has been called the "oligo-poly sequence" which is characteristic of this syndrome. The interested reader will find more information about this subject in the chapter on twins.

The use of prophylactic Rh(D) immune globulin has made isoimmunization an uncommon cause of polyhydramnios. Placental causes like hemangiomas are rare.

There is an increased fetal and maternal morbidity and mortality associated with polyhydramnios. Maternal complications include pregnancy-induced hypertension, preterm labor, premature rupture of membranes, and respiratory discomfort. Intrapartum complications include placental abruptio, cord prolapse, placental insufficiency, and an increased incidence of cesarean section. Postpartum hemorrhage is also more frequent in these patients.

Fetal morbidity and mortality is significant in cases of polyhydramnios and several studies report complications in between 16 and 69% of the cases. The major cause of fetal/neonatal mortality in polyhydramnios is congenital abnormalities incompatible with life. Morbidity is usually associated with minor abnormalities and with prematurity.

A genetic ultrasound should be performed in every patient with clinical suspicion of polyhydramnios. A fetal karyotype must be obtained using amniocentesis, cordocentesis, or placental biopsy. Fetal swallowing studies are indicated if tracheoesophageal fistula is suspected. Basic laboratory studies including maternal antibody screen, diabetic screening, and TORCH serology should be performed. If these evaluations are negative, the case should be considered as idiopathic.

Serial amniotic fluid decompression is the treatment of choice for severe polyhydramnios when a conservative management is intended. This method not only relieves maternal discomfort, but reduces excessive intrauterine

pressure that can induce preterm labor. An alternative treatment is the use of prostaglandin synthetase inhibitors. Indomethacin has been proven effective in reducing the amount of amniotic fluid. It probably acts by decreasing the fetal urinary output or by increasing the reabsorption of fluid via the fetal lungs. The recommended dosage is 2.2 mg/kg/day administered orally, every 6 hours. Gastrointestinal intolerance is common. This treatment should be suspended at 32 weeks of gestation to avoid neonatal hemodynamic complications. Periodic ultrasonographic surveillance during treatment in search for signs of ductal constriction such as tricuspid regurgitation is warranted.

Oligohydramnios

Oligohydramnios affects approximately 3.9% of all pregnancies. It has been defined as the absence of an amniotic fluid pocket, measuring less than 1 cm in vertical diameter. This definition encompasses only severe cases and it is becoming more popular to use an amniotic fluid index of less than 5 cm to define this condition.

In the majority of cases, oligohydramnios occurs in the setting of post-term pregnancy or is an expected event following PROM. In this chapter we are concerned with oligohydramnios when it is an unexpected finding in the course of a routine ultrasound examination. The most likely causes for this occurrence are undetected PROM, severe fetal growth retardation, fetal congenital abnormalities, especially those involving the urinary tract, and leaking of fluid following amniocentesis or chorionic villus biopsy (Box 3-4).

Occasionally patients confuse leaking of fluid with an increase in vaginal discharge caused by pregnancy and pose a diagnostic problem for the obstetrician who finds decreased fluid in a routine ultrasound examination. To compound the situation, verification of the presence of PROM by fern testing is equivocal during the second trimester and in some cases it is necessary to confirm the diagnosis by injecting 2 or 3 ml of indigo carmine in the amniotic cavity and verify the leakage of dye in the vagina. The prognosis for patients with PROM and oligohydramnios in the second trimester is guarded. The interested reader will find more information on this subject in the chapter on preterm rupture of membranes.

BOX 3-4

Causes of oligohydramnios

- Post-term pregnancy
- Premature rupture of membranes
- Fetal renal anomalies
  - Renal agenesis
  - Urethral obstruction
  - Prune belly syndrome
  - Bilateral multicystic dysplastic kidneys
- Nonrenal fetal abnormalities
  - Triploidy
  - Thanatophoric dwarfism
  - Thyroid gland agenesis
  - Skeletal dysplasias
  - Congenital heart block
  - Multiple anomalies
- Chronic abruptio
- Following amniocentesis or CVS

Oligohydramnios may be a sign of severe placental insufficiency. This usually happens with severe fetal growth restriction in the context of maternal conditions associated with placental insufficiency such as chronic hypertension, connective tissue disorders, severe preeclampsia, and chronic renal disease. The interested reader will find more about this subject in the chapter on fetal growth disorders.

Some fetal congenital abnormalities may be associated with oligohydramnios. Predominant among them are those affecting the urinary system, especially renal agenesis. Other conditions associated with decreased amniotic fluid are obstructive uropathy, prune belly syndrome, MDK, thanatophoric dwarfism, agenesis of the thyroid gland, skeletal dysplasias, congenital heart block, and multiple anomalies.

Iatrogenic leaking of amniotic fluid following genetic amniocentesis and more rarely CVS is a cause of oligohydramnios before 20 weeks. This complication affects less than 1% of patients undergoing these procedures. In the majority of cases the patient is aware that she is leaking fluid, and oligohydramnios can be documented on ultrasound examination. In the majority of cases leaking will stop and the fluid will return to normal with bed rest.

The history and physical examination will provide valuable information for the differential diagnosis. In most cases it will be necessary to perform amnioinfusion to improve ultrasound visualization and to confirm or rule out the possibility of PROM. Amnioinfusion in cases of oligohydramnios is not a simple procedure. The needle should be advanced slowly with continuous ultrasound visualization and when its tip has reached the interface between the fetus and the membranes, warmed saline solution should be infused. In the majority of cases 250–350 ml of saline solution will be necessary to achieve optimal ultrasound transmission and perform an adequate fetal examination. Normal fetuses will swallow the infused fluid and their bladder will be easily visualized with ultrasound in approximately 20 minutes. The bladder will not be seen in fetuses with renal agenesis. Before ending the amnioinfusion, 2–3 ml of indigo carmine is injected inside the amniotic sac. The patient is instructed to wear a tampon for a few hours following the procedure and observe it for evidence of blue discoloration. This finding will confirm the presence of PROM.

The prognosis for patients with oligohydramnios in the second trimester is poor because the two most common etiologies, preterm rupture of membranes and fetal congenital anomalies, are not amenable to successful treatments. Also, pulmonary hypoplasia occurs frequently in fetuses deprived of amniotic fluid for several weeks. The best outcomes are obtained in fetuses with severe IUGR that occasionally can be saved by early delivery and intensive neonatal care. Pulmonary hypoplasia is an almost uniformly lethal neonatal condition characterized by small, anatomically immature lungs, pulmonary hypertension, and surfactant deficiency. Pulmonary hypoplasia affects approximately 60% of fetuses with prolonged oligohydramnios before 28 weeks. The amniotic fluid pressure is abnormally low in patients with oligohydramnios and this causes a reversal of the normal amniotic-tracheal pressure gradient with the loss of pulmonary fluid and alveolar collapse. Several techniques have been described for the antenatal diagnosis of pulmonary hypoplasia with ultrasound. All of them are unreliable. The methods most commonly used are the thoracic to abdominal circumference ratio and the cardiothoracic ratio. The interested reader will find additional information in the chapter on premature rupture of membranes.

The option of termination of pregnancy should be offered to patients with lethal fetal abnormalities or with PROM before 20 weeks. One exception is patients with PROM following amniocentesis or CVS where recovery is the rule. In cases of traumatic ROM with persistent leakage and oligohydramnios, the application of an amniotic patch using a combination of platelets and cryoprecipitate (Quintero et al., 1999) may be indicated. For patients with PROM after fetal viability the management will be dictated by their gestational age as explained in the chapter on premature rupture of membranes. For patients with severe IUGR the best option may be delivery. However, expectant management with intensive fetal monitoring may be an option depending on their gestational age.

Nonimmune Fetalis Hydrops

Nonimmune hydrops fetalis, or NIHF, is defined as the accumulation of extracellular fluid in tissues and serous cavities, without evidence of circulating antibodies against red blood cell antigens. The diagnosis requires demonstration of fluid accumulation in at least two sites. The incidence of NIHF has been estimated to be around 1 in 1500 to 1 in 3500 live-born. Prior to the introduction of anti-D gamma globulin prophylaxis in 1960, 80% of cases of hydrops fetalis were secondary to Rh isoimmunization. With successful prevention of Rh disease, NIHF constitutes 75% of all cases of hydrops seen in developed countries.

BOX 3-5

Causes of nonimmunologic fetal hydrops

Cardiovascular	19.3%
Idiopathic	15.7%
Chromosomal	13.0%
Hygroma coli	10.7%
Hematologic	10.0%
Pulmonary	6.0%
Miscellaneous	4.7%
Malformation syndrome	4.3%
Hydrothorax/chylothorax	3.7%
Infection	2.7%
Urogenital	2.3%
Gastrointestinal	2.3%

From Hansman M, Gembruch U, Bald R. Management of the fetus with nonimmune hydrops. In: Harrison MR, Golbus MS, Filly RA, eds. The Unborn Patient. Philadelphia: WB Saunders Co., 1991: 248.

NIHF is the result of a heterogeneous group of conditions. Approximately 120 separate conditions have been reported in association with NIHF. With the introduction of new antenatal diagnostic techniques, the constant improvement of ultrasound imaging and detailed postnatal histopathologic examination, new etiologies are described frequently. Some of the numerous causes of NIHF are shown in Box 3-5.

Cardiovascular malformations, arrhythmias, and neoplasms are responsible for approximately 26% of all cases of NIHF. The common mechanism that leads to fetal hydrops is congestive heart failure. Fetal arrhythmias are responsive to treatment and have a reasonably good outcome, while cardiac malformations and neoplasms are associated with an extremely poor prognosis.

Chromosomal abnormalities are found in 10–16% of all cases of NIHF. The most frequent chromosomal anomalies are trisomy 21 and Turner's syndrome. Other less common abnormalities are trisomies 13, 16, and 18, triploidies, mosaicism, and unbalanced translocation. The underlying mechanisms responsible for the development of hydrops in these fetuses are cardiovascular anomalies, hypoalbuminemia, and lymphatic malformations.

The hematologic disorder most frequently associated with NIHF is alpha-thalassemia major with severe fetal anemia and high-output cardiac failure which has been reported in approximately 7–10% of cases of NIHF. Thalassemia is transmitted as an autosomal recessive trait and is more frequent in Southeast Asia, Mediterranean countries, and Central Africa. However, with increasing migration tendencies, this disease has become a worldwide health problem. The prenatal evaluation of patients of this geographical origin should include testing for red blood cell corpuscular volume and hemoglobin electrophoresis if this test is abnormal. If the thalassemia trait

is present in the mother, the husband should be tested, since the disease can only be present if both parents are carriers.

Approximately 2.0–5.0% of all cases of NIHF are secondary to infection. Several microorganisms can cause NIHF. Of all the PRATSCHEC agents (parvovirus, rubella, AIDS, toxoplasma, syphilis, CMV, herpes, echovirus, and coxsackievirus), only rubella and AIDS have not been reported in association with NIHF. Parvovirus B-19 is the most common viral infection associated with NIHF. The fetal hydrops is secondary to severe fetal anemia. Unlike other agents, parvovirus does not produce fetal malformations. CMV is also a common infectious etiology of NIHF. The major diagnostic criteria include intrauterine growth retardation, microcephaly, cerebral echogenic densities, a positive maternal IgM-specific titer for CMV, and ideally a positive viral culture from fetal blood or amniotic fluid.

Other less frequent causes of NIHF are skeletal dysplasias, fetal–maternal hemorrhage, pulmonary malformations, gastrointestinal anomalies, genitourinary anomalies, Mendelian syndromes, placental tumors, and lysosomal storage disorders. Despite thorough investigation as many as 15–30% of cases of NIHF have to be classified as idiopathic.

The ultrasound diagnosis of NIHF is simple (Figure 3-31). Common sonographic findings include polyhydramnios, skin edema greater than 5 mm in thickness, ascites, placental enlargement, pericardial or pleural effusions, and cardiomegaly. It is recommended not to diagnose NIHF when fluid accumulation is limited to one body cavity. However, since a unique fluid accumulation may be the first sign of developing NIHF, follow-up sonographic examination is warranted. Once the diagnosis has been made, a complete work-up should be performed. This should include a complete maternal health history including investigation of teratogenic or infectious exposures; a complete maternal blood work-up including blood group and typing, antinuclear antibody, glucose screen, hemoglobin electrophoresis, viral antibody titers, Kleihauer test, and glucose-6-phosphate dehydrogenase activity; a comprehensive or genetic fetal ultrasound examination, fetal ECHO, and cordocentesis for fetal karyotype, viral titers, blood count, blood gases, cultures, liver function, and metabolic testing.

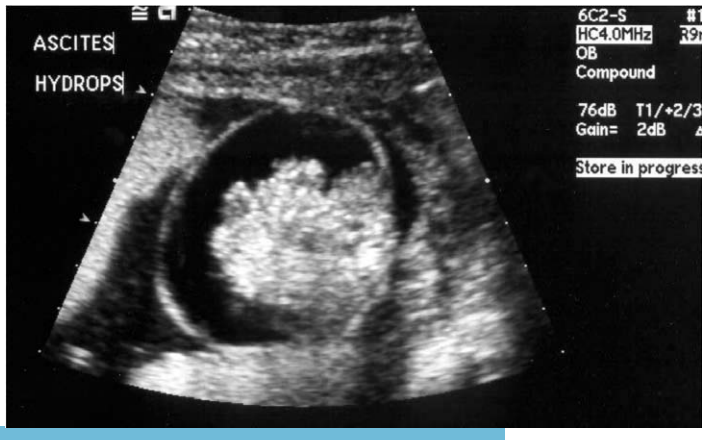


Figure 3-31. Transverse view of the abdomen in a fetus with nonimmune hydrops.

The prognosis for the fetus with NIHF is poor. The perinatal death rate is between 40 and 98%. The prognosis depends on the underlying cause of the hydrops. Anatomic malformations, found in approximately 40% of the cases, have the worst prognosis and indicate a lethal condition in virtually all cases. Preeclampsia, preterm labor, premature rupture of membranes, postpartum hemorrhage, and difficulty in removing the placenta are other factors associated with NIHF and contribute to the poor prognosis. The karyotype, severity of anemia, and amount and location of fluid collections are also important prognostic features. Only cases of CMV infection and cardiac arrhythmias without structural malformations have spontaneous resolution of the hydrops. The risk of recurrence is low unless the etiology is genetic.

The management of NIHF must be individualized and decisions should be made in conjunction with the parents. Termination of pregnancy is an option before fetal viability. In viable fetuses the management varies widely depending on the etiology and the prognosis. In cases with severe anatomical malformations or chromosomal anomalies, the management should be expectant. In contrast, fetuses with no anatomical anomalies and treatable problems such as tachyarrhythmia or parvovirus anemia should be aggressively managed. Amniocentesis has been used to remove excessive amniotic fluid, relieve maternal discomfort, and diminish the risk of premature labor. Fetal paracentesis and thoracentesis have also been used in selected cases to decrease the possibility of dystocia and to facilitate neonatal resuscitation. Other therapies that have been used are intraperitoneal injection of red blood cells or albumin, intrauterine transfusion to treat parvovirus-induced fetal anemia, and thoracoamniotic shunting in cases of pleural effusions.

ENVIRONMENTAL FETAL RISKS

Society in general and pregnant women individually are concerned about environmental effects during pregnancy. Patients frequently ask the obstetricians about the embryonic and fetal effects of radiation, alcohol, drugs, nutrients, and other potentially teratogenic agents. Obstetricians share the patient's concerns and are also deeply disturbed because of the widespread use of recreational drugs in our society and their effects on the pregnancy.

Diagnostic Radiation During Pregnancy

Fewer than 5 of each 1000 pregnant women are exposed to radiation during pregnancy. This happens because of the increased awareness of patients and physicians with respect to the fetal effects of radiation and because of the increased use of ultrasound as the diagnostic method of choice in many conditions that used to require radiological procedures. It is only occasionally that the obstetrician must counsel a patient who has had or is going to have radiological procedures during gestation and wants to know the fetal risks associated with those procedures.

The effects of x-ray on the fetus are highly variable and depend on multiple factors, the most important being gestational age at the time of exposure and amount of radiation received by the fetus. Gestational age is important because the chances of affecting the fetus are greater in early than in late pregnancy. In the first 14 days of gestation, radiation has an "all or none" effect on embryonic tissues and the outcome is pregnancy loss if the dose is high, more than 20 rads (0.2 Gy), or normal embryonic development when the dose is low. Particularly important seems to be the period of organogenesis, 2–7 weeks postconception, or 4–9 weeks from the last menstrual period, because ionizing radiation may interfere with organ development and cause malformations, but usually this does not occur if the embryonic exposure is less than 50 rads (0.5 Gy). The amount of radiation received by the fetus depends on the type of x-ray examination, the number of pictures taken, the type of equipment used, and the area of the body toward which the x-ray beam was directed. As shown in Table 3-2, the amount of radiation received by the fetus in the course of most routine diagnostic examinations rarely exceeds 5 rads (0.05 Gy) and is often less than 2 rads (0.02 Gy) (Hoffman et al., 1981). The possibility of adverse effects on the fetus at these radiation doses is minimal and the National Council on Radiation Protection and Measurements (1977) has indicated that an exposure of less than 5 rads (0.05 Gy) represents a minimal risk to the embryo.

Table 3-2. Amount of radiation received by the fetus in the course of several diagnostic procedures

Type of examination	Dose (rads per examination)	
	Mean	Range
Flat plate of the abdomen	0.144	0.024–1.416
X-ray of the pelvis	0.158	0.008–1.587
Intravenous pyelogram	0.448	0.024–3.069
Barium enema	0.574	0.005–9.218
Upper gastrointestinal series	0.091	0.001–1.228
Lumbar spine	0.068	0.002–2.901

From Hoffman D, Felton R, Cyr W. Effects of ionizing radiation on the developing embryo and fetus. A review. Rockville, MD: US Dept of Health and Human Sciences, Public Health Service, Food and Drug Administration, Bureau of Radiological Health, 1981, HHS Publication FDA 81–8170.

In counseling patients who have received radiation during pregnancy, it is important to know the precise gestational age at the time of the exposure to radiation, the type of radiation study, and the dose received by the embryo. The latter information is usually calculated by radiologists or physicists. In the large majority of cases it is possible to reassure the mother and avoid an unjustified pregnancy termination. Naturally, it is impossible to guarantee that the fetus will not have a congenital malformation.

Recreational Drugs During Pregnancy

Alcohol

Maternal alcohol ingestion is one of the most important preventable causes of fetal, neonatal, and childhood disabilities in USA. The fetal alcohol syndrome was described in 1973 in 11 children with similar dysmorphic features whose mothers drank heavily during pregnancy (Jones et al., 1973). The abnormalities noted in these children include fetal growth retardation, microcephaly, mental retardation, decreased length of the palpebral fissures, epicanthal folds, and flattened maxilla. Follow-up studies have demonstrated that in addition to the fetal alcohol syndrome, alcohol ingestion during pregnancy is associated with increased incidence of spontaneous abortion, birth defects, and CNS dysfunction.

Unfortunately, alcohol ingestion during pregnancy is a common problem and approximately 14.6% of all pregnant women consume alcohol and 2.1% consume alcohol frequently according to the study of Ebrahim et al. (1998). The prevalence of any alcohol consumption and frequent alcohol consumption among nonpregnant women is approximately 53 and 16.3%, respectively. The risk factors for alcohol consumption during pregnancy are college level education, unmarried status, being employed, being a student, having an annual household income of more than $50,000, or being a smoker. The magnitude of the problem demands active intervention from the obstetricians to identify and counsel women who consume alcohol during pregnancy and ACOG (2004) have recommended to obstetricians to screen for alcohol abuse in the first prenatal visit.

Most women who drink alcohol during pregnancy occasionally consume a few drinks. This is important because although the threshold consumption causing fetal effects has not been precisely determined, no cases of fetal alcohol syndrome have been reported in women who had occasional consumption of small amounts of alcohol during pregnancy. The incidence of fetal alcohol syndrome ranges between 0.2

and 1.0 per 1000 live births and characteristically occurs in women who frequently consume large amounts of alcohol or who binge drink. Although it is advisable to avoid completely alcoholic drinks during pregnancy, the obstetrician should reassure patients who feel guilty after occasional ingestion of a small amount of alcohol and tell them that the possibility of doing harm to the fetus is minimal (Mills et al., 1987).

Cocaine

Several million Americans including about one million women of childbearing age use cocaine, making prenatal exposure to this drug a relatively frequent problem. Cocaine exposure during pregnancy is more frequent in young African-American women who are in public assistance programs but it affects all social-economical classes and ethnic groups. Cocaine users are more likely to smoke and consume alcohol during pregnancy, come late for prenatal care, and frequently have sexually transmitted diseases. The drug inhibits the reuptake of norepinephrine and epinephrine at the presynaptic nerve endings, causing an increase in the concentration of these substances at the synapses that in turn causes overstimulation of the peripheral and the CNS. Cocaine also blocks tryptophan and serotonin uptake. The cardiovascular effects of the overstimulation of the sympathetic system are elevated blood pressure, tachycardia, and vasoconstriction. During pregnancy vasoconstriction of the uterine arteries will result in decreased placental blood flow that will affect fetal nutrition and oxygen supply and in some cases will result in catastrophic premature separation of the placenta. Cocaine is transferred through the placenta and because of its effects on the fetal circulation it may cause hypoxic-ischemic brain injuries, intracranial bleeding, fetal FHR abnormalities, and passage of meconium. Newborns who have been exposed to cocaine "in uterus" frequently exhibit abnormal symptoms in the newborn period, are lethargic, have decreased responsiveness to external stimulation, and are at high risk for sudden infant death syndrome. The effects of antenatal cocaine exposure extend into childhood and result in a higher than usual incidence of behavior problems, lagging motor skills, and decrease in cognitive abilities. The severity of the maternal and fetal/neonatal outcomes is related to sustained and heavy cocaine use during pregnancy.

Cocaine exposure during pregnancy may have acute, dramatic effects. A frequent result of cocaine binging is a clinical presentation that mimics severe preeclampsia with markedly elevated blood pressure that responds poorly to antihypertensive agents. Another consequence of cocaine binging is abruptio placenta that may be severe and cause fetal death and severe maternal bleeding. Severe hypertension with tachycardia and minimal or no proteinuria and abruptio in women with a social profile consistent with substance abuse requires screening for cocaine in a urine sample.

Prenatal care of the cocaine abuser is frustrating because of the difficulties associated with their identification and the scarcity of effective comprehensive programs that allow these women to reorient their lives and stop their dependence of the drug. They frequently have a multitude of associated social and family problems and need referral and frequent contact with social services workers. Obstetricians are obligated to report pregnant cocaine abusers to child protection services. If a social service investigation finds evidence of past neglect or likelihood that neglect may occur the case will continue through the legal system and may end with placement of the newborn in foster care.

MEDICATIONS AND PREGNANCY

In 1978 the Food and Drug Administration established five categories of medications with respect to potential effects on the fetus or in the outcome of the pregnancy:

A. Controlled studies show no risk
B. No evidence of risk in humans
C. Risk cannot be ruled out
D. Positive evidence of risk
E. Contraindicated during pregnancy

Few drugs have been classified in the first and the last two categories. This happens because few medications have undergone controlled or cohort trials showing no evidence of risk and because few definite cause and effect relationships have been demonstrated between drugs and deleterious fetal effects. Also, multiple confounding variables make it difficult to analyze the effects of medications during pregnancy and ethical constraints preclude the design and performance of randomized or cohort studies of potential teratogenic agents.

Box 3-6 shows some proven teratogenic drugs. Box 3-7 shows some nonteratogenic drugs that frequently are

BOX 3-6

Proven human teratogens

Compound	*Major effect*
Thalidomide	Phocomelia
Diethylstilboestrol	Genital tract abnormalities
Warfarin	Nasal hypoplasia, bone stippling
Androgens	Masculinization of female fetus
Folic acid antagonists	Craniofacial defects, growth retardation
Anticonvulsants	Craniofacial defects, NTD, developmental delay
Retinoic acid	Craniofacial, cardiac, thymic defects
Alcohol	Craniofacial defects, developmental delay

BOX 3-7

Medications commonly used lacking evidence of teratogenic effects

- Progesterone
- Aspirin
- Spermicides
- Tylenol
- Heparin
- Thiazides
- Diazepam
- Indomethacin
- Codeine
- Prednisone
- Caffeine
- Cephalosporins
- Penicillin
- Ampicillin
- Erythromycin
- General and local anesthetics
- Benzodiazepines
- Barbiturates
- Propanolol
- Narcotics
- Aspartame
- Antidepressants

the subject of patients' questions and concerns. Some of the compounds shown in both tables will be discussed in more detail.

Anticonvulsant Agents

Anticonvulsant therapy is frequently required during pregnancy in patients affected by seizure disorders. Unfortunately, several of the most popular anticonvulsants (phenytoin, valproic acid, carbamazepine, and trimethadione) are associated with the development of craniofacial anomalies, growth retardation, and developmental delay. Phenytoin, phenobarbital, and carbamazepine are folic acid antagonists and some of their fetal effects could be explained by folic acid deficiency. The most commonly used anticonvulsant, phenytoin, causes a two- to fivefold increase in the frequency of congenital malformations. The most common malformations constitute the "fetal hydantoin syndrome" that affects approximately 10% of pregnant patients who use the medication. It is characterized by growth retardation, mental retardation, midfacial hypoplasia, upward slant of the eyebrows, hypoplasia of the fingers and toenails, hernias, and a depressed nasal bridge. Other anticonvulsants, valproic acid, carbamazepine, and trimethadione are strongly associated with NTDs, craniofacial, and digit abnormalities and delay in psychomotor development.

It has been suggested that the fetal malformations associated with anticonvulsive therapy are the result of the inheritance of some abnormal maternal genetic makeup associated with the seizure disorder. This has been disproved by a study that compared the outcome of mothers exposed to one, two, or more anticonvulsants with that of mothers with epilepsy not exposed to anticonvulsants during pregnancy and with controls without epilepsy and not exposed to anticonvulsants (Holmes et al., 2001). This study shows that the physical abnormalities of the newborns are associated with the anticonvulsant drugs and not with the maternal epilepsy.

In view of the strong evidence of embryotoxicity of anticonvulsant drugs, it will be ideal not to use them during pregnancy. However, to indiscriminately discontinue anticonvulsants may represent a health hazard for many patients. Discontinuing the medications if the patient had no seizures for the prior 2 years and her electroencephalogram is normal usually presents no problems. Patients with difficult or inadequate seizure control before pregnancy will likely have increased seizure activity if their medications are discontinued. They should be informed about the potential fetal effects of the anticonvulsants and also about the fetal effects of increased seizure activity if they stop the medications. The patient should participate actively in the decision to continue or to withhold the medications.

Antidepressants

Antidepressant drugs, particularly serotonin reuptake inhibitors are frequently used during pregnancy. Evidence accumulated during the last decade has raised concerns about adverse fetal effects, particularly persistent pulmonary hypertension of the newborn, (Chambers et al., 2006) fetal death, and seizures (Wen et al., 2006). For that reason ACOG (2006) has recommended to avoid using these medications and individualize treatment of depression during pregnancy.

Progesterone

Progesterone is commonly administered to pregnant women during the first trimester for the prevention of early pregnancy loss secondary to insufficient progesterone production by the corpus luteum and in the second and third trimesters for the prevention of preterm birth secondary to preterm labor. The medication can be administered by vaginal suppositories, orally (micronized progesterone) or by injection (17-alpha hydroxyprogesterone caproate). The evidence indicates that there is no developmental toxicity induced by progesterone. Specifically there is no risk of cardiac anomalies or limb reduction defects.

Corticosteroids

Although glucocorticoids are potent palatal teratogens in experimental animals, there is no evidence that they cause congenital malformations in humans. This fact should help to relieve the anxiety of some mothers in whom glucocorticoid treatment is being considered to improve fetal lung maturation. Also, when glucocorticoids are given to accelerate the production of pulmonary surfactant, they are usually administered several weeks after organ and limb development have taken place.

Diazepam

It has been theorized that diazepam ingestion during pregnancy increases the risk of cleft lip with or without cleft palate in the offspring. However, case control studies indicate that exposure to diazepam during the first trimester of pregnancy does not increase the fetal risk of oral defects.

Aspirin

Aspirin is one medication commonly used during pregnancy. Women taking high doses of aspirin during pregnancy have prolonged pregnancies, longer duration of labor, and more bleeding during parturition than control patients. Occasional consumption of aspirin has no harmful fetal or maternal effects. There is no evidence that aspirin causes fetal malformations, specifically cardiac anomalies. The theoretical concern about aspirin causing premature closure of the ductus arteriosus has not been confirmed.

Metronidazole

Metronidazole (Flagyl) is used during pregnancy for the treatment of symptomatic *Trichomonas vaginalis* infections. There is no evidence that this drug has teratogenic effects on the human fetus.

Vaginal Spermicides

One prospective study found an excess of limb reduction deformities and chromosome abnormalities among the infants of women who used vaginal spermicides 10 months prior to conception when compared with control patients. However, the accumulated evidence of the last few years has failed to substantiate such an association.

Coffee

In 1980, the United States Food and Drug Administration, concerned about the possibility of caffeine causing limb reduction defects, advised pregnant women to avoid caffeine-containing food and drugs. Two subsequent studies have presented convincing evidence suggesting that coffee consumption does not cause limb reduction defects.

Aspartame

Aspartame is an artificial sweetener widely used in a variety of soft drinks and food products. It is a dipeptide made by combining aspartic acid and phenylalanine. A concern has been raised about the potential effects of elevated maternal serum phenylalanine levels following the ingestion of food or soft drinks containing aspartame. The following facts demonstrate that there should be no concern: (a) phenylalanine serum levels of less than 60 µmole/dl have not been associated with mental retardation; (b) the acceptable daily intake of aspartame is 50 mg/k and this correspond to approximately 62 cans of soda sweetened with aspartame, an amount difficult to be ingested regularly; (c) the ingestion of twice the acceptable daily dose (100 mg/k) by volunteer heterozygotes for phenylketonuria raised their phenylalanine blood level to 42 µmole/dl, well below the 60 µmole/dl associated with fetal toxicity.

INDIAN EXPERIENCE OF FETAL DYSMORPHOLOGY

Clinicians have realized the need to investigate the fetoplacental unit for a better and meaningful understanding of the process of satisfactory fetal development and the effects of dysfunction on fetal health and morphology. The availability of biophysical methods of fetal health monitoring have contributed significantly in identifying fetuses at high risk and enabled the clinician to institute suitable obstetric interventions to improve perinatal outcome. Some of the obstetric conditions in this category will be discussed in light of the Indian experiences.

Liquor Amnii and its Significance in Monitoring Fetal Health

There are three major determinants influencing amniotic fluid volumes: transfer of water and solutes within and across the membranes, fetal physiologic regulation through acts of swallowing and urine production, and transplacental fluid movement. The mechanism, production, composition, and consumption of amniotic fluid is also regulated by gestation maturity. Presence of excess fluid (> 2000 ml) is termed as polyhydramnios and its deficiency has been termed as oligohydramnios.

Hydramnios: The incidence of polyhydramnios has been variously estimated during pregnancy to range between 0.4 and 1.5% (Das, 2001). With ultrasonographic scans, it is now possible to estimate amniotic fluid volumes more precisely. Amniotic fluid index (AFI) provides a common standard for evaluation of liquor amnii volume and its role in assessing fetal health prognosis. An AFI > 24 or vertical height of largest amniotic fluid pocket > 8.0 cm is now commonly accepted as the standard for detecting hydramnios in clinical practice (Table 3-3).

Moni Bansal (1986) reported an incidence of hydramnios in diabetic pregnant patients to be about 28%. The incidence of polyhydramnios in diabetic subjects following strict glycemic control is now reducing. Also the routine practice of blood group determination during antenatal care, identifying all Rh-negative gravidae and the widespread acceptance of use of anti-D immunoprophylaxis has

Table 3-3. Etiological factors associated with hydramnios

Etiology	Incidence (%)
Idiopathic	34.0
Gestation diabetes mellitus	24.6
Congenital fetal anomalies	20.0
Erythroblastosis fetalis	11.5
Multiple pregnancies	8.4
Acute polyhydramnios	1.5

Adapted from Das V. Hydramnios. In: Krishna U, Tank DK, Daftary SN, eds. Pregnancy at Risk: Current Concepts (4th edn). New Delhi: FOGSI Publication, Jaypee Publishers, 2001: Chap. 65; 380.

definitely reduced the incidence of hydrops fetalis. On sonography, hydrops fetalis is characterized by skin thickening > 5 mm, placental thickening > 4 cm, presence of ascites, pleural and pericardial effusion, and hydramnios. In the absence of blood group incompatibility, this fetal condition has been designated as nonimmune hydrops fetalis (Malhotra et al., 2004).

With increase in use of ovulation induction drugs and wider use of assisted reproductive technology (ART) in the treatment of infertility, there has been a rise in the incidence of multiple births, monozygotic twins with complications like twin to twin transfusion with associated hydramnios.

Placental anomalies like chorioangioma occur in 1–5% patients, but these are often small and clinically insignificant. Large chorioangiomas > 5.0 cm in size are associated with obstetric complications like hydramnios. Color Doppler reveals prominent vessels at that site (Malhotra et al., 2004).

Routine sonographic scans in early pregnancy help to detect several NTDs early in pregnancy. Timely terminations of these pregnancies reduce the incidence of hydramnios from these causes. Lastly the recognition of the importance of folic acid prior to conception and during early pregnancy has helped to reduce the incidence of NTDs.

Treatment of acute and severe hydramnios with intermittent amniocentesis has also helped in prolonging pregnancies and improving perinatal outcome. The use of indomethacin to control amniotic fluid volumes is fraught with possible occurrence of neonatal problems (early closure of ductus arteriosus) and hence is often not desirable. The prognostic significance based on assessing the dimension of single largest vertical pocket (mean vertical pocket, or MVP; Gandhi, 2004) is shown in Table 3-4.

Table 3-4 shows the association between oligohydramnios and poor fetal prognosis.

Oligohydramnios affects about 3.9% of all pregnancies. It has been defined as the absence of an amniotic fluid pocket, or one measuring < 1 cm in vertical diameter, or more popularly an AFI < 5 cm. The common causes associated with oligohydramnios include postdatism, IUGR, fetal congenital anomalies, particularly

Table 3-4. Fetal prognosis based on dimension of single largest vertical pocket (AF)

Parameter (MVP)	Normal	Marginal	Decreased
Size	2–8 cm	1–2 cm	< 1.0 cm
PNMR/1000	4.5/1000	56.6/1000	187.5/1000

those affecting the fetal urinary system and leakage of the amniotic fluid.

Lowered AFI in a case of suspected IUGR is indicative of deteriorating fetal prognosis. Color Doppler flow studies of the umbilical vessels of the fetus in utero provide further clues to the decision for pregnancy termination (Coyaji, 2001; Dasgupta, 2004) The perinatal mortality rises 10–30 times with increasing severity of oligohydramnios (Gandhi, 2004).

Postdatism is associated with oligohydramnios in about 30–70% of cases depending on the duration of prolongation of pregnancy. It constitutes an indication for induction of labor. Unlike the Western World, fetuses of some ethnic groups including Indians tend to mature early. This may predispose them to the same hazards as postdatism earlier in pregnancy (before 40 completed weeks of gestation) (Tambyraja, 1992).

Fetal Congenital Malformations

The incidence of fetal congenital malformations varies from 3 to 5%. Many of these are minor; however, about 15–20% are major. These are often lethal. Congenital fetal malformations account for almost one-fifth of total perinatal mortality. Congenital abnormalities may pose life-threatening risks, contribute to infant morbidity, or require cosmetic corrections. In an analytical study from Goa, the authors (Kamat and Jindal, 2001) reported that congenital fetal malformations accounted for 13% of perinatal deaths.

Congenital malformations and genetic disorders play an important role in perinatal morbidity and mortality. Birth defects of genetic disorders are often multifactorial in origin. These include chromosomal disorders, sex-linked diseases, environmental factors (nutrition, occupational hazards, exposure to teratogens, infections), and many as yet indeterminate causes. Factors that should alert the clinician toward the possibility of occurrence of fetal malformations include elderly age of parents, positive family history, exposure to teratogens, alterations in volume of amniotic fluid, abnormal serum marker screen, ultrasound imaging, IUGR, presence of multiple pregnancy, and pregnancies that occur following infertility treatments (ART). Consanguineous marriages predispose to genetic defects. In an interesting case of consanguinity from Amritsar, the authors reported three successive births with congenital defects: the first baby suffered from anencephaly, the second died of congenital heart defects,

and the third one had major renal anomalies. All the three babies succumbed (Kaur et al., 2000).

The role of routine ultrasound screening during pregnancy for assessing fetal growth and health is now universally recognized. The importance of midpregnancy fetal anomaly scan is also a commonly accepted practice. Additionally the implementation of triple marker screening, amniocentesis, and in selected cases CVS is now often recommended in high-risk cases.

Moral and ethical issues are involved in the management of affected pregnancies, which may lead to medicolegal problems. NTDs contribute to the majority of birth defects. The role of preconception and postconception administration of folic acid supplements has been recognized in the prevention of NTDs; these often tend to be recurrent. In an interesting case of recurrent NTDs by Sheth et al. (2003)-meningomyelocele in four successive births-the fault was attributed to vitamin B_{12} deficiency, beyond folate deficiency. Investigations revealed no chromosomal defects. This patient suffered from hyperhomocysteinemia associated with impairment of folate/cobalamin metabolic pathways predisposing to embryopathy. Alternatively, defective methionine synthesis and methylation capacity lead to NTDs. In yet another case of recurrent NTD (three times anencephaly), administration of folic acid lead to the birth of a normal infant subsequently (Banerjee et al., 2002).

Facial defects like cleft lip and palate pose medical and cosmetic problems. These affect 1:1000 to 1:1500 births (Adenwalla et al., 2004). Rearing difficulties in the neonatal period and the need for cosmetic report later on are matters of concern. These defects are often familial in origin.

In an interesting study from Punjab on congenital anomalies of the renal tract (CARUT) detected on sonographic scans, the authors (Debnath et al., 2004) reported an incidence of fetal urinary tract abnormality to be 0.56%. The mean gestational age at diagnosis was 27.8 weeks (22–34 weeks) The abnormalities detected included unilateral renal agenesis (two cases), multicystic dysplastic kidneys (five cases), unilateral vesicoureteric junction obstruction (one case), unilateral pelviureteric junction obstruction (one case), bladder outflow obstruction (one case), and congenital hydronephrosis (three cases). Oligohydramnios indicated poor prognosis. Viral infections are known to cause fetal malformations. Rubella and cytomegalovirus are well-recognized offenders, but herpes, varicella, and HIV have also been implicated, although the evidence to that effect is not undisputable.

Monozygotic twins (dysmorphism) can cause anomalies, and conjoint defects are known to be sharing body parts and harbor malformations. Lastly, exposure to teratogenic drugs, irradiation, or pollutants can also contribute to birth defects.

IMPORTANT POINTS

1. Spina bifida is the NTD most difficult to diagnose by ultrasound. There are sonographic signs in the CNS useful in this diagnosis. They include the lemon and banana signs, obliteration of the cisterna magna, and hydrocephalus.
2. Recent studies have shown no benefit of abdominal over vaginal delivery in patients with spina bifida.
3. A transverse atrial diameter exceeding 10 mm is an early and accurate sign of fetal hydrocephalus.
4. The three main types of fetal hydrocephalus are aqueductal stenosis, communicating hydrocephalus, and Dandy–Walker malformation.
5. The most important factor in the prognosis of patients with hydrocephalus is the presence of associated anomalies.
6. The most common chromosomal abnormality associated with cystic hygroma is Turner's syndrome. Other conditions are trisomies 21 and 18 and mosaicisms.
7. The sonographic diagnosis of CDH is based on inability to visualize the fetal stomach, presence of a cystic or solid intrathoracic mass containing abdominal organs, mediastinal displacement, and smaller than expected abdominal circumference.
8. The mortality in fetuses with gastroschisis is between 8 and 14%. This figure has been decreasing in later years due to advances in postnatal intensive care and surgery.
9. Several recent studies have failed to demonstrate any advantage of cesarean section over vaginal delivery in fetuses with gastroschisis. In these patients, cesarean should be performed only for obstetric indications.
10. The major prognostic factor in fetuses with omphalocele is the presence of associated anomalies. They occur in 50–80% of the cases. Chromosome abnormalities have been reported in as many as 43% of the cases.
11. Fetal renal cysts are usually due to MDK or to obstructive uropathy.
12. UPJ obstruction is the most common congenital malformation of the urinary tract, representing approximately 40% of all obstructive uropathies and 20–50% of all urologic congenital anomalies detected in utero.
13. A complete evaluation of the fetus with outlet bladder obstruction should include a level II ultrasound examination, echocardiography, karyotype, and evaluation of the fetal renal function.
14. The best index of fetal renal function is the determination of urinary sodium concentration.
15. Fetal surgery may be the procedure of choice for ST when the diagnosis is made early in gestation.

16. The most common maternal causes of polyhydramnios are diabetes and Rh isoimmunization. The most common fetal causes are congenital abnormalities. No etiologic factor will be identified in approximately 65% of the cases.
17. The most common causes of unexpected oligohydramnios in the second trimester are undetected PROM, severe fetal growth retardation, and fetal congenital abnormalities.
18. The most common causes of nonimmunologic fetal hydrops are cardiovascular malformations, chromosomal abnormalities, and hematologic and pulmonary problems.
19. Irregular rhythms account for over 85% of all fetal arrhythmias. Most irregular rhythms are due to PACs and resolve spontaneously during pregnancy or at delivery.

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4

Fetal Growth Restriction

CHAPTER OUTLINE

Fetal weight is determined by the genetic growth potential, the health of the fetus, the capacity of the mother to supply adequate quality and quantities of substrates required for growth, and the ability of the placenta to transport these nutritional substrates to the fetus. The genetic growth potential varies from race to race and from individual to individual and this variation is evident in population studies of healthy term newborns showing a symmetrical distribution curve of their birth weights. Normal fetuses at either extreme of this normal biological distribution curve will be combined with others whose growth has been restricted or accelerated due to pathological influences. In the chapter on Diabetes the reader will find information about the problems associated with large fetal size. In this chapter we will analyze the problems associated with restriction of the fetal growth.

The fetus requires several substrates for normal growth. The most important are oxygen, glucose, and amino acids. Oxygen crosses the placenta by simple diffusion and is necessary for the formation of chemical energy in the form of adenosine triphosphate (ATP). Glucose crosses the placenta by facilitated diffusion and its concentration in the fetus is determined by the maternal plasma glucose levels. Glucose is utilized in the production of energy and in the provision of carbon-building blocks for the synthesis of lipids, glycogen, nucleotides, and other molecules. Amino acids cross the placenta by active transport and are essential for the synthesis of proteins. Any persistent decrease in the availability of these substrates will limit the ability of the fetus to reach his/her growth potential, and a severe substrate deficiency may threaten the ability of the fetus to survive. The availability of substrates necessary for fetal growth may be limited by pathological conditions affecting the placenta, the fetus, and the mother. A partial list of these conditions is shown in Box 4-1. The majority of conditions affecting fetal growth are placental or fetal in origin. The most common placental conditions are alterations in the uteroplacental and fetal–placental circulations and the most common fetal conditions are chromosomal abnormalities and multifactorial malformations. Most maternal

BOX 4-1

Maternal, placental, and fetal conditions associated with fetal growth restriction

Maternal

1. Associated with placental vascular insufficiency:
   - Preeclampsia
   - Chronic hypertension
   - Chronic renal disease
   - Connective tissue disorder
   - Diabetes with vascular lesions
   - Sickle cell anemia
   - Cardiac disease class III or IV
   - Multiple gestation
2. Not associated with placental insufficiency
   - Severe malnutrition
   - Smoking
   - Alcohol ingestion
   - Hemoglobinopathies

Placental

- Abnormal placentation
- Chronic villitis
- Placental infarcts
- Placental hemangiomas
- Chorioangiosis
- Hemorrhagic endovasculitis
- Placenta previa

Fetal

- Chromosomal abnormalities
- Multifactorial defects
- Inborn errors of metabolism
- Infections

medical conditions are associated with fetal growth restriction (FGR) only when there is simultaneous placental compromise. There are a few maternal conditions that do not affect the placenta and are associated with FGR, the most common being maternal alcoholism and severe maternal protein-caloric malnutrition.

The problems in diagnosing and managing pregnancies with impaired fetal growth are substantial. This is due to the confusion between fetuses that are small and healthy and those who have a pathological restriction in their growth, to our inability to know what is the growth potential of a given fetus, to the occurrence of FGR in patients without recognizable high-risk factors, to the proliferation of measurements to assess fetal growth, to the difficulties in estimating gestational age, and to different opinions about the ideal time to deliver these small fetuses. For the practicing obstetrician, these problems can be summarized in following three questions: How to recognize that the fetus is small? How to differentiate between the fetuses that are small and healthy and the fetuses that have pathological growth restriction? How to manage the pregnancies afflicted by pathological fetal growth restriction (PFGR)?

DEFINITIONS

Small for Gestational Age

Pediatricians use the term "small for gestational age" (SGA) to identify term newborns with a birth weight less than the 10th percentile for their gestational age. The purpose of this definition was to distinguish newborns that were at term and small from newborns that were small because of being preterm. This distinction is important because the complications associated with these conditions are different. The preterm newborns exhibit complications predominantly related to the immaturity of several organs. In contrast, term babies that are small are affected mainly by metabolic and nutritional problems. The use of the term SGA was later extended to cover earlier gestational ages.

There are several sources to determine the percentile distribution of birth weights at different gestational ages. One of them is the nomogram by Brenner et al. (1976) which is useful for infants born in USA near sea level and may be inappropriate for other countries or for babies born at different altitudes. The nomogram from Alexander et al. (1996) was constructed with data from close to 4 million single births in USA (Table 4-1). Another useful table was developed from the tabulation of birth registration forms from over 1 million cases in Canada (Arbuckle et al., 1993). Finally, some institutions with large number of deliveries have developed their own birth weight percentile nomograms (McIntire et al., 1999).

Term SGA newborns may be affected by chromosomal abnormalities, infections, multifactorial disorders or be the result of placental vascular insufficiency or maternal malnutrition. However, in the majority of term SGA infants it is possible to rule out a pathological cause for the low birth weight and they can be designated as normal SGA (Soothill et al., 1999). In contrast, the majority of preterm SGA newborns are afflicted by a pathological restriction in their growth potential.

One problem with the definition of SGA is the variation in birth weight for gestational age associated with ethnicity and with altitude. Ethnic influences are apparent when we compare the mean birth weight for the Cheyenne Indians in USA, which is 3700 g, with the birth weight of the Lummy tribe in New Guinea, which is 2400 g. The effect of altitude can be appreciated easily by comparing population studies from Australia, where the 10th percentile at 40 weeks was 2980 g, with similar studies from Denver, Colorado, USA, where the 10th percentile was 2535 g.

The definition of SGA does not include newborns with restricted growth and birth weight above the 10th percentile for their gestational age. One example of this situation is a

Table 4-1. Fetal weight percentiles throughout pregnancy

Gestational age (weeks)	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
20	249	275	412	772	912
21	280	314	433	790	957
22	330	376	496	826	1023
23	385	440	582	882	1107
24	435	498	674	977	1223
25	480	558	779	1138	1397
26	529	625	899	1362	1640
27	591	702	1035	1635	1927
28	670	798	1196	1977	2237
29	772	925	1394	2361	2553
30	910	1085	1637	2710	2847
31	1088	1278	1918	2986	3108
32	1294	1495	2203	3200	3338
33	1513	1725	2458	3370	3536
34	1735	1950	2667	3502	3697
35	1950	2159	2831	3596	3812
36	2156	2354	2974	3668	3888
37	2357	2541	3117	3755	3956
38	2543	2714	3263	3867	4027
39	2685	2852	3400	3980	4107
40	2761	2929	3495	4060	4185
41	2777	2948	3527	4094	4217
42	2764	2935	3522	4098	4213
43	2741	2907	3505	4096	4178
44	2724	2885	3491	4096	4122

From Alexander GR, Himes JH, Kaufman RB, et al. A United States national reference for fetal growth. Obstet Gynecol 1996; 87: 163.

newborn that has the potential to reach a birth weight of 8 lbs but because of a pathological influence weighs 6 lbs at birth and is classified as "appropriate for gestational age" (AGA). Most probably this is a theoretical rather than a practical problem, because there is no evidence that this situation results in neonatal morbidity or mortality.

Fetal Growth Restriction

With the development of ultrasound technology, obstetricians became capable of diagnosing small fetuses "in utero" and the term "intrauterine growth retardation" (IUGR) was designed to identify fetuses with estimated weight below the 10th percentile for their gestational ages. This term has been replaced by "fetal growth restriction," or FGR, to avoid the erroneous assumption that these newborns were mentally retarded. However, the pediatric definition (SGA) is also frequently used to identify these small fetuses. To estimate the fetal weight using ultrasonic measurements of the biparietal diameter (BPD), head circumference (HC), AC, and femur length (FL), investigators developed mathematical formulas and constructed percentile nomograms of estimation of fetal weight (EFW) at different gestational ages. The most commonly used equations and nomograms are those of Shepard et al. (1982) and Hadlock et al. (1985, 1991) and most ultrasound machines have incorporated into their software one or both of these nomograms.

The majority of the literature defines FGR as all the fetuses with sonographic estimated weight below the 10th percentile for the gestational age. There are variations in this definition that depend on the growth percentile selected to determine whether or not an EFW is consistent with FGR. In addition to the 10th percentile, investigators have used the 5th, the 3rd, and the 2.5th percentiles of the EFW at a given gestational age to define FGR. The rational behind this variation is that the lower the percentile, the higher the probability of selecting fetuses with pathological growth restriction. Other investigators use a fetal abdominal circumference (AC) < 2.5 SD below the mean for the gestational age or a head to abdomen circumference ratio (H/A ratio) or femur to abdomen ratio (F/A ratio) greater than 2 SD from the mean for the gestational age rather than the EFW to designate a fetus as FGR. The idea behind the use of the AC alone or in combination with measurements of the head or the femur to diagnose FGR is that the fetal abdomen is the variable most affected in pathological growth restriction, while the HC and the FL are relatively spared. The diagnostic accuracy of EFW and AC is similar.

The similarity between the obstetrical and the pediatric definitions of fetus or newborns below the 10th percentile for the gestational age is obvious because both attempt to identify fetuses or newborns that are small for reasons other than being preterm. Also both terms include normal and pathologically small fetuses. The terms are frequently used interchangeably, although some investigators believe that the term FGR should be exclusively used to identify fetuses that are small because of a pathological restriction in their growth while the term SGA should be used to identify fetuses and newborns that are small but healthy. However, ultrasonically estimated fetal weight and birth weight are not criteria that independently allow one to determine the presence or absence of pathological conditions affecting the fetal or neonatal growth. The definitions of IUGR, FGR, and SGA are similar and the only difference between them is that IUGR and FGR are used during intrauterine life while SGA is used after birth. Following the birth of a SGA baby the pediatricians use clinical and laboratory observations to determine whether or not a pathological cause for the low birth weight is present. Similarly, the finding of a small fetus by ultrasound examination demands from the obstetrician further testing to identify those babies that are small because of a pathological condition.

INCIDENCE

The incidence of FGR should be, by definition, close to 10% of all births. However, only 20–30% of these fetuses are small because of a pathological restriction of their growth (PFGR) and a majority are normal small for gestational age

fetuses (normal SGA). There are variations in the frequency of fetuses with PFGR reported in literature that depends on the characteristics of the population (low-risk, high-risk, unselected) being studied.

Low birth weight is a major problem in India; nearly 3 million low birth weight babies are born annually and it accounts for nearly half of the neonatal deaths (Dasgupta, 2003). The problem of low birth weight continues to remain an unanswered perinatal challenge in developing countries. The universally accepted cutoff point of birth weight of 2500 g to define low birth weights requires a second look. Factors which affect birth weight include a variety of determinants like maternal age, malnutrition, ethnicity, and other factors. Hence the importance of evolving parameters to suit the population served. In India, many obstetricians accept cutoff birth weights below 2250 g as being more appropriate to the Indian population. The incidence of low birth weight in the Indian population was estimated to be 28% (Tambyraja, 1992).

Mongelli et al., (1998) further emphasized that the chances of wrongly diagnosed FGR based on fetal growth velocity increased from 11.8 to 30.8% with advancing gestational age and the lengthening of intervals between sonography scans.

CLASSIFICATION

A method to classify FGR fetuses is based on the presence or absence of symmetry among different anatomic structures. Type I or symmetric FGR corresponds to fetuses that are symmetrically small and have normal H/A and F/A ratios. Type II or asymmetric FGR corresponds to fetuses that have an AC that is smaller than the HC and the FL resulting in abnormally high H/A and F/A ratios. Type III or intermediate FGR corresponds to fetuses that are initially symmetric but become asymmetric later in the pregnancy. The main problem with this classification is that the three groups include normal and pathologically restricted FGR and therefore its prognostic value is poor.

Another method to classify FGR fetuses is based on the origin of the problem and subdivides them into four categories: intrinsic, extrinsic, combined, and idiopathic. "Intrinsic" FGR occurs when the fetuses are small due to fetal conditions such as viral infections or chromosomal abnormalities. "Extrinsic" FGR occurs when the growth failure is due to an element outside of the fetus such as a placental condition or a maternal disease. "Combined" FGR occurs when there are extrinsic and intrinsic factors causing the growth failure and "Idiopathic" FGR when the cause of the fetal growth failure is unknown. Similarly to the previous classification, this has poor prognostic value since all four groups may contain severely affected babies. A classification of FGR fetuses should have prognostic value and should respond to the need to differentiate between fetuses who are small but healthy (normal SGA) and those who are small because of a pathological restriction in their ability to grow (pathological FGR or PFGR).

ETIOLOGY OF PFGR

As shown in Box 4-1, pathological conditions affecting the placenta, the mother, or the fetus may impair the ability of the fetus to grow. The relative frequency of these conditions is shown in Box 4-2.

BOX 4-2

Relative frequency of different etiologic factors in PFGR

Placental insufficiency	75–80%
Maternal conditions not associated with placental insufficiency	5%
Fetal chromosome abnormalities	5%
Multifactorial fetal abnormalities	2–3%
Fetal infections	1%

Placental Abnormalities

The most common causes (75–80% of the cases) of PFGR are abnormalities of the placenta, affecting the maternal or the fetal circulation or both. In the majority of these cases, there is diminished maternal uteroplacental blood flow caused by insufficient or incomplete trophoblastic invasion of the spiral arteries in the placental bed. Under normal conditions, trophoblastic cells first infiltrate the decidua and then the myometrial portion of the spiral arteries, destroying the elastic and muscular layers and replacing them with fibrinoid material. Another feature of abnormal placentation is the deposition of lipoprotein and the infiltration by foamy macrophages of the vascular wall, giving the appearance of accelerated atherosclerosis. The rigid vessel walls are transformed into flaccid sac-like structures that can accommodate the increased uteroplacental blood flow that occurs during pregnancy. These transformed spiral arteries are not affected by maternal vasoregulatory mechanisms. The initial phase of the trophoblastic invasion of the spiral arteries usually ends by the 16th week of gestation, but in many cases completion of the adaptative changes does not occur until 20–22 weeks. When placentation is abnormal, trophoblastic invasion is largely confined to the decidual layer with absent or incomplete changes in the myometrial portion of the spiral and radial arteries. The presence of spiral and radial arteries with intact muscular and elastic layers causes increased vascular resistance and decreased blood flow to the intervillous space, restricting the maternal capacity to provide oxygen and nutrients to the fetus. Also, the

vessels with absent or incomplete transformation remain reactive to vasoactive substances produced or ingested by the mother. This placentation defect is not exclusive of FGR and is also found in placentas of women with preeclampsia, preterm labor, and preterm premature rupture of the fetal membranes.

The fetal side of the placenta may show changes secondary to or independent of the alterations in the maternal side. The most common lesions found on the fetal side of the placenta are increased number of syncytial knots, obliteration of arteries in the tertiary stem villi, reduction in the vascularity of terminal villi, and stromal fibrosis. These alterations in the fetal circulation in cases of decreased uterine blood flow have been attributed by some investigators to defective angiogenesis (Jackson et al., 1995; Kreckzy et al., 1995) while others believe that they correspond to adaptative changes to the ischemia present in the maternal side of the placenta (Stock et al., 1980). Thrombosis in the maternal side of the placenta frequently coexists with alterations in uteroplacental blood flow. Clotting in the spiral arteries or the intervillous space results in placental infarcts that reduce the number of functioning villi and will have an effect on the supply of oxygen and nutrients to the fetus, particularly if they are numerous or extensive. Placental infarcts are present in up to 10% of normal pregnancies and they probably result from the hypercoagulability of pregnancy combined with the slow blood flow through the intervillous space. The presence of multiple infarcts is strongly suggestive of the possibility of congenital or acquired maternal thrombophilia. Antiphospholipid antibodies are the most common cause of acquired thrombophilia and factor V Leiden mutation, prothrombin promoter mutation, homozygosity for the methylene-tetra-hydro-folate reductase C677T mutation, and decreased protein S activity are the most common congenitally acquired thrombophilic states.

A lesion in the maternal side associated with PFGR is massive perivillous fibrin deposition. In these cases the intervillous space is occupied by fibrin and the villi embedded within the fibrinous mass are nonfunctional. In one study the incidence of PFGR in cases of massive perivillous fibrin deposition was 62.9% (Fuke et al., 1994). This lesion is also present in some cases of fetal demise and is strongly suggestive of the possibility of maternal thrombophilia.

Maternal floor infarction is another placental lesion associated with PFGR and fetal demise. Pathologically, this condition is characterized by massive deposition of fibrin in the maternal floor of the placenta encasing the contiguous villi that become necrotic or atrophic. This lesion is apparent macroscopically and can be identified easily by looking at the maternal side of the placenta which will be covered by pale, glassy, smooth tissue with an appearance that vaguely resembles the surface of a brain. Maternal floor infarct is found in 5 per 1000 to 9 per 10,000 births. It is associated with PFGR in more than 50% of cases and is a common finding in cases of fetal death (Mandsager et al., 1994). Unfortunately, this condition frequently reoccurs in successive pregnancies. The pathophysiological basis for maternal floor infarct is unknown but maternal thrombophilia is a good possibility and should be researched systematically. Some investigators consider that maternal floor infarction and massive perivillous fibrin deposition are related conditions (Katzman et al., 2002).

Other placental lesions associated with PFGR are chronic villitis, hemorrhagic endovasculitis, and confined placental mosaicism. Lymphocytic and histiocytic infiltration of the villi are the markers of chronic villitis (Althabe and Labarrere, 1985), a nonspecific lesion that may occur in isolation but frequently is associated with vascular lesions in the maternal or fetal side of the placenta. Chronic villitis may be immunological or viral in origin. When cell infiltration by plasma cells occurs, the possibility of infection by cytomegalic virus is high. Chronic villitis occurs in approximately 8% of normal pregnancies but the incidence increases three- to fourfold in cases of PFGR. Pathological fetal growth restriction is present in approximately 30% of patients with chronic villitis.

Hemorrhagic endovasculitis is another lesion associated with poor pregnancy outcome and is histologically characterized by the presence of numerous extravascular erythrocytes infiltrating the villi. It is generally believed that hemorrhagic endovasculitis is another histological manifestation of maternal/fetal thrombophilia. Both chronic villitis and hemorrhagic endovasculitis are frequently present in placentas from women with preeclampsia.

In cases of confined placental mosaicism, the chromosomal composition of the placenta is not the same as that of the fetus. In these cases the placenta is usually trisomic and the fetus has a normal karyotype but inherits both homologous chromosomes from one of the parents. Most commonly the placenta is trisomic for chromosome 16 but up to 12 other chromosomes could be involved. Most likely the zygote is originally trisomic with subsequent expulsion of one of the trisomic chromosomes from the embryonic but not from the trophoblastic tissue (Robinson et al., 1997). Confined placental mosaicism and fetal uniparental disomy is a condition associated with severe PFGR but may also occur in newborns with normal weight and in some that are large for gestational age.

Clotting and thrombosis may also be present in the fetal side of the placental circulation. In these cases the intravascular clotting affects the chorionic stem vessels, causing an infarct with avascular fibrous villi in the distribution territory of the affected vessel. This lesion has been named fetal thrombotic vasculopathy (Redline and Pappin, 1995). In many cases the lesions in the fetal circulation occur simultaneously with infarcts or decidual

vasculopathy in the maternal side of the placenta but in other cases they may occur without apparent maternal side lesions. In any case, the presence of fetal thrombotic vasculopathy has a strong association with poor pregnancy outcome (Arias et al., 1998). Of particular importance is the possibility of an association between this placental lesion and thromboembolic lesions in the fetal brain (Rayne and Kraus, 1993).

Placental vascular insufficiency and impaired fetal growth of one or more fetuses are a relatively common finding in multifetal pregnancies. When the restriction in growth affects only one of the fetuses is named "selective FGR" condition that may occur in up to 21% of multifetal pregnancy. The problem occurs more frequently in twins with monochorionic placentation. Abnormal insertion of the umbilical cord, torsion of the cord, hemangiomas of the placenta, and placenta previa are situations also frequently associated with selective FGR. The overall prevalence of these abnormalities is low.

Fetal Abnormalities

The frequency of congenitally abnormal newborns among severely affected PFGR fetuses is approximately 10%. The majority of these genetically affected babies have asymmetric measurements in prenatal ultrasound examination with the head being larger than the abdomen. PFGR is common in chromosomal disorders, especially in somatic trisomies. It also occurs in patients with familial dysautonomy, osteogenesis imperfecta, and other multifactorial disorders. Single gene mutations do not affect fetal growth as much as do chromosomal defects. The possibility of a fetal congenital disorder should always be considered in patients with "idiopathic" or "unexplained" FGR.

In a study of more than 13,000 malformed infants born in Atlanta (Khoury et al., 1988) the overall frequency of PFGR was 22.3%. The most common abnormalities associated with PFGR were chromosomal, particularly trisomy 18. The mechanism of fetal growth impairment secondary to genetic syndromes is unknown but it is possible that chromosomal defects cause alterations in placental function, resulting in fetal malnutrition. A large number of fetuses affected by genetic conditions can be detected by a comprehensive or genetic ultrasound examination. This topic is addressed extensively in Chapter 2 (Prenatal Diagnosis of Chromosomal Abnormalities) and in Chapter 3 (Fetal Dysmorphology).

Fetal infections are not a common cause of PFGR. Bacterial infections usually have acute courses and cause preterm labor, preterm rupture of membranes, or fetal death. Viral infections on the other hand may be chronic and affect fetal growth. The viral infections associated with impaired fetal growth are congenital rubella, cytomegalic virus, congenital varicella, human immunodeficiency virus, and acute herpes simplex virus infections.

Maternal Conditions

Maternal conditions associated with PFGR interfere with fetal growth by one of the three mechanisms:

1. Causing or aggravating placental vascular insufficiency
2. Limiting the availability of substrates required for fetal growth and development or
3. Transferring to the fetus substances that affect the fetal growth

A list of maternal conditions associated with placental vascular insufficiency and PFGR is shown in Box 4-1. The mechanism explaining the development of placental vascular lesions in maternal conditions as varied as chronic hypertension, chronic renal disease, autoimmune disorders, and diabetes is unknown. The common link between these conditions and placental vascular insufficiency may be an underlying alteration of the maternal or the fetal hemostatic systems or vasoconstriction, causing ischemic infarcts and decreased perfusion. Irrespective of the mechanism, the practical point is that the association between maternal chronic medical conditions, placental vascular insufficiency, and FGR is robust and surveillance of fetal growth is a fundamental aspect of the prenatal care of women afflicted with these conditions.

Women with chronic medical conditions do not necessarily develop placental insufficiency and PFGR in all their pregnancies. The question why these associations may occur in one pregnancy and not in another remains unanswered. Most probably another factor or factors have to be present for the association to exist. It is tempting to speculate that one of these factors is the genetic composition of the fetal tissues. Support for this idea is given by the study by Abuzzahab et al. (2003) of 42 children with unexplained FGR. One of these children was compound heterozygote for point mutations in one of the exons coding for the insulin-like growth factor I receptor (IGF-IR), suggesting that alterations in this receptor's gene may be a cause of FGR. Another factor that may be of importance in determining the placental and fetal response to the altered maternal environment is the presence and characteristics of hereditary thrombophilia.

There are some maternal conditions that cause FGR by limiting the availability of substrates which the fetus requires for normal growth and development. One of these conditions is severe maternal malnutrition. Studies on the siege of Leningrad during World War II and the Dutch famine during the winter of 1944 demonstrated that severe protein-caloric malnutrition, especially during the second half of the pregnancy, causes decreased fetal weight. For practical purposes, this problem is nonexistent in USA. The average caloric intake of the low socioeconomic sectors of the US population is adequate for normal fetal growth. The opposite is true for other countries where

protein-caloric malnutrition is endemic. Another example of FGR secondary to maternal malnutrition may occur in women who become pregnant after gastric bypass operations for the treatment of morbid obesity. In this situation the incidence of FGR babies is between 20 and 40%.

The relationship between maternal nutrition and fetal growth has been exaggerated out of proportion in USA, where there is a generalized belief that it is necessary to "eat for two" during pregnancy, a philosophy that frequently leads to massive increases in maternal weight gain. Few mothers are capable of returning to their prepregnancy weight and with each successive pregnancy, additional weight is added until they become obese. For many women, overeating during pregnancy is the basis for medical problems associated with gross obesity. The reality is that there is no evidence that increasing markedly the caloric intake during pregnancy translates into advantages for the fetus.

A third group of maternal conditions affect fetal growth by supplying the fetus with substances toxic for growth and development. A classical example of this group is maternal smoking. For women who smoke during pregnancy, the reduction in fetal growth at term reaches between 150 and 400 g, but the effect of smoking is evident at every gestational age. Tobacco-chewing gravidas and women exposed to second-hand smoking also have reduced fetal weight. The mechanism behind the decrease in fetal growth caused by maternal smoking has not been clarified, but it probably results from a combination of factors such as reduced intervillous blood flow, the effect of carbon monoxide and thiocyanate on the fetus, and reduced prostacyclin production. Maternal alcohol ingestion is another well-recognized cause of FGR due to the effects of a toxin upon the fetus. The alcohol effect is synergistic with that from smoking. In one series of 76 babies with fetal alcohol syndrome, PFGR occurred in 91%. The fetal effects of alcohol are more severe in heavy drinkers. The chronic ingestion of heroin, morphine, cocaine, and other addictive substances is also frequently associated with FGR. Similar to alcohol and tobacco the mechanism most probably involves a direct drug effect on the fetus in addition to maternal malnutrition which is common in drug abusers. The use of certain medications during pregnancy is also associated with PFGR. Cancer chemotherapeutic agents, Coumadin, and phenytoin (Dilantin) are drugs that have the potential to cause PFGR. Fortunately, these medications are not commonly used during pregnancy.

Indian women racially give birth to low birth weight infants. Malnutrition and anemia are rampant in the country. The incidence of anemia in pregnancy varies between 15 and 70% in different regions of the country. Awasthi et al. (2001) reported an incidence of IUGR of 37% among women suffering from moderately severe anemia (Hb < 8.0 g%).

In clinical practice in India, preeclampsia has been reported to be associated with a 10–25% incidence of FGR (Bhide, 2007). Daftary and Desai (2006) observed that the incidence of rheumatic heart disease affects 0.5–1.0% of the pregnant population; these women often drop a grade because of the stress of pregnancy. The incidence of low birth weight babies among them is > 30% (preterm + FGR). The Indian population is more prone to diabetes. Genetic and environmental factors contribute to this enhanced susceptibility. Hence the incidence of 2–5%, reported by Indian authors, of gestational diabetes is considerably high (Maheshwari et al., 1989; Kumar et al., 1993; Ganguli et al., 1995; Bhattacharya et al., 2001), but the highest incidence of 12.7% was reported by Sridhar and Nagamani from Vishakhapatnam (2003). The National Diabetes Data Group reported that women with pregestational diabetes mellitus account for 4–15/1000 pregnancies and women with gestational diabetes mellitus account for 25–50/1000 pregnancies.

Vertical transmission of TORCH infections like rubella, cytomegalovirus, and toxoplasmosis can adversely affect fetal growth, leading to IUGR (Maria and Deoran, 2004). In India, where the policy of universal immunization against rubella is not prevalent, neonatal morbidity following rubella infection in pregnancy continues to be observed in clinical practice.

Although smoking is not as common in India as in the West, Indian women are known to use tobacco in the form of snuff, and often chew tobacco. Mehta and Mehta (2001) reported an increase in the incidence of low birth weight babies and an increase in perinatal mortality among tobacco users.

FETAL AND NEONATAL PROBLEMS ASSOCIATED WITH FGR

The importance of FGR for the obstetrician is derived from its association with problems during the newborn period and in adult life but especially during intrauterine life. Recognition of FGR, adequate surveillance of the pregnancy, and timely delivery of the compromised infant will have a significant impact in decreasing the morbidity and mortality associated with this condition. We will analyze these problems separately.

Antepartum Complications

Fetal hypoxia and acidosis

Prenatal and intrapartum hypoxia and acidosis are the most important and frequent complications of FGR particularly when the growth disturbance is due to placental insufficiency. This is the reason why early diagnosis and adequate surveillance of pregnancies complicated by

PFGR secondary to placental insufficiency is so important. When PFGR fetuses are assessed with electronic fetal heart rate (FHR) monitoring, nonreassuring signs such as late decelerations, severe variable decelerations, decreased beat-to-beat variability, and episodes of bradycardia are more frequent than in normally grown fetuses and acidosis during labor occurs in as many as 40% of PFGR fetuses (Lin et al., 1980). As a result the incidence of cesarean delivery is high.

Stillbirth

There is a clear relationship between FGR and stillbirths. One study (Manara, 1980) found that approximately 20% of all stillborns show signs of growth restriction. Another study (Morrison and Olsen, 1985) found that FGR was associated with and is probably responsible for 26% of stillborns among infants with a birth weight less than 2500 g. Fetal death in FGR babies may occur at any time but is more frequent after 35 weeks of gestation.

Oligohydramnios

Oligohydramnios is a common finding in FGR. There is a strong association between decreased amniotic fluid volume and the incidence of FGR. In the study of Chamberlain et al. (1984) the incidence of FGR when the amniotic fluid volume was normal was 5% but when oligohydramnios was present it increased to approximately 40%. The cause of oligohydramnios in PFGR babies is decreased fetal urinary output secondary to redistribution of the blood flow with decreased renal perfusion and preferential shunting to the brain.

Intrapartum Complications

The main problem during labor of fetuses with FGR is the high incidence of intrapartum hypoxia and acidosis. For this reason, labor in the FGR fetus should be closely monitored and delivery by cesarean should be performed if there are nonreassuring FHR patterns. The reader will find more information about this topic later in this chapter.

Neonatal Complications

The diagnosis of FGR is easier after the baby is born. At birth, the FGR infant shows signs of soft tissue wasting. The skin is loose and thin, and there is little subcutaneous fat. The abdomen is scaphoid, the ribs are protuberant, and the muscle mass of the arms, buttocks, and thighs is reduced. The umbilical cord is limp, thin, and frequently meconium-stained. Most of the time it is apparent that the HC is larger than the AC. The birth weight and in most cases the placental weight are below the 10th percentile. Fetuses with pathological growth restriction frequently have thrombocytopenia and elevated nucleated red blood cell count (Minior et al., 2000). In contrast, the normal SGA baby has symmetric development of the head and abdomen and a normal amount of subcutaneous fat (Box 4-3).

BOX 4-3

Comparison between PFGR and small and healthy babies

Pathological growth restriction (PFGR)	Normal, small for gestational age (small and healthy)
Birth weight usually < 10% but may be < 25%	Birth weight < 10%
Birth weight usually < 2500 g but may be larger	Birth weight < 2500 g
Low ponderal index	Normal ponderal index
Decreased subcutaneous fat	Normal subcutaneous fat
Frequently develops complications in the neonatal period such as hypoglycemia, hyperbilirubinemia, hypocalcemia, hyperviscosity, necrotizing enterocolitis	Usually have an uneventful neonatal course
Elevated nucleated blood red cells and thrombocytopenia	Normal nucleated blood red cells and normal platelet count

The neonatal course of the PFGR infant is different from that of the normal SGA baby. Small and healthy newborns rarely have significant problems and in the majority of cases go home after an uneventful stay in the nursery. In contrast, the PFGR newborn frequently develops complications. The most important ones are related to perinatal asphyxia and fetal distress (persistent fetal circulation, meconium aspiration syndrome, hypoxic-ischemic encephalopathy); to metabolic alterations (hypoglycemia, hypocalcemia, hyperviscosity syndrome, hyperglycemia, and hypothermia); and to the specific cause of the growth restriction (infections, congenital malformations, chromosomal abnormalities).

Respiratory distress syndrome

Respiratory distress syndrome is the main cause of morbidity and mortality in preterm FGR infants. Initial observations suggested that PFGR infants had a stress-induced acceleration of pulmonary maturity but more recent studies indicate that the opposite is true and respiratory distress syndrome occurs more frequently in PFGR newborns of less than 28 weeks than in their AGA counterparts (Ley et al., 1997). It is possible that the lungs of the preterm PFGR fetuses are more vulnerable than the lungs of the preterm AGA ones because intrauterine hypoxia and ischemia may cause leakage of protein with inhibitory surfactant activity into the alveoli.

Meconium aspiration syndrome

Meconium aspiration was a major cause of mortality and morbidity in the PFGR baby. Amnioinfusion has been used for several years in attempts to dilute the meconium and avoid impaction of meconium into the fetal airways but recent clinical trials have demonstrated that amnioinfusion results are not better than no treatment (Fraser et al., 2005; ACOG, 2006).

Persistent fetal circulation

Persistent fetal circulation is a frequent sequela of perinatal hypoxia and acidosis. The pathophysiology is characterized by severe pulmonary vasoconstriction with persistent blood flow through the ductus arteriosus. The main signs are hypoxia with moderate hypercarbia, right-to-left shunting without evidence of intrinsic heart disease, and cardiomegaly. The treatment is adequate ventilation, minimal stimulation, and the use of pulmonary vasodilators.

Intraventricular bleeding

Intraventricular bleeding (IVH) grade III and IV and periventricular leukomalacia are the most common neurological lesions in preterm PFGR infants. Initial studies demonstrated a decreased incidence of IVH in preterm FGR infants. More recent observations demonstrate that the opposite is true and the incidence of grade III and IV IVH is larger in preterm PFGR than in AGA infants (Spinillo et al., 1997).

Neonatal encephalopathy

Neonatal encephalopathy is a nonspecific diagnosis to describe a variety of neurological signs and symptoms that frequently occur after episodes of severe birth asphyxia. The injury to the brain may range from cerebral edema to diverse forms of intracranial bleeding to nonspecific asphyxial injuries. The symptoms include seizures, irritability, twitching, and apnea. Neonatal encephalopathy is an essential component of cases of cerebral palsy secondary to fetal asphyxia. Neonatal encephalopathy occurs more frequently in PFGR than in AGA infants.

Hypoglycemia

Hypoglycemia occurs in approximately 25% of term and in as many as 67% of preterm PFGR infants. The condition is due to lack of adequate glycogen stores in the liver and muscle, decreased subcutaneous fat, and a relative deficiency of hepatic gluconeogenic enzymes. The most common definition of neonatal hypoglycemia is a blood glucose below 30 mg/dl. The symptoms are nonspecific: jitteriness, twitching, apnea, tachypnea, and occasionally seizures. Early feeding, orally or intravenously, can minimize or prevent hypoglycemia.

Hypocalcemia

Hypocalcemia, particularly during the first day of life, is common in PFGR babies. Relative hypoparathyroidism, increased calcitonin level secondary to chronic asphyxia, and increased phosphorus levels resulting from increased tissue catabolism seem to be responsible for this problem. Symptoms are nearly identical to those of hypoglycemia.

Hyperviscosity syndrome

Hyperviscosity syndrome affects approximately 18% of all PFGR babies. The main sign is polycythemia, defined as a central hematocrit in excess of 65% or hemoglobin concentration above 22 g/dl. Blood viscosity is linearly related to the hematocrit at levels below 60%, but the relation becomes exponential once the hematocrit increases beyond 65%. Polycythemia is probably secondary to a chronic hypoxic stimulation of the fetal hematopoietic system. Hyperviscosity slows the blood flow in the microcirculation, causing pulmonary infarcts and necrotizing enterocolitis. The destruction of a large number of red cells results in hyperbilirubinemia. Also, volume overload may lead to pulmonary edema and congestive heart failure. Treatment of the hyperviscosity syndrome involves partial exchange transfusions with plasma or albumin replacing blood.

Inadequate temperature control

The PFGR fetus has poor temperature control and a tendency toward hypothermia due to deficient energy stores and the small size of the subcutaneous fat layer. The treatment consists of artificial warming during the first few days of life.

LONG-TERM PROGNOSIS

Today, a large number of FGR babies survive the neonatal period; therefore, more and more attention is focused on their long-term growth and development. The main question is whether these babies will recover completely from the intrauterine malnutrition or if they will permanently suffer the consequences of the fetal insult. The most important areas with respect to long-term prognosis are the growth pattern after birth, the relation of FGR with neurological development, and the potential effects of FGR in adult disease.

Postnatal growth

The first follow-up studies of FGR babies born between 1950 and 1960 found a significant incidence of poor

growth and neurological and developmental sequelae. However, more recent studies have demonstrated better outcomes. A nearly universal finding is that FGR babies as a group remain smaller than their AGA cohorts in follow-up examinations. This is found despite the occurrence, in some cases, of "catch-up growth" during the first 6 months of life. Several years after birth, 30% of FGR babies will remain below the 30th percentile for weight of children of equal age and only 10–20% will be above the 50th percentile (Hill, 1978).

Several studies have looked for characteristics that may help to differentiate those FGR babies who will remain growth-stunted and those who will move into more normal growth patterns. Fitzhardinge and Steven (1972) found that if growth is to catch up, acceleration of growth has to occur during the first 6 months of life. They also found that the degree of initial growth failure does not have predictive value and that babies who are severely affected at birth have as good a chance as less affected infants of growing into normal percentiles. In another study (Fancourt et al., 1976), it was found that infants whose growth retardation started before 34 weeks of gestation are more likely to be below the 10th percentile at 4 years of age than are babies whose growth impairment was diagnosed after 34 weeks.

Cerebral palsy

FGR is universally recognized as an important risk factor for abnormal neurological development and cerebral palsy. Follow-up studies between 3 and 9 years of age have clearly demonstrated that intelligence, motor skills, and speech and reading abilities are affected in PFGR (Robertson et al., 1990; Kok et al., 1998). PFGR secondary to congenital anomalies and infections has a significant incidence of major neurological problems later in life. Minimal brain dysfunction (hyperactivity, decreased attention span, learning difficulties, poor coordination) affects approximately 25% of PFGR infants. Other investigators have found a mean developmental quotient depressed by nearly 10 points in infants whose growth failure had an early onset as compared to either late-onset or normal controls. In summary:

1. The length of the insult seems to be more important than its severity in terms of both somatic growth and neurological development: the earlier in pregnancy FGR is detected, the greater the probability of developmental problems later in life.
2. The probability of developmental problems is lower when there is catch-up growth during the first 6 months of life.
3. The worst prognosis is for babies with FGR secondary to congenital infections or abnormalities or chromosomal defects.
4. The outcome of FGR and AGA fetuses experiencing asphyxia at birth is different and FGR fetuses have a higher probability than AGA fetuses of developing neurological problems in early childhood.

Adult disease

Several epidemiologic studies have suggested an association between low birth weight and the development of chronic hypertension, abnormal lipid profile, ischemic heart disease, and type II diabetes in adult life. The most commonly accepted explanation for this association is that the maturation of different organs and systems is programmed to occur at critical periods during intrauterine life and that an insult or perturbation of this program by a condition that causes low birth weight will result in long-term effects on organ or system function that will be apparent during adult life.

The initial evidence linking low birth weight and adult disease came from studies in England and Wales showing that regional differences in the rate of ischemic heart disease and stroke were parallel to differences in neonatal mortality 70 years previously (Barker and Osmond, 1986). At that time neonatal mortality was strongly associated with low birth weight. Several ulterior studies have supported not only that association but also the relationship between low birth weight with chronic hypertension (Law and Shiell, 1996) and noninsulin-dependent diabetes (Hales et al., 1991). However, a recent review of 55 studies on the relation of adult blood pressure with birth weight suggests that the latter is of little relevance to the first in later life (Huxley, 2002).

The possibility that problems during fetal life could have important effects during the adult years is intriguing and has significant potential importance. If prospective studies confirm this hypothesis, prenatal care may hold the key to the prevention of important adult disorders that shorten life and have significant impact on the health care budget.

IDENTIFICATION AND FOLLOW-UP OF PATIENTS AT RISK

Women at risk of FGR characteristically belong to two groups: women with high risk factors for FGR in their medical or obstetrical history and women without historical risk factors who present with signs suggestive of FGR during the prenatal care. Approximately 40% of the cases of FGR occur in women without high-risk factors. Adequate use and interpretation of ultrasound examinations will allow the clinicians to identify the majority of cases of FGR.

Historical Factors

Box 4-1 contains a noninclusive list of women at risk for FGR. Mothers with significant medical or obstetrical problems such as chronic hypertension, preeclampsia, hematologic conditions, chronic renal disease, twin pregnancies, and insulin-dependent diabetes with microvascular disease are at high risk for PFGR. The obstetrical history is also of importance, and women who previously delivered an FGR newborn are at high risk of having a similar problem in a current pregnancy. All pregnant women with high-risk factors for FGR should be followed with serial ultrasound examinations.

Risk Factors During Prenatal Care

Poor maternal weight gain

Poor maternal weight gain during pregnancy is a relatively insensitive sign of inadequate fetal growth. Some studies have found that this association has questionable clinical value and that weight gain is normal in a significant number of mothers who deliver small babies. A recent study (Neufeld et al., 2004) in a poor rural population in Guatemala found inadequate weight gain from the first to the second trimester in mothers who delivered SGA infants. It is not clear, however, if this finding can be applicable to populations with different socioeconomical characteristics. However, it is a generalized practice to assess fetal growth with ultrasound if the maternal weight gain during pregnancy is poor.

Discordance between gestational age and uterine size

Discordance between the gestational age and the size of the uterus is the most common finding in women at risk of FGR. Measurement of uterine height is a simple method to estimate the fetal growth and identify women at risk of FGR in low-risk populations. The uterine height should be measured in centimeters from the upper border of the pubic symphysis to the fundus of the uterus. In some cases, the uterine fundus is deviated toward one side of the abdomen, and measurements taken in the middle will be inaccurate. Also, it is a good idea to place the numbered side of the tape measure against the patient's skin so that the numbers cannot be seen during the measurement. Fundal height measurements are open to error in obese patients, underweight patients, nulliparas with a strong anterior abdominal wall, multiparas with flaccid anterior abdominal muscles, and in patients with breech presentations or transverse lies. The best way to use uterine height measurements is to plot them against a standard curve derived from a normal obstetrical population such as that developed by Belizan et al. (1978). The use of this curve has a sensitivity of 86% with 10% false positive results for the diagnosis of SGA newborns. All discrepancies between the clinical dating and the fundal height measurements should be followed by ultrasound examination.

Inability to assess uterine growth during pregnancy

Obesity in USA is a medical problem of epidemic proportions affecting all socioeconomic levels and ethnic groups but most severely the young African-American population. Evaluation of the uterine height is difficult and frequently in error in obese women and the only way to recognize abnormalities in the fetal growth is by means of serial ultrasound examinations which should be an integral part of their prenatal care. Similar considerations apply to multifetal pregnancies.

Early preeclampsia

Preeclampsia is the maternal condition most frequently associated with PFGR. This association is stronger when preeclampsia develops before 32 weeks. Due to the high incidence of PFGR, fetal growth assessment and screening for placental vascular insufficiency should be an integral part of the initial assessment of women developing preeclampsia early in gestation.

Follow-up of High-Risk Patients

Women identified as high-risk for FGR by the criteria enumerated above should be further screened with uterine artery Doppler. Those testing positive should be followed with serial ultrasound examinations every 3–4 weeks and the diagnosis of FGR made when the EFW falls below the 10th percentile for the gestational age. Women with negative uterine Doppler screening are at low risk for FGR (negative predictive value 97–99%) and can be followed as normal pregnancies or as determined by the presence of maternal or fetal conditions.

Uterine artery Doppler screening

Several studies have evaluated the presence of decreased diastolic blood flow and protodiastolic notching in the uterine arteries as a predictor of the development of FGR in women at high- and low-risk. Unfortunately, these studies have fundamental differences in the gestational age used for the screening, equipment used for the test, site of the artery used for the measurement, cutoff adopted to define a test as abnormal, risk level of the population under study, and diverse definition of outcomes. However, several conclusions can be derived from the literature (Albaiges et al., 2000; Antsaklis et al., 2000):

1. Screening for FGR with uterine artery Doppler is more accurate in high- than in low-risk populations.
2. Uterine artery screening is better for the prediction of severe, early FGR.

3. The waveforms should be obtained from a site identified with color Doppler immediately after the uterine artery crosses the external iliac artery.
4. A positive test is the presence of bilateral early diastolic notching, or ipsilateral notch in a lateral placenta, or an S/D or PI (pulsatility index) at or above the 95th percentile in the uterine arteries' waveforms.
5. The best gestational age for one-stage screening is 23–24 weeks.
6. Screening can be performed before 23 weeks but abnormal testing results should be repeated at 23–24 weeks (two-stage screening).
7. The most useful part of the test is the negative predictive value. A negative test at 23 weeks in a high-risk population indicates a 97–99% probability that FGR will not be present.
8. The positive predictive value of the test is between 25 and 50%. The positive predictive value increases in patients with unexplained elevated alpha-fetoprotein or beta human chorionic gonadotropin in triple or quad tests screening for aneuploidy. The positive predictive value is also better if bilateral notches and elevated S/D or PI are present at the same time.

DIAGNOSIS

The diagnosis of FGR requires precise knowledge of the gestational age of the fetus. Unfortunately in many cases the gestational age is not certain and the diagnosis of FGR is less accurate.

Determination of Gestational Age

It is impossible to make an accurate diagnosis of FGR if the gestational age of the fetus is not accurately known. Most false positive diagnoses of FGR are due to an erroneous determination of gestational age. The criteria to determine gestational age are extensively analyzed in the first chapter of this book. At this time, however, it is pertinent to reinforce that an accurate determination of gestational age requires the following:

1. Known last menstrual period (LMP), history of regular cycles, absence of hormonal contraception, and confirmation of expected date of delivery (EDD) by ultrasound examination before 24 weeks
2. A negative pregnancy test followed by a positive one at adequate times after a known LMP
3. A history of conception achieved by infertility treatment with documented date of conception or date of artificial insemination
4. Unreliable LMP but EDD determined by two ultrasound examinations 3–4 weeks apart in the first and/or second trimester

If these criteria are not met, determination of gestational age will depend on serial ultrasound measurements of the fetus or the use of variables such as the transverse diameter of the cerebellum or the FL, which seem to be minimally affected by FGR.

Diagnosis when the Gestational Age is Certain

The methods most commonly used to diagnose FGR when the gestational age is well known are the EFW, the fetal AC, and the F/A) ratio. The first attempts to diagnose FGR utilized serial measurements of the fetal BPD. This method demonstrated two distinct patterns of impaired fetal growth. Some fetuses exhibit continuous BPD growth during the entire pregnancy but the measurements remain at all times below the 10th percentile for the gestational age. This type of abnormal growth was named slow growth profile. Other fetuses exhibit normal BPD growth during the first two trimesters of pregnancy followed by arrest of growth during the last trimester. This pattern was called late flattening profile. Fetuses demonstrating late flattening profile are more likely to be PFGR babies and to develop antepartum and neonatal problems versus fetuses with slow growth profile. The sensitivity and specificity of serial isolated BPD measurements are too low to be used as the primary method for evaluating the suspected small fetus.

Estimated fetal weight

The determination of EFW is based on accurate ultrasound measurements of four anatomic landmarks: the BPD, HC, AC, and FL. These measurements are plotted into mathematical equations derived from the analysis of thousands of observations to determine the estimated fetal weight. The value obtained is compared with tables, showing the normal percentile distribution of EFW at different gestational ages. As mentioned before, the most commonly used formula to determine EFW and the most commonly used percentile distribution nomograms are from Hadlock et al. (1984, 1991).

Ultrasonic fetal weight estimates are usually within 5–10% of the true fetal weight. This margin of error is unimportant when the birth weight is less than 2000 g. However, with larger fetal sizes, the error of this method may be as large as 1 lbs for a term fetus. Fetal weight estimates have a sensitivity of 89%, specificity of 88%, positive predictive value of 45%, and negative predictive value of 99% for the detection of FGR (Ott, 1997). Chervenak et al. (1984) found that when the estimated fetal weight is below the 0.5% confidence limit the probability that the fetus is small is 82%. If the estimated fetal weight is between the 0.5 and 20.0% confidence limits the probability that the fetus is small is 24.0%.

Abdominal circumference

The best single measurement to diagnose FGR in women with accurate LMP is the AC. An AC value at or below the 10th percentile for the gestational age has a negative predictive value of 93% and a positive predictive value of 47% for the diagnosis of FGR. A value at the 5th percentile has similar negative predictive value but the positive predictive value increases to 67%. An AC greater than the 25th percentile value for the gestational age has a negative predictive value of 95% and practically rules out the possibility that the baby is FGR (David et al., 1996). These predictive values of a single AC measurement are similar to that of the EFW. In term pregnancies with an EFW above the 10th percentile and a normal fluid volume, the presence of an AC less than the 2.5th percentile for the gestational age has a positive predictive value of 41% (Gerber and Parilla, 1999). The AC should be measured at the level of the bifurcation of the hepatic vein in the center of the fetal liver. Measurements taken at the entrance of the umbilical vein in the abdomen are in an oblique cross section and produce erroneously large values. Table 1-4 shows the AC percentiles at different gestational ages.

Head to abdomen ratio

A useful measurement in the evaluation of small babies with known gestational age is the H/A ratio. This ratio compares the most preserved organ in the malnourished fetus, the brain, represented by the circumference of the fetal head, with the most compromised organ, the liver, represented by the fetal AC. This measurement is of significant value in identifying FGR babies with asymmetric head to abdomen measurements. Pathological restriction of the fetal growth is usually present when the H/A ratio is above the 95th percentile for the gestational age. However, a normal H/A ratio is not a guarantee that the fetus is normal. A fetus with normal H/A ratio may be affected by PFGR but the majority of them will be small and healthy. The fetal HC should be measured at the level of the thalami. An advantage of using the HC instead of the BPD is that the effect of head molding at the end of the pregnancy is minimized.

The reason why the use of the H/A ratio should be restricted to fetuses with certain gestational age is that this ratio is gestational age-dependent. Dashe et al. (2000) developed a percentile nomogram for H/A ratio versus gestational age (Figure 4-1) from a database of more than 33,000 live births without congenital abnormalities. The same investigators found that among 1364 infants classified as SGA at birth that had ultrasound examinations within 4 weeks of delivery, 20% had H/A ratios above the 95th percentile for their gestational age. Major congenital abnormalities were more frequent in SGA newborns with

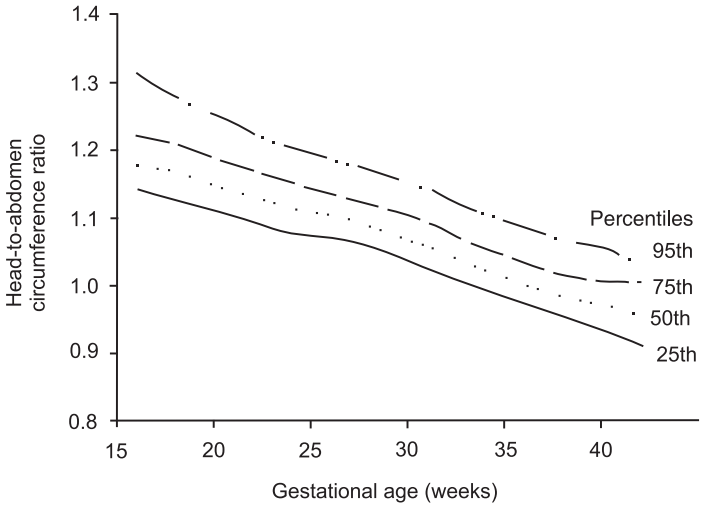

Figure 4-1. Head/abdomen circumference ratio at different gestational ages.

asymmetric H/A ratio than in SGA infants with symmetric H/A ratio or in AGA infants (14 vs 4 vs 3%, respectively). Preeclampsia before 32 weeks, cesarean delivery for nonreassuring FHR, and neonatal morbidity were significantly more frequent in SGA newborns with asymmetric H/A ratios than in AGA newborns. Also, SGA infants with symmetric H/A ratios did not have increased morbidity as compared with AGA newborns. This work indicates that measurement of the H/A ratio is of importance in the evaluation and prognosis of the FGR infants.

Diagnosis when the Gestational Age is Uncertain

Frequently the obstetrician is faced with the problem of determining if FGR is present in women with uncertain dates. In these cases repeating the ultrasound examination in 3–4 weeks and analyzing the growth of the fetus during this time will be useful to diagnose FGR. However, in the large majority of cases an immediate answer to the question of the diagnosis is required and it is necessary to use gestational age-independent ultrasound markers of FGR to make a diagnosis. These markers are the transverse cerebellar diameter to abdominal circumference (TCD/AC) ratio, the F/A ratio, and the fetal ponderal index (FPI).

TCD/AC ratio

The distance between the outer borders of the cerebellum or transverse cerebellar diameter (TCD) is not markedly affected in cases of FGR and can be used as index of the gestational age in combination with AC measurements (Meyer et al., 1994; Goldstein and Reece, 1996). The normal TCD/AC ratio is 0.137 ± 0.012. However, other investigations have cast doubts regarding the usefulness of the measurement (Hill et al., 1990).

The TCD in centimeters is equal to the gestational age in weeks until approximately 32 weeks. After 32 weeks there are variations in the measurement.

Femur to abdomen ratio

An important index in the evaluation of patients suspected of carrying small fetuses with uncertain dates is the femur to abdomen ratio (F/A ratio). This method compares the FL which is minimally affected by fetal growth impairment with the AC which is the most affected. The FL is easy to obtain and is not affected by molding or abnormal fetal presentations or positions. The femur to abdomen ratio remains constant after 20 weeks. The normal value for this index is 22 ± 2. An upper limit of 23.5 (90th percentile) has a sensitivity of 63.3% and a specificity of 90% for the diagnosis of FGR in a general population (Hadlock et al., 1983). When the F/A ratio is abnormally high, PFGR should be strongly suspected. However, when the F/A ratio is normal, PFGR still may be present or the baby may be small and healthy.

Fetal ponderal index

Another ultrasound measurement useful for the diagnosis of FGR when the gestational age is uncertain is the FPI. The FPI is gestational age-independent and has a constant value throughout the second part of the pregnancy. The FPI is obtained by dividing the estimated fetal weight by the third power of the FL (Vintzileos et al., 1986) and its normal value is 8.325 ± 2.5 (2 SD). An FPI of 7.0 or less should be considered abnormal and suggestive of PFGR. A significant source of error with this method is that the use of the third power of the FL considerably magnifies any imprecision in femur measurements. Despite this possibility of error, the FPI is useful in the evaluation of the fetuses suspected of FGR in mothers with uncertain dates. The importance of the FPI for the clinician is the negative predictive value of 96.4% that basically reassures that PFGR is not present. The positive predictive value is only 35.7%.

Table 4-2 summarizes the accuracy of the measurements used in the sonographic diagnosis of FGR.

Table 4-2. Expected accuracy of ultrasound measurements in the diagnosis of small babies in a general population assuming a 10% prevalence of SGA

Parameter	Ultrasound parameters					
	BPD	FL	AC	FL/AC	PI	EFW
Sensitivity	75	45	95	55	55	65
Specificity	70	97	60	75	71	96
Predictive value:						
Positive	21	64	21	20	18	65
Negative	96	94	99	94	92	96

BPD = biparietal diameter; FL = femur length; AC = abdominal circumference; FL/AC = femur length/abdominal circumference; PI = ponderal index; EFW = estimated fetal weight.

From Brown HL, Miller JM, Jr, Gabert HA, et al. Ultrasonic recognition of the small-for-gestational-age fetus. Obstet Gynecol 1987; 69: 631–5.

Differential Diagnosis Between Normal and Pathological FGR

Once the diagnosis of FGR has been established, the next question for the obstetrician is whether or not the baby is small due to pathological growth restriction (PFGR). Several causes of PFGR can be ruled out in the initial evaluation. Fetal chromosomal abnormalities will be rare if the mother had a low risk for aneuploidy as shown by triple or quad test or by comprehensive ultrasound examination in the second trimester of pregnancy.

The ultrasound examination will also be useful to rule out the possibility of a fetal anatomical abnormality causing the PFGR. Chronic fetal infections causing PFGR are quite rare. Thus, in the majority of cases the pathology to rule in or rule out is placental vascular insufficiency which is the most common cause of PFGR (Box 4-2). Fortunately, with the advent of Doppler ultrasound it is possible to determine if placental vascular insufficiency is present, to identify the presence of fetal hemodynamic adaptation to decreased placental blood flow, and to determine the presence of fetal hemodynamic decompensation, hypoxemia, and acidosis.

Color mapping has greatly facilitated the performance of Doppler studies with improved visualization of the vessels of interest. Since most measurements used in fetal evaluation are ratios, the angle of insonation of the vessel is not of critical importance but it is good practice to try to keep the angle between the Doppler beam and the direction of flow at < 30° at all times. Vessels with low resistance will produce waveforms with significant flow during diastole while vessels with high resistance will show decreased or absent diastolic flow (ADF). The measurements most commonly used to indicate vascular resistance are the peak systolic to end diastolic ratio (S/D ratio), the PI, and the RI (resistance index). An important qualitative index is the presence or absence of early diastolic (protodiastolic) notches in the uterine artery waveforms. The S/D ratio, also called A/B ratio, is the result of dividing the peak velocity during systole by the end diastolic velocity measured just before the beginning of the next systolic wave. The PI is calculated using the following equation: peak systolic velocity – end diastolic velocity/mean systolic velocity. The RI is calculated using the equation: peak systolic velocity – end diastolic velocity/peak systolic velocity. Values are obtained and averaged from a minimum of three to four consecutive waveforms.

The Doppler measurements of interest in the diagnosis and evaluation of PFGR are those from the uterine artery, the umbilical artery (UA), the middle cerebral artery (MCA), and the ductus venosus (DV). The uterine artery Doppler indicates to the clinician the presence or absence of abnormal resistance to blood flow in the uteroplacental circulation. The UA Doppler is an index of resistance to flow in the fetal–placental circulation and has a strong correlation with the presence or absence of fetal hypoxia and acidosis. The MCA Doppler indicates whether or not the fetus is compensating for the decreased oxygen supply by preferentially increasing blood flow to the brain. The DV Doppler indicates the presence or absence of fetal cardiac failure secondary to hypoxia and acidosis.

Multiple studies have demonstrated that Doppler examination of the placental vasculature is useful in making the critical distinction between the fetus that is small and healthy and the fetus with pathological restriction of growth. The first work in this subject was by Trudinger et al. (1985). These authors reported that small babies with normal umbilical and uterine waveforms are not at increased risk of fetal or neonatal morbidity. Two years later Rochelson et al. (1987) studied 54 SGA newborns, 42 with high and 12 with normal umbilical S/D ratios. Only one of the babies with normal S/D ratios showed signs of fetal distress during labor while 25 of the 42 babies with abnormal S/D ratios exhibited electronic fetal monitoring signs of distress before or during labor. Two of the mothers in the normal S/D ratio group had hypertension as compared with 50% of the mothers in the abnormal S/D ratio group. Fourteen women in the abnormal S/D ratio group had decreased amniotic fluid. There were 4 stillborns and 2 neonatal deaths in the abnormal S/D ratio group and none in the normal S/D group. In another study (Burke et al., 1990) 124 of 179 babies had normal UA S/D ratios and there was only 1 abnormal outcome and 1 delivery before 34 weeks. The incidence of cesarean section for fetal distress was 3.8%. Other authors (Reuwer et al., 1987; Dempster et al., 1989) have also found normal Doppler studies in babies that are small but healthy and markedly abnormal findings in compromised, malnourished babies. The accumulated evidence in the literature strongly suggests that assessment of the umbilical and uterine arteries Doppler waveforms can distinguish between the PFGR fetus that is at high risk and the normal FGR fetus that is at little or no risk.

In order to rule out placental insufficiency in the evaluation of FGR fetuses, it is necessary to demonstrate normal Doppler waveforms in the uterine, umbilical, and fetal cerebral circulations. This is necessary because the UA Doppler reflects resistance in the fetal side of the placenta, the uterine artery Doppler reflects resistance in the maternal side of the placenta, and the MCA Doppler reflects redistribution of blood flow. In most severe PFGR cases, all three Doppler indices are altered but uterine artery Doppler may be abnormal when the UA velocimetry is normal. Also, redistribution of flow with changes in the UA/MCA ratio may occur in the presence of normal UA Doppler waveforms (Hershkovitz et al., 2000) and a decrease in MCA resistance or in the UA/MCA ratio after 34 weeks is suggestive of FGR even if the UA resistance is normal. When uterine, umbilical, and midcerebral waveforms are normal in the absence of maternal complications and fetal congenital abnormalities, the fetus is small but healthy and is not at higher risk than that of the normal population.

Uterine artery Doppler

The uterine artery Doppler indicates to the clinician whether or not there is increased resistance to blood flow in the uteroplacental circulation. If increased resistance is present, increased S/D ratios and/or early diastolic notches will appear in the waveforms. To obtain consistent measurements of the uterine arteries they should be insonated in the area immediately following their crossing of the external iliac artery, an anatomic landmark that is relatively easy to determine by color Doppler. Under normal conditions the uterine arteries resistance has a significant drop after 14 weeks and waveforms showing abundant diastolic flow remain relatively unchanged from this time until the end of the pregnancy. However, an elevated uterine artery resistance before 23 weeks does not necessarily reflect abnormality because a significant number of cases showing bilateral or unilateral notching and increased S/D ratios in the first half of the second trimester will become normal after 23 weeks. For this reason when the uterine artery waveforms are being used for screening of women at risk for FGR or preeclampsia, it is preferable to use a two-stage screening if the initial evaluation is done before 23–24 weeks.

The S/D ratios of the left and right uterine arteries are not identical. The mean difference (0.3) is small and some investigators recommend averaging the values obtained in the right and the left side and expressing the uterine arteries S/D ratio as a single number. In most pregnancies each uterine artery contributes equally to the placental blood flow and even when the placenta is located laterally, the contralateral artery has a significant contribution resulting from the development of collateral circulation. However, in some cases the difference between the S/D ratios of the left and right uterine arteries is greater than 2 SD. This usually occurs when the placenta has a lateral implantation and in those cases the S/D ratio of the artery located on the placental side is lower than the ratio of the artery on the nonplacental side, indicating that the ipsilateral artery is more important than the contralateral in determining the uteroplacental flow. Therefore, in lateral

placentas, abnormalities of the ipsilateral uterine artery have more prognostic importance than similar abnormalities in the contralateral artery and the incidence of preeclampsia and FGR is elevated when the ipsilateral artery shows notching or an elevated S/D ratio even if the combined S/D ratio of both uterine arteries is within normal limits. It is interesting that some investigators have reported an incidence of preeclampsia and PFGR higher in women with lateral rather than centrally located placentas (Kofinas et al., 1989).

An increased S/D ratio and the presence of protodiastolic notching have similar sensitivity for the prediction of PFGR and preeclampsia. However, both parameters should be evaluated because the prognosis is worse for women with waveforms with bilateral notching and decreased diastolic flow.

Umbilical artery Doppler

The UA Doppler indicates to the obstetrician the presence or absence of placental resistance to the blood flow from the fetus to the placenta and has a strong correlation with the acid/base balance of the fetus. The measurement of interest to assess the fetal–placental circulation is the UA S/D ratio. In European countries the PI is used more frequently than the S/D ratio. The PI has the advantage of producing a numerical value even when diastolic flow is absent. To obtain more consistent results, the UA S/D ratio should be obtained in a free loop of cord midway between the placental insertion, the site of less resistance, and the fetal insertion, the site of maximal resistance to flow. The measurements should be taken when the fetus is not moving.

During normal pregnancy the UAs have low resistance demonstrated by the presence of abundant diastolic flow and reflected in low S/D ratios. During normal pregnancy there is a slow and continuous decline in the S/D ratio that reaches its lowest value after 36 weeks' gestation. A simple rule to remember is that the UA S/D ratio should be under 3.0 (mean 2.5) after 30 weeks of gestation. When the pregnancy is complicated by increased placental vascular insufficiency causing PFGR, diastolic flow decreases causing the UA S/D ratio to increase to values 2 SD or higher above the mean for the gestational age (see Table 1-7 and Figures 1-9–1-11). An increase in UA S/D ratio even if it is marked is not an indication of fetal hypoxemia or acidosis. However, with the progression of placental vascular insufficiency the UA waveforms will show ADF and finally reversed diastolic flow (RDF) which indicate to the clinician the presence of fetal hypoxemia and the need to deliver the fetus.

The evidence supporting a role for UA Doppler in the surveillance of high-risk pregnancy is robust. Randomized clinical trials and meta-analysis have conclusively demonstrated that the use of UA Doppler in high-risk pregnancies results in an approximately one-third decrease in perinatal mortality (Alfirevic and Neilson, 1995; Divon, 1996; Goffinet et al., 1997). Studies have also demonstrated a strong relationship between the results of UA velocimetry and the presence of fetal acidemia in blood samples obtained by cordocentesis or at the time of cesarean (Vintzileos et al., 1991b; Yoon et al., 1993).

Middle cerebral artery Doppler

When the placental vascular resistance increases above a certain threshold, the fetus develops a compensatory response, increasing the blood flow to vital organs such as the heart and the brain and decreasing the blood flow to the mesenteric, renal, and peripheral circulations. This hemodynamic adaptation protects the integrity of the fetal brain in the face of diminished availability of nutrients and can be assessed by comparing the UA and MCA Doppler waveforms. Under normal conditions the UA waveforms are characterized by abundant diastolic flow corresponding to a minimal resistance to flow in the fetal–placental circulation. The MCA waveforms are completely different and show minimal or no diastolic flow indicating high resistance to flow (Figure 1-10). During the initial stages of placental insufficiency the UA diastolic flow decreases and the S/D ratio increases while the compensatory increase of the brain circulation causes increase in diastolic flow with resulting decrease in the MCA S/D ratio. With progression of placental insufficiency, the UA and MCA S/D ratios become similar and eventually the MCA S/D ratio will become smaller than the UA S/D ratio. This is called "brain sparing effect" or "centralization" of flow. Centralization of flow is not an indication of fetal hypoxemia or acidosis. Centralization is a signal that the fetus is under appreciable placental resistance to flow and is adequately compensating for this problem by improving the blood flow to the brain. This fetal compensation may persist for several days and weeks and as we will discuss later on in this Chapter is not an indication for early delivery.

In one of the first studies on this subject Arduini et al. (1987) studied 75 patients at risk for having growth-restricted babies. Of them, 53% had hypertension, 24% were heavy smokers, 14.7% had a history of malnourished fetuses, and 8% had renal disease. The study was done at 26–28 weeks of gestation and before any of the fetuses exhibited ultrasonic signs of growth impairment. At birth, 52 neonates (69.3%) had normal birth weights and 23 (30.7%) were small and had signs of malnutrition. According to these investigators the ratio between the PI of the fetal umbilical and carotid arteries predicted the occurrence of fetal malnutrition with a specificity of 92.3%, a sensitivity of 78.2%, and positive and negative predictive values of 81.8 and 91.5%, respectively. Other investigations (Arias, 1994) have found that a UA/MCA ratio ≤ 1.0

identifies the fetuses at risk for PFGR and poor neonatal outcomes. The predictive value of the UA/MCA ratio loses value after 34 weeks (Bahado-Sing et al., 1999).

MANAGEMENT

The management of pregnant women with PFGR fetuses consists of close fetal surveillance to avoid fetal hypoxia and acidosis and determination of the optimal time for delivery. A second management issue is whether or not delivery should be by cesarean section. Once PFGR is identified, there are multiple tests available for fetal surveillance including FHR monitoring, UA and MCA Doppler studies, Doppler of the fetal venous circulation, assessment of the amniotic fluid volume, biophysical profile (BPP), and the contraction stress test (CST). In the following paragraphs we will analyze the value of each of these tests individually, recommend a sequence of testing consistent with the pathophysiology of FGR, and discuss the best way to deliver these fetuses.

Methods for Surveillance of the Pathological Growth-Retarded Fetus

FHR monitoring

FHR monitoring is an important tool in the follow-up of PFGR fetus. When PFGR is detected in early stages, FHR monitoring will show a sequence of changes that correlate with worsening in the fetal situation. The usual order of appearance of FHR monitoring changes is lack of accelerations, decreased variability, and onset of spontaneous decelerations. All, some, or none of these abnormalities may be present in the initial evaluation of PFGR. They not only are dependent on the severity of the fetal compromise but also on the gestational age at the time of the fetal assessment. At less than 32 weeks' gestation it is unusual to obtain an accelerative pattern even if the fetus is not compromised. When accelerations are present they are usually not more than 10 bpm above the baseline. A similar situation occurs with variability which is normally decreased in fetuses of less than 32 weeks. Lack of awareness of these FHR changes associated with early gestational age may lead to unnecessary preterm delivery. The usual frequency of FHR monitoring for PFGR fetuses is twice every week for 30 minutes, although daily monitoring is sometimes performed in pregnant patients remote from term admitted to the hospital secondary to maternal conditions associated with PFGR.

FHR monitoring is a sensitive indicator of fetal hypoxia and acidosis but lacks specificity and has a significant number of false positive results. For that reason the presence of FHR abnormalities is not by itself an indication for preterm delivery unless the pattern is ominous with repetitive spontaneous decelerations and absent variability. This pattern indicates exhaustion of the fetal compensatory mechanisms, hypoxia, and metabolic acidosis. Other abnormal FHR patterns, particularly decreased variability without associated decelerations, are not reassuring and demand confirmatory backup testing using arterial or venous Doppler, contractions stress testing, or BPP. A comparison between FHR monitoring and UA velocimetry demonstrated that UA velocimetry is more effective than FHR monitoring in the surveillance of the FGR fetus (Almstrom et al., 1992).

Biophysical profile

The BPP is a combination of observation of the fetal behavior with ultrasound (fetal breathing movements, fetal movements, fetal tone, and amniotic fluid volume) and FHR monitoring and is a sensitive test to determine exhaustion of the fetal reserve. Vintzileos et al. (1991a) demonstrated that the components of the BPP follow a sequential order in their disappearance that is directly related to the severity of fetal acidosis. The first variables in the test that are affected by fetal acidosis are the reactivity of the FHR and the fetal respiratory movements. Next affected are the fetal movements and the last variable to disappear, when acidosis is severe, is the muscle tone. This property makes the test valuable because when the NST (nonstress test) is not reactive and the other components of the BPP are present, the fetus is not acidotic. When the NST is nonreactive and oligohydramnios is present (BPP score of 6) but fetal movements and muscle tone are present, the fetus may be compensating adequately or may be mildly acidotic and UA Doppler assessment is necessary to make the differential diagnosis between these situations. Similarly, Doppler assessment is necessary to confirm or rule out acidosis when the NST is nonreactive, oligohydramnios is present, and fetal breathing movements are not seen (BPP score of 4). BPP scores less than 4 are indicators of fetal acidosis and no backup testing is necessary. The usual frequency of BPP observations in the surveillance of the FGR fetus is weekly or twice a week.

The BPP requires familiarity with the use of ultrasound and consumes a significant amount of operator's time. For these reasons many institutions use the modified biophysical profile (MBPP) consisting of NST plus assessment of the amniotic fluid volume and only perform the complete BPP when one or both of these variables are altered. Another reason to use the modified BPP is that the complete BPP is not sensitive to the fetal adaptative hemodynamic changes and usually deteriorates abruptly just before delivery. UA Doppler velocimetry is better than the BPP in predicting fetal acidemia (Yoon et al., 1993). Once the BPP score reaches 6 (nonreactive

NST + decreased amniotic fluid or nonreactive NST + absent breathing movements), it should not be used further and fetal assessment will depend on other tests (UA and venous Doppler), offering earlier warning of the presence of fetal acidemia.

Umbilical and middle cerebral artery Doppler

Doppler velocimetry is the best method of surveillance for fetal hypoxemia/acidemia in PFGR secondary to placental insufficiency as demonstrated by comparative trials with FHR monitoring and BPP (Almstrom et al., 1992; Yoon et al., 1993). Furthermore, Doppler velocimetry demonstrates fetal hemodynamic alterations secondary to PFGR much before FHR monitoring and BPP exhibit abnormalities. Similar to FHR and BPP the UA and MCA Doppler follow sequential changes that parallel the extent of the fetal compromise. Initially the UA S/D ratio increases and the MCA S/D ratio decreases, indicating increased placental vascular resistance. Then the MCA S/D ratio becomes lower than the UA S/D, indicating centralization of flow. Next, the UA Doppler shows ADF and finally RDF is observed, indicating that fetal compensation is exhausted and hypoxia and acidosis are present. Each of these changes corresponds to more severe stages of fetal deterioration and when RDF is present fetal death is imminent. Similarly to FHR monitoring all, some, or none of the UA and MCA Doppler changes may be found at the initial evaluation of PFGR.

The presence of increased UA S/D ratio with concomitant decrease in MCA S/D ratio or the presence of centralization (UA/MCA ≤ 1.0) are not indications for preterm delivery of the PFGR fetus. In contrast, ADF and RDF are signs of decompensation of the fetal homeostatic mechanisms and are an indication for delivery. In some occasions, these Doppler markers of severe fetal compromise appear at early gestational age and there is a tendency to prolong the pregnancy using daily testing rather than to deliver. This is an error because 97% of fetuses with ADF have abnormal blood gases in umbilical cord blood samples (Donner et al., 1995). The fetus, despite its precarious situation, will be better outside of the uterus than under continuous intrauterine conditions of hypoxia and acidosis.

Venous Doppler

Fetuses with severe PFGR secondary to placental insufficiency usually follow a characteristic sequence of Doppler changes. In the initial stages of placental insufficiency, there is increased resistance to UA flow. This is followed by early Doppler changes consisting in decreased central, cerebral, and heart vascular resistance and an increased peripheral, splacnic, and placental resistance causing redistribution of the blood flow and maximum oxygen delivery to the brain and myocardium. As placental insufficiency increases, the fetus is no longer able to deliver an adequate oxygen supply to the myocardium and signs of heart failure appear in the venous flow velocity waveforms (late Doppler changes). The period of time between early and late Doppler changes varies between 1 and 9 weeks (Arduini et al., 1993).

A considerable amount of the oxygenated blood coming from the placenta to the fetus by the umbilical vein bypasses the liver and goes directly to the right atrium through the DV and then through the foramen ovale to the left atrium and ventricle to satisfy the oxygen needs of the upper part of the body and particularly of the brain and the heart. The DV is relatively easy to identify with the help of color Doppler which shows a vascular structure with marked turbulence of flow between the inferior vena cava just below the connection with the right atrium and the portal vein. The turbulence is a reflection of the fast blood flow through the infundibular structure of the DV. Doppler waveforms from this vessel show continuous forward flow with two distinct peaks that correspond to the systolic and diastolic phases of the cardiac cycle and a nadir that corresponds to atrial contraction (Figure 1-12). During ventricular systole the atria relaxes and there is rapid forward flow from the ductus into the left atrium. The forward flow in the ductus continues when the mitral valve opens to initiate the passive filling of the left ventricle. When atrial contraction and active ventricular filling occurs the foramen ovale closes and the resistance to flow is indicated by a nadir in the DV waveform. Abnormal waveforms are characterized by interruption of the forward flow and in more severe cases by reverse flow in the atrial phase of the cardiac contraction. Although the blood flow from the DV goes to the left side of the heart, abnormalities in its waveforms reflect right ventricular dysfunction. The explanation for this is that the foramen ovale closes at the time of left atrial contraction and therefore the DV waveforms reflect the contraction of the right rather than the left atrium. These alterations in DV waveforms indicate the presence of right ventricular dysfunction and the proximity of fetal death.

The alterations in venous flow characteristic of fetal hemodynamic decompensation and proximity of fetal death are the presence of end-diastolic pulsations in the umbilical vein, interrupted forward flow in the DV, and increase in reverse velocity during atrial contraction in the inferior vena cava. These alterations have a strong correlation with the presence of fetal acidemia (Baschat et al., 2003) and with poor neonatal outcome. It is not clear which of the venous vessels waveforms has the best correlation with poor fetal outcome, but the DV and the inferior vena cava are relatively easy to interrogate and are not affected by factors known to produce umbilical vein pulsations in the absence of fetal deterioration.

The value of venous Doppler in the assessment of the FGR fetus is controversial. Initially it was thought that changes in venous Doppler followed abnormal UA velocimetry and preceded the deterioration of biophysical parameters characteristic of fetal acidosis (Harrington, 2000). However, in a longitudinal study (Hecher et al., 2001) of FGR fetuses, more than 50% of cases before 32 weeks' gestation exhibited severe FHR abnormalities when the DV waveforms were still normal. This observation was confirmed in another study (Ferrazzi et al., 2002). The same studies found a significant correlation between perinatal mortality and abnormal venous Doppler. Since the pattern of Doppler deterioration in the FGR fetus does not follow a predictable pattern and since venous Doppler abnormalities are associated with high perinatal mortality, it is not adequate to use abnormal venous Doppler as an early indicator of fetal decompensation. However, venous Doppler is useful when used together with FHR monitoring and UA Doppler in the multivessel surveillance of FGR cases with centralization of flow because interruption or reverse forward flow in DV waveforms is by itself an indication for delivery and will separate those fetuses that will need cesarean from those that most likely will not show evidence of decompensation within the following days.

Amniotic fluid volume

Measurement of the amniotic fluid volume is important in the surveillance of PFGR. This evaluation should be performed every week, and the frequency of nonstress testing should be increased if the amount of fluid decreases. The presence of oligohydramnios, defined as the largest umbilical cord free pocket of fluid with diameter ≤ 2 cm, suggests severe fetal compromise in PFGR pregnancies but is not by itself an indication for delivery. This finding requires prompt evaluation with NST and with Doppler. If the Doppler shows absent or reversed diastolic blood flow, the fetal prognosis is poor and delivery is the best management. Also, if the NST shows spontaneous decelerations with absent variability the patient should be delivered. If FHR monitoring and UA Doppler do not show severe abnormalities the pregnancy can continue under close surveillance.

The possibility of a severe congenital fetal malformation must be considered when severe oligohydramnios is found in the initial evaluation of PFGR. Severe PFGR with oligohydramnios is a common presentation of fetuses with bilateral renal agenesis or obstructive uropathy.

Amniocentesis

There are few reasons for performing amniocentesis for fetal pulmonary maturity in PFGR. Delivery should be for maternal or fetal indications before 36 weeks. After 36 weeks, little is gained by keeping the fetus in the uterus and delivery should be the rule.

Umbilical cord blood sampling

Umbilical cord blood sampling is rarely indicated in the management of PFGR. The most common indication for this procedure is the need to make a rapid determination of the fetal karyotype when a chromosomal defect is suspected. However, with present technology, a rapid karyotype can be obtained using amniotic fluid obtained by amniocentesis—a procedure with much less risk than cordocentesis—in almost the same time that it takes to obtain results from a sample of fetal blood. Some investigators have suggested using umbilical cord blood sampling to assess the degree of fetal hypoxia and acidosis. There are few occasions when this evaluation is necessary or useful. Nicolini et al. (1990) found similar umbilical blood gases measurements in PFGR fetuses that survived and in those who died in the perinatal period indicating that fetal blood sampling has a limited value in the evaluation of PFGR fetuses. Umbilical blood sampling is more dangerous in the PFGR than in other fetuses, and they frequently develop prolonged, severe bradycardia during the procedure, requiring emergency cesarean delivery.

Management of the Pathological Growth Restricted Fetus

The optimal system to monitor the FGR fetus has not been defined by randomized clinical trials. Some centers rely on FHR monitoring (the NST), others on the BPP, others on UA velocimetry alone or in combination with MCA velocimetry, others on venous Doppler, and others on a combination of these tests. An optimal methodology should recognize the significant differences that exist when FGR is of early or late onset, will differentiate between small and healthy fetuses and small fetuses because of pathological growth restriction, and will allow for individualization of testing according to the severity of the placental insufficiency and the hemodynamic situation of the fetus. Furthermore, optimal management will avoid delivery of the preterm PFGR infant that is adequately compensating for the placental failure and will recommend delivery when initial signs of acidemia (Box 4-4) are detected. Once acidemia is established (Box 4-5) the probability of a poor neonatal outcome is significant.

The prognosis and surveillance of PFGR is different depending on the gestational age at the time of diagnosis. It is possible to distinguish three groups of patients: (a) PFGR before 24 weeks (b) PFGR between 24 and 32 weeks, and (c) PFGR after 32 weeks.

BOX 4-4

Beginning of fetal acidosis

Fetal heart rate monitoring	No accelerations. Absent or minimal variability
Umbilical artery Doppler	Absent diastolic flow
Biophysical profile	6
Ductus venosus	Decreased or absent forward flow during atrial contraction

BOX 4-5

Established fetal acidosis

Fetal heart rate monitoring	No accelerations. Absent or markedly decreased variability. Repetitive spontaneous decelerations
Umbilical artery Doppler	Reversed diastolic blood flow
Biophysical profile	4 or less
Ductus venosus	Reversed flow during atrial contraction

Before 24 weeks of gestation

PFGR before 24 weeks is uncommon and the prognosis is extremely poor. This situation occurs in the most severe cases of abnormal placentation or is genetic in origin. Genetic FGR is usually accompanied by normal or increased amniotic fluid volume, is asymmetric with elevated F/A and H/A ratios, and exceptionally shows ADF or RDF or centralization. Early severe placental insufficiency usually presents with decreased amniotic fluid and markedly abnormal uterine artery and UA velocimetry. In these cases the placenta is small and has marked histological changes. The prognosis is poor and attempts to prolong the pregnancy usually end in fetal death. Unfortunately, early delivery usually ends in neonatal death. When early severe placental insufficiency occurs, the risk of recurrence in subsequent pregnancies is high.

Monitoring of pregnancies less than 24 weeks with severe growth restriction consists mainly of the use of UA and DV Doppler. At this early gestational age, variability is minimal and accelerations are not present. Therefore, two of the main variables of fetal well-being assessment with FHR monitoring cannot be reliably used. However, spontaneous decelerations of the FHR will occur when the fetus is in terminal stage. A similar situation occurs with the BPP. In this particular situation the NST is nonreactive, the amniotic fluid is decreased, and respiratory movements are not present. Therefore, in the majority of cases the baseline BPP will be 4 and the two remaining variables will disappear shortly and relatively suddenly preceding death. This leaves UA, MCA, and DV Doppler velocimetry as the most reliable tools for evaluation of the fetus at this early gestational age. Unfortunately, in the majority of these cases Doppler changes are already severe at the time of the initial evaluation or deteriorate rapidly. If UA diastolic flow is present and the DV has uninterrupted forward flow, expectancy is clearly the best management. If the UA has RDF or the DV shows interrupted forward flow, the fetus is acidotic and hypoxic and death is imminent. A management problem is when the UA diastolic flow is absent because the interval between this abnormality and further changes in the UA can be of several days and occasionally more than 1 week. In these cases, since death is almost certain if these tiny fetuses are delivered before 24 weeks, most likely the best option will be not to deliver although it is possible that waiting could be as harmful as delivery.

Making a decision between continuation and interruption of the pregnancy in fetuses of less than 24 weeks with ADF or RDF with or without interrupted DV atrial flow is extremely difficult. These fetuses have exhausted their compensatory mechanisms and prolongation of the pregnancy will keep them in an acidemic milieu, further reducing their limited capacity for adaptation to the extrauterine environment. Delivery, on the other hand, is of little or no benefit. The multiple metabolic effects of severe placental insufficiency added to the early gestational age drastically limit the probabilities of fetal survival and in the few that survive, the sequelae of prematurity are severe. Parents should be extensively counseled and involved in the decision to deliver and how to deliver.

There is no evidence that corticosteroids accelerate the fetal pulmonary maturity or prevent the development of IVH in PFGR fetuses of less than 24 weeks. On the other hand, there is evidence suggesting that the use of corticosteroids in severely PFGR fetuses may cause hemodynamic decompensation and worsen the outcome of the pregnancy (Simchen et al., 2004). Other studies have found no effect of antenatal steroids in UA, MCA, and DV waveforms (Wijnberger et al., 2004).

Between 24 and 32 weeks of gestation

There are changes in the etiology of FGR with advances in the gestational age. The majority of cases of FGR between 24 and 32 weeks are placental in origin and approximately 20% have a genetic basis. Also, approximately 20% of the cases correspond to fetuses that are small but healthy. The differential diagnosis among these conditions is based on their ultrasonic characteristics and Doppler waveforms. Monitoring of fetuses with PFGR secondary to placental insufficiency is based on FHR, UA, and DV Doppler. FHR variability is present at this gestational age although it is decreased as compared with pregnancies in the third trimester. Also, discrete accelerations

of no more than 10 bpm start to develop after 24 weeks and are always present after 32 weeks. When these variations in FHR secondary to gestational age are taken into consideration, FHR monitoring becomes a useful instrument to monitor PFGR at this gestational age. Fetal breathing movements also appear between 24 and 30 weeks, facilitating the use of the BPP for the monitoring of these fetuses. However, the basis for the surveillance of the fetal well-being at this gestational age is the UA, MCA, and DV Doppler waveforms. The frequency of fetal testing is related to the severity of the fetal compromise as shown by UA velocimetry. If the UA diastolic blood flow is preserved and there is no centralization of flow, UA Doppler studies are performed once every week. When centralization of flow is present, FHR monitoring twice per week is added to the weekly UA velocimetry. When UA shows ADF and the FHR monitoring does not exhibit spontaneous decelerations the DV may help in the decision to deliver or to continue the pregnancy particularly if the gestation is of less than 28 weeks.

Fetuses with placental insufficiency detected between 24 and 32 weeks are at significant risk of fetal and neonatal complications but when they are delivered before advanced decompensation the prognosis is fairly good. Since prolongation of pregnancy, even for a few days, has a significant impact in neonatal morbidity, investigators have proposed the use of DV Doppler as an indicator of the possibility of prolongation of pregnancy in PFGR fetuses with UA ADF. If the DV waveforms show interruption or reversed forward flow or the PI is > 3.0 standard deviations from the mean, the fetal prognosis is poor and delivery is indicated. If none of these alterations exist it is permissible to continue the pregnancy with daily monitoring until further deterioration is indicated by spontaneous decelerations of the FHR, RDF in the UA, or interrupted forward flow in the DV (Baschat, 2004; Bilardo et al., 2004). One problem with this recommendation is that the fetus with UA ADF is already hypoxic and acidotic as demonstrated by cordocentesis or by arterial blood gases at the time of delivery. Therefore, continuation of the pregnancy when UA ADF is present is equivalent to keeping the fetus in an acidemic environment with potential serious consequences. Another objection to this management is that the end point to deliver the fetus is one associated with extremely poor outcome begging the question if it is not better to deliver them before complete exhaustion of the reserves and compensation mechanism occurs.

Between 32 and 36 weeks of gestation

Between 32 and 36 weeks the genetic etiology drops to less than 5% and the frequency of fetuses that are small but healthy increases to more than 50%. Small and normal fetuses have a normal amniotic fluid volume, symmetric anthropometric measurements, normal UA and MCA and uterine Doppler, and in follow-up ultrasounds they grow linearly in the same percentile of the growth curve (low-growth profile). Small fetuses because of placental insufficiency do not grow linearly and repeated ultrasounds show that the EFW falls into lower percentiles with each subsequent measurement.

Fetuses with placental insufficiency in the third trimester of pregnancy can be classified in three groups depending on the findings in Doppler velocimetry, similarly to the classification proposed by Ducey et al. (1987) for women with preeclampsia.

1. Women with abnormal uterine and normal umbilical Doppler
2. Women with normal uterine and abnormal umbilical Doppler
3. Women with abnormal uterine and umbilical Doppler

FGR with abnormal uterine and normal umbilical Doppler

Approximately 30% of PFGR fetuses with normal UA Doppler waveforms have abnormal uterine artery Doppler (McCowan et al., 2000). Patients in this group may have unilateral or bilateral uterine artery notching but diastolic flow in the UAs is preserved. Progression of the Doppler changes is unusual in this group but their potential for adaptation is low and they frequently develop nonreassuring FHR monitoring patterns and meconium-stained fluid during labor. These PFGR fetuses have a fourfold increase in adverse outcomes (Vergani et al., 2002) and approximately 10% of them (McCowan et al., 2000) will develop centralization of flow despite the normal umbilical S/D ratio. A decrease in MCA resistance with UA/MCA ratio < 1.0 in fetuses with normal UA and abnormal uterine Doppler is associated with an 88% incidence of FHR abnormalities and cesarean delivery (Severi et al., 2002). Antepartum surveillance will be adequate with weekly MBPP (NST + amniotic fluid volume) and UA and MCA Doppler. If the tests remain normal, delivery can wait until 38 weeks. An oxytocin challenge test before induction of labor may be useful for the early detection of those destined to develop FHR alterations during labor.

FGR with normal uterine and abnormal umbilical Doppler

PFGR pregnancies with normal uterine and abnormal UA Doppler are rare and are at high-risk for fetal and neonatal complications. In these cases the placental pathology is localized in the fetal side and neonatal problems may be frequent and severe. Neonatal thrombocytopenia is common. Abnormal FHR patterns develop in approximately 40% of these cases. Surveillance should include MBPP (NST +

amniotic fluid volume) twice a week and UA and MCA Doppler every week. Parents should be cautioned of the possibility of abnormal outcome even if the fetus is delivered by cesarean.

FGR with abnormal uterine and umbilical Doppler

The group with abnormal uterine artery and UA Doppler waveforms is the one at highest risk for fetal and neonatal complications. In these cases PFGR is usually discovered early and delivery is usually required before 34 weeks. Antenatal surveillance should include the MBPP (NST + amniotic fluid volume) twice per week, UA, MCA, and venous Doppler every week, and delivery will be indicated when any of these tests indicates fetal decompensation.

After 36 weeks of gestation

After 36 weeks of gestation PFGR of genetic origin is uncommon and the majority of cases correspond to fetuses that are small and healthy. Constitutionally small, healthy fetuses characteristically have normal fluid volume, symmetric measurements, and normal umbilical, cerebral, and uterine Doppler. They have no placental insufficiency, can be followed like any other normal pregnancy, and delivered at term. At this gestational age, severe abnormalities of the UA or DV waveforms are rarely seen. However, when abnormal umbilical or uterine Doppler resistance is detected indicating placental insufficiency or the NST is nonreactive, the advantages of delivery over expectancy are clear. Figure 4-2 is a flow diagram of the clinical progression of PFGR and the alterations in surveillance tests associated with increased severity of the condition. Figure 4-3 is a flow diagram of the management of PFGR.

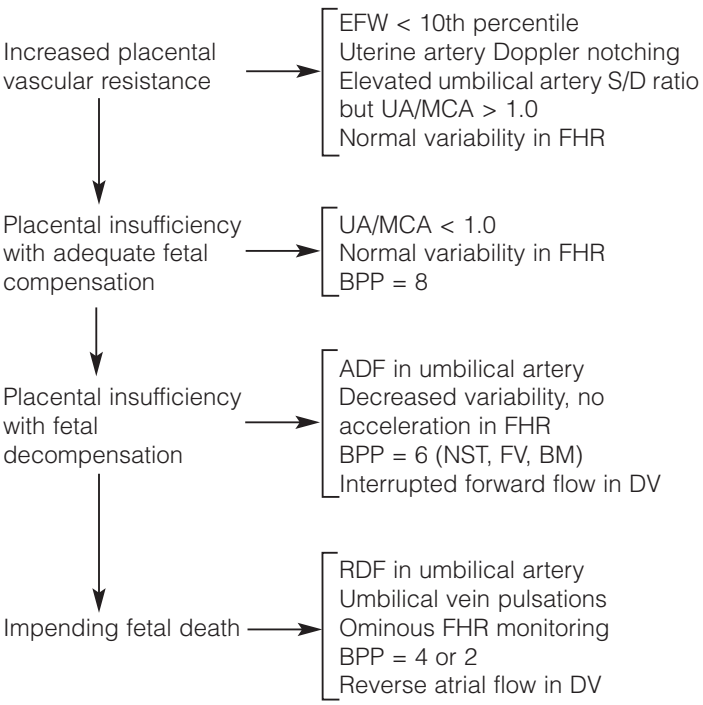

Figure 4-2. Progression of placental insufficiency and its effects on surveillance tests.

Delivery of the Pathological Growth-Retarded Fetus

The full-term fetus has a large capacity to tolerate the hypoxic stress of labor. This capacity is substantially reduced in PFGR due to the marked depletion of energy stores in the liver and subcutaneous tissues. With hypoxia, the energy reserves are rapidly consumed and the fetus must switch to anaerobic metabolism for the generation of energy. Unfortunately, anaerobic metabolism produces a large number of hydrogen ions, and metabolic acidosis appears. Thus, it is not surprising that intrapartum asphyxia is the major cause of perinatal morbidity and mortality in PFGR. Therefore, when umbilical Doppler shows ADF or RDF, conditions strongly associated with fetal hypoxia and acidosis, or when the FHR shows an ominous pattern, delivery by cesarean section is indicated. The question is how to deliver the PFGR fetus having lesser degrees of Doppler or FHR abnormalities.

In an attempt to determine if women with increased resistance in UA velocimetry could be delivered safely by the vaginal route, a group of investigators (Skinner et al., 1998) compared 45 patients delivered by elective cesarean section with 73 who were allowed to labor. The incidence of emergency cesarean in the group allowed to labor was 9.8% and three newborns had a pH < 7.20. In another study Li et al. (2003) compared 51 cases of suspected FGR with normal UA Doppler with 33 cases with abnormal Doppler results. They found a higher incidence of positive CSTs in the group with abnormal velocimetry (33%) than in the group with normal UA Doppler (16%). The incidence of cesarean delivery was 63 and 40%, respectively. The conclusion from these studies is that vaginal delivery is not contraindicated in patients with increased resistance in UA velocimetry but cesarean delivery should be anticipated in a large number of them. A CST at the time of admission may be useful for the early identification of some of the patients that will require cesarean. Some common indications for cesarean delivery in women with PFGR are shown in Box 4-6.

In cases expected to have a large enough fetal reserve to tolerate the effect of uterine contractions, direct fetal

BOX 4-6

Indications for cesarean delivery in PFGR pregnancies

- Initial or established fetal acidosis
- No increase in EFW in ultrasound examinations 3 weeks apart
- Oligohydramnios with repetitive variable decelerations

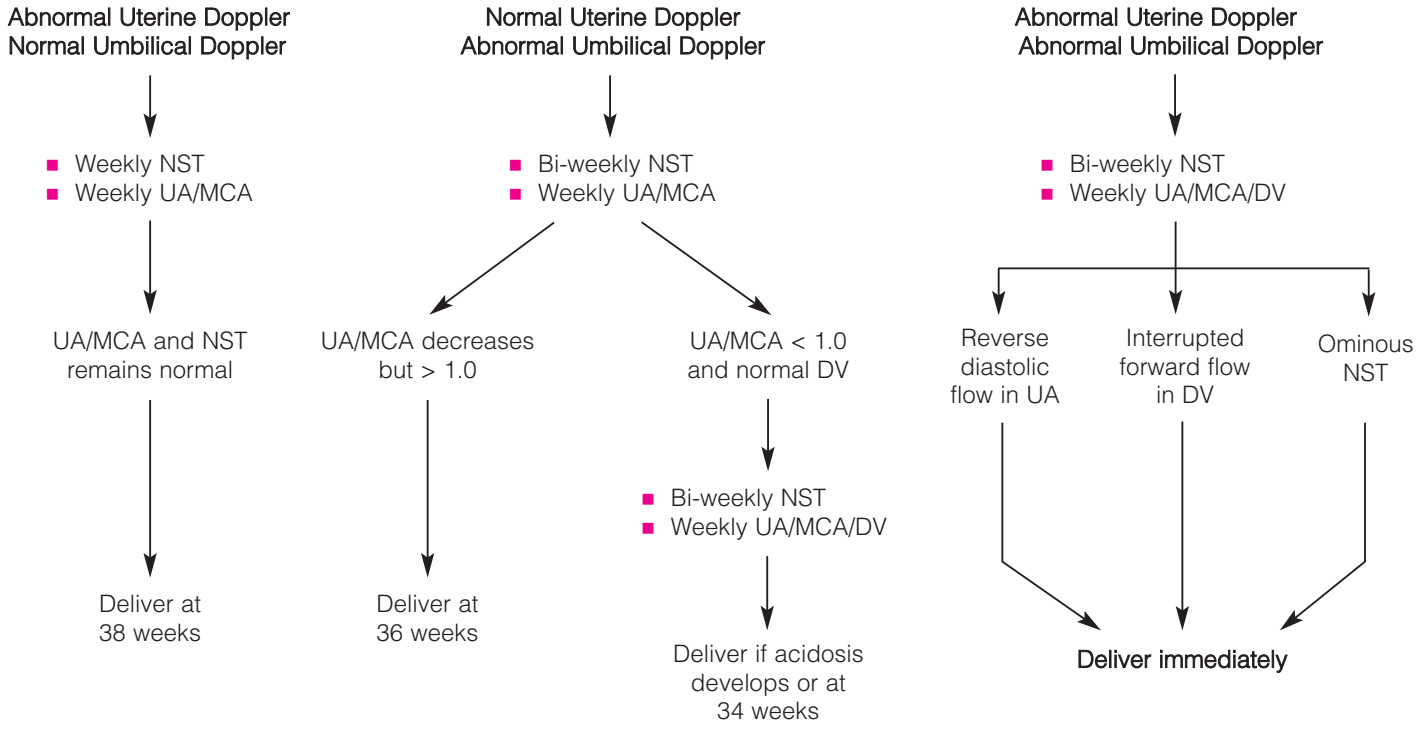

Figure 4-3. Management of fetal growth restriction secondary to placental insufficiency.

monitoring using a scalp electrode and a uterine pressure catheter should be utilized as early as possible. Amnioinfusion should be performed early in labor if the amniotic fluid volume is decreased. Alterations of FHR monitoring suggesting fetal compromise should be followed by cesarean delivery. The second stage of labor requires special attention and the obstetrician should be ready to intervene and deliver by cesarean if repetitive decelerations and decreased variability occur. In most cases it is preferable to avoid pushing during the second stage and let the fetus descend under the exclusive effect of the uterine contractions. In cases of PFGR it is not recommended to prolong the duration of the second stage for more than 2 hours in nulliparous and 1 hour in multiparous patients.

The best choice for pain relief during labor in PFGR is epidural anesthesia. However, these patients may develop hypotension even after proper intravascular volume loading with lactated Ringer's solution. Also, epidural anesthesia is associated with prolongation of the second stage of labor. These inconveniences are not insurmountable and epidural anesthesia in the hands of a competent obstetric anesthesiologist is the procedure of choice.

The placenta in PFGR cases needs careful examination by a competent placental pathologist because in many cases this examination will provide evidence about the etiology of the problem (Rayburn et al., 1989). Fetal stem arteries thrombosis, infarcts, fibrin deposition, insufficient invasion of spiral arteries, and cord insertion abnormalities are some of the findings in the placenta in FGR cases.

Ideally, a neonatologist should be present at the time of delivery in PFGR cases. The neonatal course of the infant will be better if sophisticated neonatal treatment begins shortly after childbirth.

TREATMENT OF FGR

There are no effective therapies for FGR. The reasons behind the failed attempts to modify the fetal situation are multiple but perhaps the most important one is that there are no available means for the early detection and modification of poor placentation—a condition that starts a few weeks after conception but is not usually detected until several weeks later.

Bed Rest

The rational behind bed rest in the treatment of FGR is the idea that blood flow to the placenta will increase if the activities of other organs such as legs and arms is decreased. However, randomized clinical trials have demonstrated no benefit of bed rest in FGR (Laurin and Person, 1987).

Nutritional Supplementation

The rationale behind provision of additional protein-caloric supplementation to the mother of the FGR fetus are observations of reduced birth weight in situations of

severe maternal nutritional deprivation (total daily caloric intake of less than 500 calories). Unfortunately, most studies in protein-caloric supplementation have reduced number of subjects and have shown no effect or minimal effect on impaired fetal weight.

Hyperoxygenation

Fetal oxygenation is crucial for fetal growth as demonstrated by observations of FGR in mothers with cyanotic heart disease and the increased occurrence of lower birth weights at high altitudes. In an investigation using historical controls Nicolaides et al. (1987) found a significant decrease in fetal mortality (85 to 20%) in cases of severe PFGR when the mother received oxygen supplementation (8 L/min by face mask, continuously). In a similar study Battaglia et al. (1992) found a significant decrease in perinatal mortality in the group treated with hyperoxygenation (29%) as compared with the untreated control group (68%). The number of patients in these studies is small and there is a theoretical potential for fetal and maternal oxygen toxicity that make further investigation necessary before oxygen therapy becomes an accepted therapy for PFGR.

The fetal response to hyperoxygenation as evaluated by Doppler velocimetry of the arterial circulation may be an important test to predict the fetal outcome in cases of PFGR. A positive response to oxygenation demonstrated by decreased resistance in the placental circulation is a marker of good prognosis and the lack of response is an indication of poor outcome (Bilardo et al., 1991; de Rochambeau et al., 1992).

Aspirin

Aspirin in low doses (1–2 mg/k/day) inhibits the production of thromboxane A2 by the platelets and changes the thromboxane to prostacyclin ratio. Theoretically these changes should result in vasodilatation of the uteroplacental circulation. For this reason aspirin has been extensively studied in the prevention and treatment of PFGR and preeclampsia with confusing results. Trudinger et al. (1988) administered 150 mg/day of aspirin to 22 patients with abnormal UA velocimetry and found a mean birth weight increase of 516 g in patients who received aspirin when compared with controls. The EPREDA trial randomized 323 patients among placebo, aspirin, and aspirin plus dipyridamole and found an incidence of FGR of 13% in the aspirin-treated group compared with 26% in the group taking placebo. The Italian study randomized 1106 women to receive either 50 mg daily of aspirin or no treatment and found no differences between the groups in the incidence of FGR. The Maternal–Fetal Medicine network randomized 3135 women to receive 60 mg/day aspirin or placebo and found no significant difference in the incidence of PFGR. The CLASP study randomized 9364 women to receive 60 mg/day of aspirin or placebo and found a similar incidence of PFGR (CLASP Collaborative Group, 1994). However, a meta-analysis of 13 published randomized clinical trials (Leitich et al., 1997) showed that early aspirin treatment reduces the risk of FGR. Since low-dose aspirin has little or no maternal and fetal risk, administration of this medication to women at risk of PFGR is probably justified.

INDIAN EXPERIENCE OF FETAL GROWTH RESTRICTION

Low birth weight is a major problem in India. Nearly 3 million low birth weight babies are born annually in India (Tambyraja, 1992). It accounts for more than half of neonatal deaths (Dasgupta, 2003).

The incidence of low birth weight in India varies from 15 to 25%. Of these more than 50% are due to IUGR. The main contributory causes include poor maternal nutrition, hypertensive disorders complicating pregnancy, maternal medical disorders (anemia, heart disease, diabetes, epilepsy, infections), obstetric disorders (hydramnios, multiple pregnancy, congenital fetal malformations), lifestyle influences (physically strenuous occupations, exposure to toxic chemicals, smoking, alcohol in excess and drug abuse, infections, etc.). In important contributions on the subject, Chandra and Mathews (2003), from Goa, reported that the incidence of low birth weight babies in their hospital was 23.8%; of these, 14.1% were due to IUGR. Some highlights of comparative studies of fetal outcome in low birth weight infants designated as appropriate for gestation age (preterm) as compared to those classified as light for gestational age (IUGR) have been tabulated below. Table 4-3 shows that IUGR infants are more prone to birth asphyxia, polycythemia, and metabolic disorders, whereas small, preterm babies are more prone to respiratory distress syndrome, birth injuries, infection, and perinatal loss.

Table 4-3. Comparison of fetal outcome of IUGR infants and low birth weight, preterm infants

Fetal complication	IUGR	Preterm
Birth asphyxia	12.32%	3.58%
Polycythemia	8.81%	3.51%
Hyperbilirubinemia	6.49%	3.65%
Hypoglycemia	4.70%	1.94%
Hypothermia	3.36%	2.53%
Hypocalcemia	1.94%	2.53%
Septicemia	1.05%	1.57%
Respiratory distress syndrome	-	4.10%
Birth injuries	1.51%	3.37%
Perinatal mortality	4.85%	8.7%

Table 4-4. Comparison of obstetric outcome of IUGR births and normal controls

Parameter of comparison	IUGR	Normal controls
Incidence of operative delivery	22.0%	15.3%
Early neonatal morbidity	31.33%	4.6%
Early neonatal mortality	10.6%	0.1%
Late neonatal morbidity	14.0%	Insignificant

Table 4-5. Perinatal outcome in mothers with anemia complicating pregnancy

Parameter of comparison	Moderate anemia (Hb < 8.0 g%)	Nonanemic controls (Hb > 10.5 g%)
Preterm births	13.2%	3.1%
IUGR births	37.5%	7.5%
Neonatal asphyxia	7.0%	3.0%
Congenital malformations	1.5%	1.0%
Stillbirths	6.5%	2.0%
Neonatal deaths	4.5%	1.0%
Average birth weight	2.05 kg	2.5 kg
Perinatal mortality rate	117.6/1000	30.6/1000

In another interesting study on the subject, from Pune (Sambrey and Bhangale, 2001), comparing the perinatal outcome of patients with IUGR versus normal controls, the following observations were recorded (Table 4-4).

The predominant indication for cesarean delivery was fetal distress in the IUGR group, but the dominant indication in the control group was cephalopelvic disproportion. Early neonatal morbidity was principally respiratory distress at birth. Late neonatal morbidity included poor weight gain, diarrhea, and respiratory infections.

Among the medical disorders contributing to poor intrauterine fetal growth, anemia heads the list. In an interesting study from Indore on the subject of the effects of anemia on perinatal outcome, Awasthi et al. (2001) reported the following observations (Table 4-5).

Table 4-5 clearly points out the need to detect and treat anemia during pregnancy. It is the single most important cause contributing to adverse obstetric outcome. Heart disease is associated with a higher incidence of preterm births and low birth weight infants. The incidence of low birth weight babies is as high as 30% in pregnant women suffering from cyanotic heart disease (Daftary and Desai, 2006).

Diabetes complicating pregnancy occurs in 3–5% of women. Almost 90% of these are cases of gestation diabetes. These women are more prone to develop pregnancy-induced hypertension, placental insufficiency, IUGR, hydramnios leading to preterm births, congenital fetal anomalies, and higher perinatal loss. Uncontrolled diabetes is often associated with fetal macrosomia. Infants of diabetic mothers are highly vulnerable to problems of respiratory distress after birth and birth trauma-particularly in women with poor glycemic control. Uncontrolled hypothyroidism also predisposes to low birth weight and congenital fetal malformation (Majumdar et al., 2003).

Hypertensive disorders in pregnancy are associated with low birth weight infants (preterm + IUGR). Perinatal mortality is higher in affected pregnancies. In a study of fetal well-being in normal and hypertensive pregnancies, from Aligarh (Saxena et al., 2001), based on blood flow in the evaluation of fetal well-being, the incidence of IUGR was reported to be 33.37%. The mean birth weight of affected infants was 2.4 kg (controls 2.85 kg) and a perinatal loss of 30/1000. On color Doppler, the middle cerebral artery blood flow is a better indicator of fetal compromise.

Ultrasonography plays an important role in identifying growth-retarded fetuses and in assessing intrauterine fetal well-being. Sonographic estimations of fetal diameters (BPD, AC, FL) estimated fetal weight, placental grading, amniotic fluid index (AFI), and umbilical artery Doppler waveforms provide clues to the diagnosis of IUGR and fetal well-being.

Coyaji and Otiv (2001) from Pune compared the sensitivity of individual ultrasonographic parameters for detecting fetal growth retardation (Table 4-6).

Of all the fetal measurements, the one single measurement of greatest value in suspecting the possibility of IUGR is AC. If this reading is normal, it almost excludes the diagnosis of IUGR. Umbilical artery Doppler waveforms provide the guidelines for instituting obstetric intervention to save the fetus.

Evaluation of placental grading and its correlation with perinatal outcome in IUGR revealed that placental grading has no correlation with the incidence of fetal distress or meconium-stained liquor; however, the birth weight was significantly lower in IUGR babies with grade 3 placentas (Kumari et al., 2001). In this study from Chandigarh, fetal outcome in women with grade 3 placentas could be summarized as follows. The incidence of grade 3 placentas in IUGR cases was 58%, with mean birth weight of 1482.3 ± 320.5 g and a higher perinatal

Table 4-6. Sensitivity of ultrasonographic diameters for detecting IUGR

Parameter	Sensitivity (%)
Abdominal circumference (AC)	96–100
Femur length (FL)	20–45
Head/abdominal circumference (HC/AC)	About 70
Femur length/abdominal circumference (FL/AC)	About 63
Estimated fetal weight percentile	About 87
Ponderal index (PI)	47–54

mortality as compared to controls which showed incidence of grade 3 placentas in 36%, a mean birth weight of 1766 ± 484.7 g and no perinatal loss. In a study from Gwalior (Agarwal and Jain, 2000), evaluating placental grading and its correlation with fetal outcome, the authors included 125 high-risk pregnant patients and 125 normal controls. The authors concluded that in women with PIH and IUGR pregnancies, placental grading was accelerated. Placental grade did not correlate with birth weight or Apgar scores. But it correlated well with pulmonary maturity.

An attempt to correlate fetal BPP in IUGR cases with fetal outcome from Jammu (Kumar et al., 2000) reported that high BPP scores correlate well with fetal well-being. In this study of 50 cases, 14 cases (28%) had abnormal or low scores, with 6 perinatal deaths. Of the remaining 36 cases having satisfactory BPP scores, only 2 died; of these, 1 baby had multiple congenital malformations. The authors concluded that BPP has 66% sensitivity and 87% specificity in predicting fetal distress in labor in suspected cases of IUGR.

In Lucknow (Das et al., 2001) a study was undertaken to evaluate the usefulness of amnioinfusion during labor complicated with meconium. The incidence of meconium staining of liquor amnii during labor has been variously reported to be between 9 and 20%. Meconium aspiration syndrome affects 2–4% of these neonates, with an overall perinatal morbidity ranging from 8 to 22%. The authors compared their results of fetal outcome in 100 study cases of meconium-stained liquor treated with amnioinfusion with 290 controls. The results are shown in Table 4-7.

The above findings emphasize the need for resorting to amnioinfusion in cases of meconium-stained liquor detected in labor to improve fetal salvage rate and minimize perinatal morbidity.

AFI forms a part of the BPP used for assessing fetal well-being. AFI has been recognized as an important component of evaluation of fetal well-being, as it is the only indicator of placental perfusion and fetal urine output. A threshold of a single maximum vertical pocket of 1.0 cm of amniotic fluid volume was originally considered satisfactory in BPP by Manning et al. (1980). But later investigations revealed that 2–8 cm was the norm in the third trimester. A mean amniotic fluid pocket of 1–2 cm was considered marginal. The perinatal mortality increased as the fetal outcome of patients with normal AFI (4.5/1000), marginal AFI (956/1000), and diminished AFI (187.5/1000) were compared (Gandhi, 2003).

Table 4-7. Comparative fetal outcome in women with meconium staining treated with amnioinfusion and controls

Parameter of comparison	Amnioinfusion group (100 cases)	Control group (290 cases)
Incidence of cesarean section	59.0%	73.0%
Low Apgar scores (< 5 after 5 minutes)	1.0%	6.8%
Neonatal intensive care	5.0%	21.0%
Meconium in trachea	5.0%	22.0%
Meconium aspiration syndrome	1.0%	17.3%
Neonatal death	1.0%	8.4%
Need for antibiotic administration	27.0%	34.0%

IMPORTANT POINTS

1. The fetus requires several substrates for normal growth. The most important are oxygen, glucose, and amino acids. The availability of substrates may be limited by pathological conditions affecting the mother, the placenta, or the fetus.
2. The term "small for gestational age," or SGA, designates newborns with birth weight less than the 10th percentile for their gestational age. The term "fetal growth restriction," or FGR, is used to designate fetuses with sonographic estimated weight less than the 10th percentile for their gestational age. The similarity between the terms is obvious. Both terms include newborns and fetuses that are small and normal (NFGR) and newborns and fetuses that are affected by pathological (PFGR) conditions restricting their growth.
3. The neonatal diagnosis of PFGR secondary to placental insufficiency is relatively simple because these newborns have decreased subcutaneous fat, abnormal ponderal index, hypoglycemia, hyperviscosity, necrotizing enterocolitis, or other complications of intrauterine malnutrition.
4. To classify a newborn as SGA it is necessary to use an adequate table of birth weight for gestational age. There are several tables available (Brenner's, Alexander) for infants born in USA at sea level and many institutions have developed their own tables.
5. The main antepartum complications of true IUGR fetuses are an increased incidence of stillbirth, oligohydramnios, and antepartum fetal distress.
6. The main intrapartum complications of the true IUGR baby are fetal hypoxia, acidosis, and high rate of cesarean delivery.
7. The neonatal complications of the true IUGR baby are multiple and include hypoglycemia, hyperbilirubinemia, meconium aspiration, persistent fetal circulation, hypoxic-ischemic encephalopathy, hypocalcemia, hyperviscosity syndrome, and necrotizing enterocolitis.
8. The most common causes of IUGR are placental vascular insufficiency, fetal genetic conditions, and maternal conditions.

9. In the majority of cases the clinical findings and ultrasound measurements allow only the diagnosis of "small fetus." The majority of small fetuses are healthy. Only a modest proportion of small fetuses are truly undernourished or PFGR.
10. To distinguish between fetuses that are small and healthy and PFGR it is necessary to use Doppler assessment of the uterine, umbilical, and midcerebral artery resistance.
11. Uterine artery, UA, and MCA Doppler do not identify all PFGR fetuses. Doppler technology is exclusively for the identification of PFGR because of placental insufficiency. Small fetal size in the presence of normal uterine, umbilical, and midcerebral Doppler rules out placental insufficiency.
12. Patients with high-risk factors, unreliable dates, and abnormal or difficult to assess uterine growth are at risk for carrying small fetuses.
13. The most important tests to follow the PFGR fetus are the FHR monitoring and the umbilical and cerebral Doppler. As long as the FHR monitoring is normal and the Doppler does not show fetal decompensation (ADF or RDF) expectant management is adequate.
14. Amnioinfusion with saline solution should be one of the initial steps in the intrapartum management of the PFGR fetus with decreased amniotic fluid volume.
15. The placentas of all PFGR babies should be examined by a competent placental pathologist. In many cases the placenta will provide evidence regarding the etiology of the problem.
16. The earlier in gestation IUGR is detected, the greater the possibility of developmental problems later in life. The worst prognosis is for IUGR secondary to congenital infections, congenital abnormalities, and chromosomal defects.

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5

Fetal Infections

CHAPTER OUTLINE

- Group B Streptococcal Infection
  - Description of the organism
  - Maternal and neonatal colonization and infection
  - Diagnosis
  - Prevention of neonatal infection
  - Treatment of maternal infection
  - Immunization
  - Group B streptococci infection: Indian experience
- Syphilis
  - Maternal infection
  - Serology
  - Congenital syphilis
  - Diagnosis
  - Treatment
  - Management of the penicillin-sensitive patient
  - Serologic follow-up
- Cytomegalovirus Infection
  - The virus
  - Transmission
  - Severe congenital infection
  - Late sequelae
  - Diagnosis
  - Prevention
  - Treatment
  - CMV infection: Indian experience
- Rubella
  - Signs and symptoms
  - Immunity
  - Congenital rubella
  - Diagnosis
  - Management
  - Vaccination
  - Rubella epidemiology: Indian experience
- Human Immunodeficiency Virus Infection
  - Virology
  - Maternal infection
  - Diagnosis
  - Fetal transmission
  - Detection of HIV infection during pregnancy
  - Antepartum care
  - Intrapartum management
  - Postpartum care
  - HIV in pregnancy: Indian experience
- Genital Herpes
  - The virus
  - Maternal infection
  - Neonatal infection
  - Hematogenous transmission
  - Transmission at delivery
  - Diagnosis
  - Identification of women at risk of vertical transmission
  - Antiviral suppressive therapy
  - Cesarean delivery for women with genital HSV lesions
  - Treatment
  - HSV infection: Indian experience
- Varicella
  - The virus
  - Transmission
  - Maternal infection
  - Fetal infection
  - Diagnosis
  - Management
- Viral Hepatitis
  - Transmission
  - Maternal infection
  - Diagnosis
  - Screening
  - Neonatal transmission
  - Prevention of neonatal infection
  - Viral hepatitis: Indian experience
- Parvovirus B19 Infection
  - Maternal infection
  - Fetal transmission
  - Diagnosis
  - Management
- Toxoplasmosis
  - The parasite
  - Maternal infection
  - Congenital transmission
  - Congenital infection
  - Diagnosis
  - Treatment
  - Prevention

Fetal infections are an important cause of mortality and morbidity. Fetal infections may occur at any time during gestation and their severity will vary depending on the virulence of the agent, the susceptibility and gestational age of the fetus, and the route of the infection. In this chapter we discuss the most common and important fetal infections caused by bacterial, viral, and protozoan agents.

GROUP B STREPTOCOCCAL INFECTION

Group B streptococcus (*Streptococcus agalactiae*, or GBS) is the cause of a severe congenital infection that affects 1 neonate out of every 1000 live births every year in USA. GBS also causes maternal infection in particular chorioamnionitis, postpartum endometritis, wound infection, and sepsis and is an important cause of intrauterine asphyxia (Peevy and Chalhub, 1983).

BOX 5-1

Risk factors for early-onset GBS infection

- Ruptured membranes for more than 18 hours
- Preterm delivery
- Term or preterm ruptured membranes at least 1 hour before the onset of contractions
- Multifetal pregnancy
- Intrapartum fever
- GBS bacteriuria
- Multiple digital pelvic examinations during labor
- Previous baby with GBS invasive disease
- Chorioamnionitis

There are two types of GBS neonatal infection: early-onset and late-onset. Early-onset infection usually presents during the first hours of life, is caused by any of five GBS serotypes, and has the clinical characteristics of an overwhelming sepsis. Early-onset disease is often associated with risk factors, especially premature labor, rupture of the membranes for more than 12 hours, and development of fever during labor (Box 5-1). Late-onset infection usually appears 1 week or more after birth and the predominant manifestation is meningitis. Mortality rate is approximately 4.7% for early-onset and 2.8% for late-onset disease (Schrag et al., 2000). With modern intrapartum antibiotic prophylaxis the incidence of early- versus late-onset disease is similar, about 0.5 per 1000 births (Gibbs et al., 2004). The focus of this chapter is the early-onset disease because it is acquired by vertical transmission from mother to fetus. The mechanism of transmission of late-onset disease is different, and nosocomial or community acquisitions are predominant.

Description of the Organism

GBS is a Gram-positive diplococcus that is beta hemolytic, meaning that it shows complete hemolysis on blood agar plates. GBS differs from group A streptococcus (*S. pyogenes*) by the presence of a specific carbohydrate antigen on the cell wall. GBS also produces type-specific polysaccharides antigens that encapsulate the organism and allow its classification into five serotypes. All the capsular polysaccharides have a terminal sialic acid side chain which is their major antigenic determinant. The distribution of isolates from early neonatal sepsis is 38% Ia, 11% Ib, 7% II, 26% III, and 18% V. In cases of late-onset disease the predominant isolate (64% of the cases) is type III.

Maternal and Neonatal Colonization and Infection

GBS colonizes the genitourinary tract of 20–30% of all pregnant women. Colonization may be intermittent or transient. The incidence of colonization varies among different populations and is higher in women of African-American ethnicity. The incidence of colonization varies with the screening methods and is higher when selective broth rather than Agar plates is used as the culture medium and when samples are taken from the lower third of the vagina and the rectum. The rectal sample is of particular importance because colonization of the birth canal is secondary to colonization of the anal-rectal region, which is the major locus for the bacteria. The distribution of serotypes of GBS isolated from rectovaginal cultures is similar to the genital isolates of neonates with early-onset infection. On average approximately 15.0% of all women will be colonized at the time of delivery. However, only a few of these women will have intrapartum or postpartum infections due to GBS.

Antepartum cultures are predictive of intrapartum colonization only if they are obtained within 6 weeks of

delivery (Yancey et al., 1996). Boyer et al. (1983) found 100% predictability for intrapartum colonization if antepartum cultures were obtained less than 6 weeks, 72% when they were obtained 6–10 weeks, 66% if they were obtained 11–30 weeks, and 43% if they were obtained more than 30 weeks before delivery. The predictability of colonization at delivery is 100% for patients with heavy colonization, such as those with GBS bacteriuria or those with a prior GBS-infected infant.

Between 40 and 50% of infants born to untreated women with positive intrapartum cultures for GBS will be colonized at the time of delivery and will exhibit positive surface cultures for the same maternal GBS serotype. However, the overall early-onset infection rate in colonized newborns is less than 1% and is directly related to the severity of the colonization. This low attack rate is surprising in view of the fact that 81–86% of untreated vaginal carriers have positive amniotic fluid cultures for GBS at the time of labor.

GBS infection is an important cause of stillbirth, particularly before 28 weeks of gestation (Goldenberg and Thompson, 2003). Hood et al. (1961) isolated GBS from internal organs in 9.3% of stillbirths. Contrary to the expectation of maternal sepsis concomitant with the stillbirth, most lethal fetal infections by GBS occur in asymptomatic mothers.

The most common maternal GBS infection is asymptomatic bacteriuria. Symptomatic maternal GBS infections are chorioamnionitis and postpartum endometritis. In these cases GBS is usually a component of polymicrobial infections. When bacteremia is present GBS is identified by blood cultures in approximately 15% of the cases (Blanco et al., 1981).

Diagnosis

The diagnosis of antepartum maternal colonization is made by obtaining a sample from the lower third of the vagina and the anorectal region, which is cultured in enriched broth medium. The number of positive cultures is similar in specimens obtained in the anorectal, vaginoperineal, or perianal regions (Orafu et al., 2002). It takes 24–48 hours to obtain results and for this reason cultures are only adequate for antepartum screening.

A considerable amount of research effort has been dedicated to the finding of a rapid test for the diagnosis of GBS infection. An accurate rapid test would allow intrapartum treatment of colonized women that is an ideal approach to the prevention of early onset GBS infection. One of these tests is the Gram stain. The problem with this technique is that it requires an experienced microbiologist to obtain an adequate interpretation of the smear. Also, the sensitivity is low, 25%, and the positive predictive value is only 44%. Other methods use immunofluorescent antibodies, latex agglutination, colorimetric assays, and enzyme immunoassays (EIAs). The Federal Drug Administration (FDA) of USA has approved one of these tests based on polymerase chain reaction (PCR). The PCR test has shown excellent results (Bergeron et al., 2000) with a positive predictive value of 100% and a negative predictive value of 98.8%. However, the availability of a rapid test for intrapartum use requires adequate trials to demonstrate that the test is as efficacious as antepartum screening. The reported turn-around time of the test is between 40 and 100 minutes, time that has to be added to the 4 hours required for adequate antepartum prophylaxis using penicillin.

Prevention of Neonatal Infection

The history of prevention of early-onset GBS by using antepartum screening and intrapartum treatment of colonized women is a triumph of modern medicine. In the 1970 GBS was the leading cause of neonatal infection, with mortality reaching as high as 40–50%. At that time approximately 6100 cases of early-onset disease occurred yearly in USA. By the mid 1980s it was clearly demonstrated that penicillin and ampicillin treatment of women in labor was effective in preventing early-onset disease (Boyer and Gotoff, 1986). However, the systematic use of antepartum prophylaxis only started in 1996 when the Center for Disease Control (CDC) produced a set of recommendations destined to prevent early-onset GBS neonatal infection. The initial CDC recommendations asked clinicians to adopt one of two protocols to determine the need for prophylactic treatment. The "risk-factor protocol" consisted in giving intrapartum antibiotics to women with any of three risk factors: pregnancy less than 37 weeks, more than 18 hours of ruptured membranes, or fever during labor, defined as a temperature of ≥ 100.4 F or 38°C. The "screening-based protocol" consisted in screening all pregnant women at 35–37 weeks for anogenital colonization and treat all those identified as GBS carriers by bacteriological cultures. The CDC recommendations were followed rather quickly by studies demonstrating the superiority of the screening-base approach (Main and Slagle, 2000; Schrag et al., 2002). The study by Schrag et al. (2002) was performed in a stratified random sample of 629,912 births happening during 1 year in eight geographical areas. The study included 5144 births of which 312 had early-onset GBS infection. They found that routine screening during pregnancy prevented more cases of early-onset GBS neonatal infection than the risk-based approach. In view of these results and other clinical trials the CDC adopted new guidelines in 1996 and recommended rectal-vaginal GBS cultures for all pregnant women except for women that had GBS bacteriuria during the current pregnancy or had a previous infant with invasive GBS disease, because in these cases it is assumed that they are colonized and

BOX 5-2

Indications for intrapartum prophylaxis of GBS infection

1. Positive GBS screening during the present pregnancy unless a planned cesarean delivery, in the absence of labor or ruptured membranes, is performed
2. GBS bacteriuria during the present pregnancy
3. Previous infant with invasive GBS disease
4. Unknown GBS status and any of the following:
   - Delivery at < 37 weeks' gestation
   - Rupture of membranes ≥ 18 hours
   - Intrapartum temperature ≥ 100.4 F (38.0°C)

BOX 5-3

Situations where intrapartum GBS prophylaxis is not indicated

1. Previous pregnancy with a positive GBS screening culture but negative screening during the present pregnancy
2. Planned cesarean delivery performed in the absence of labor or ruptured membranes (regardless of maternal GBS culture status)
3. Negative anal–vaginal screening at 35–37 weeks' gestation in the present pregnancy, regardless of intrapartum risk factors

BOX 5-4

Intrapartum prophylaxis for GBS infection

- Penicillin 5 mU IVPB (intravenous piggy back) initial dose followed by 2.5 mU IVPB every 4 hours until delivery
  Or
- Ampicillin 2 g IVPB initial dose followed by 1 g every 4 hours until delivery

Patients with nonanaphylactic reaction to penicillin

- Cefazolin 2 g IVPB initial dose followed by 1 g IVPB every 8 hours until delivery

Patients with severe allergic reactions to penicillin

- Vancomycin 150 mg IVPB every 6 hours until delivery

require intrapartum treatment. All women with positive cultures should also receive intrapartum antibiotics. Women with unknown GBS status, because cultures were not done or their results are unknown, should receive prophylaxis if they have the risk factors used in the risk-factors approach, that is delivery at ≤ 37 weeks' gestation, amniotic membrane rupture ≥ 18 hours, and intrapartum temperature ≥ 100.4 F (≥ 38.0°C). Boxes 5-2 and 5-3 summarize the situations where intrapartum prophylaxis is and is not indicated (ACOG, 2002). These recommendations lead to a 70% decline in the incidence of early neonatal GBS infection that reached a low frequency of 0.5 per 1000 live births.

The recommended treatment for intrapartum prophylaxis is penicillin G or ampicillin (Box 5-4). So far no GBS resistance to penicillin or ampicillin has been detected. The most commonly used antibiotic is penicillin because it has a narrow spectrum of activity which theoretically should result in less selection of penicillin-resistant bacteria. However, penicillin transfers slowly through the placenta and an interval of at least 4 hours between administration of the drug and delivery is required to consider that the drug has reached adequate bactericidal concentration in the fetus. In our opinion, ampicillin is a better choice for prophylactic treatment because it is transported easily through the placenta into the fetus and into the amniotic fluid. This is important because as many as 81% of colonized mothers without signs of infection have GBS in the amniotic fluid and two-thirds of these babies will be colonized although few will be infected. The antibiotic of choice for women allergic to penicillin who are not at high risk for anaphylaxis is cefazolin, 2 g IV initial dose, followed by 1 g IV every 8 hours until delivery. For patients allergic to penicillin and at high risk for anaphylaxis the best choice is vancomycin, 1 g IV every 12 hours until delivery. Erythromycin and clindamycin are poor choices for women allergic to penicillin due to the high frequency of GBS strains resistant to these antibiotics and due to their slow transfer through the placenta which may result in subtherapeutic levels of the drug in the fetus and the amniotic fluid.

Prevention of GBS infection by antepartum screening is not perfect because the correlation between antepartum and intrapartum colonization is not perfect. Approximately 4–9% of women that will test negative in antepartum screening will be colonized at the time of delivery and at risk of neonatal infection. Approximately 33–43% of women testing positive for GBS antepartum will not be colonized at the time of delivery and will receive unnecessary treatment. Furthermore, antepartum screening at 35–37 weeks excludes patients delivering preterm, which is the group at highest risk. Despite these problems, GBS prophylaxis has been very successful and has significantly decreased the occurrence of this disease.

Another successful approach to the prevention of early-onset neonatal GBS infection consists in the intrapartum administration of ampicillin to women with high risk factors combined with the intramuscular administration of penicillin G to all neonates (Wendel et al., 2002). This method was used in a cohort of 13,887 live births and resulted in an incidence of early-onset GBS infection of 0.4/1000, similar to that obtained with the protocol recommended by the CDC.

Treatment of Maternal Infection

GBS is a beta-lactam-sensitive organism that responds to penicillin or ampicillin treatment. However, chorioamnionitis is a polymicrobial infection and it is preferable to use a broad spectrum antibiotic or a combination of antibiotics to treat this infection. An antibiotic combination used frequently is gentamycin, 1.5 mg/kg IV every 8 hours plus ampicillin, 2 g IV every 6 hours. Others use gentamycin 1.5 mg/kg IV every 8 hours and clindamycin 900 mg IV every

8 hours. If monotherapy is desired, ampicillin–sulbactam 1.5–3 g IV every 6 hours, piperacillin–tazobactam 3.375–4.5 g IV every 6 hours, or ceftizoxime 1–2 g IV every 8 hours will be adequate. The treatment of GBS postpartum endometritis is similar to that of chorioamnionitis. The infection is polymicrobial and it is necessary to use broad spectrum antibiotics or a combination of antibiotics.

Immunization

Active immunization against GBS using a vaccine should potentially result in the eradication of this perinatal problem. A caveat is that women who deliver newborns who develop early-onset disease seem to be unresponsive to the immunologic challenge posed by the GBS infection (Christensen et al., 1982) and may not respond to vaccination. The results of vaccination trials have been disappointing and only 57% of vaccinated pregnant women have an adequate serum antibody response (Baker et al., 1988). The design of vaccines capable of eliciting a stronger induction of antibodies is an area of active research at the present time.

Group B Streptococci Infection: Indian Experience

Daftary and Desai (2006) reported that these organisms can be isolated from the vagina and rectum or both in 15–40% of obstetric patients. Maternal–fetal transmission may occur via an ascending route in utero or during the passage of the baby through the birth canal during delivery. Vertical transmission varies between 40 and 70%. Whereas no more than 1–2% of full-term infants born to infected mothers suffer from severe clinical sequelae like sepsis, pneumonia, or meningitis. It may be the cause of preterm rupture of membranes and preterm labor. Morbidity and mortality is much higher in these preterm infants.

SYPHILIS

Syphilis is the result of infection by *Treponema pallidum*, a spirochete 6–15 µm in length, not visible by light microscopy but readily identifiable by dark field microscopy. Worldwide, approximate 1 million pregnancies are affected by syphilis and 460,000 of them result in abortion or perinatal death, 270,000 babies are born prematurely, and 270,000 babies are born with congenital syphilis (Doroshenko et al., 2006). The number of reported cases of primary and secondary syphilis in USA has steadily decreased since the early 1990s and was 11.2 per 100,000 births in 2002. However, the problem is still significant and in 2001 there were 441 cases of congenital syphilis reported in USA. In the same year the number of cases of syphilis reported to the CDC was 6103 (Carey, 2003). Most of the cases occur in the South and Southwest areas of USA in individuals under 25 years of age, Blacks and Hispanics, unmarried, and living in large urban areas. The frequency of syphilis in African Americans is nearly 30 times the rate for Whites. Syphilis is frequently seen in association with human immunodeficiency viral disease.

The incidence of congenital syphilis is significantly greater in underdeveloped than in industrialized countries. It is 12 per 1000 live births in Honduras while is 0.1 per 1000 live births in USA. This is a reflection of the high incidence of syphilis in pregnant women in Latin-American countries which reaches an average of 3.1% with a range between 1% in Peru and 6.1% in Paraguay (Organizacion Panamericana de la Salud, 2004). Difficult access to health care services, inadequate use of screening programs, and lack of vigorous public health measures are some of the factors that help to maintain this intolerably high incidence (Valderrama et al., 2004).

Maternal Infection

In women, syphilis is almost always acquired by sexual contact. The risk of acquiring the disease following exposure to an infected sexual partner is approximately 30%. The *Treponema* enters the body through small abrasions of the skin or the genital mucosa and after an incubation period of approximately 3 weeks, a primary chancre appears. The chancre is a painless, red, round ulceration with an indurated base and well-formed borders. Local, painless adenopathy is always present. If untreated, the chancre disappears spontaneously in 3–8 weeks. However, the *Treponema* spreads hematogenously through the body, causing genital and extragenital lesions known as secondary syphilis. The occurrence of palmar and plantar target-like lesions is a characteristic feature of secondary syphilis. Other lesions are cutaneous rash, mucous patches in the tongue or mouth, condyloma latum of the genitalia, and generalized lymphadenopathy. Although neurosyphilis is characteristically a tertiary lesion, central nervous system (CNS) involvement is found in approximately one-third of patients with secondary syphilis. Untreated secondary syphilis lasts 3–12 weeks, and latent syphilis begins. This stage is characterized by serologic evidence of syphilis without signs or symptoms of primary or secondary disease. Latent syphilis is called early when it is less than 1 year in duration and late when has lasted more than 1 year. After several years of latent syphilis approximately 30% of affected individuals develop tertiary syphilitic lesions that predominantly affect the central nervous and cardiovascular systems, the bones, and other viscera.

Serology

Syphilis causes distinctive serologic reactions that are used to confirm the presence of the disease. Some of these reactions are nonspecific and are caused by anticardiolipin antibodies. The most common tests using nonspecific

antibodies are the rapid plasma reagin (RPR) and the venereal disease research laboratory (VDRL). Specific serologic reactions for syphilis are the fluorescent treponemal antibody absorption test (FTA-ABS) and the micro-agglutination assay for antibodies against *T. pallidum* (MHA-TP). These tests are positive in 80% of patients with primary syphilis and in almost all patients with secondary and early latent disease.

Approximately 1–5% of positive RPR and VDRL results are false positive as demonstrated by negative specific antibody testing with FTA-ABS. False positive results usually have low titers and suggest the possibility of autoimmune disease, particularly antiphospholipid antibody syndrome.

Congenital Syphilis

T. pallidum can cross the placenta and cause congenital fetal infection at any time during pregnancy. Congenital syphilis is a multisystem disease that has different forms of presentation and there is a wide variation in its severity. The organism may cause stillbirth, preterm labor, growth retardation, fetal hydrops, and neonatal infection. The manifestations resemble those of adult secondary syphilis but unlike secondary syphilis frequently there is skeletal involvement such as osteomyelitis, osteochondritis, or periostitis. A list of the most common manifestations of congenital syphilis is shown in Box 5-5.

Examination of the placenta is often helpful in the diagnosis of congenital syphilis. On gross examination the placenta is large, pale, and edematous. Microscopically, the *T. pallidum* can often be identified with silver stain. The villi are often immature, enlarged, and with bullous projections and the vessels have endovascular and perivascular proliferation. It has long been held that the placenta, via Langhans' cells, acts as a barrier for the first 16–18 weeks of pregnancy and protects the fetus from early infection. However, the *Treponema* has been clearly identified in first-trimester abortus of women with recent syphilitic infections.

A concept in congenital syphilis is that the more recent the maternal infection, the more severe the congenital disease. The incidence of preterm delivery is 50% in mothers with primary and secondary infections, 20% in mothers with latent syphilis, and 9% in patients with late syphilis. Congenital syphilis will be present in 50% of the offspring of mothers with primary and secondary syphilis and the other 50% will have neonatal disease, while only 40% of newborns from patients with early latent disease and 10% of newborns from patients with late latent syphilis exhibit congenital syphilis. The severity of congenital syphilis is also related to the gestational age of the fetus at the time of infection. Fetal morbidity will be severe when the infection occurs in the first and second trimesters while many fetuses infected in the third trimester will be asymptomatic and will have negative serology. The presence of anti-treponemal IgM antibodies in neonates is diagnostic of congenital syphilis. IgG antibodies are not specific for neonatal infection and may be the result of transplacental transmission from a mother who has been adequately treated. An RPR or VDRL titer in the neonate four times greater than the maternal titer is also consistent with congenital syphilis.

BOX 5-5

Manifestations of congenital syphilis

Most infants look healthy at birth. A few have vesicular-bullous eruptions, usually in palm and soles

From 4 days to 3 weeks of life, symptoms may begin and may be grouped as follows:

1. *Flu-like syndrome*
   - Meningeal signs
   - Lacrimation (iritis)
   - Nasal discharge; mucous membranes red, swollen, eroded, loaded with *Treponema pallidum*
   - Sore throat—pharynx with mucous patches
   - Generalized arthralgia—splinting of arms and legs; osteochondritis on x-ray film; often periostitis, particularly of tibia (saber shin)
2. *Generalized lymphadenopathy*
   - Cervical, epitrochlear, inguinal, axillary, popliteal
   - Hepatosplenomegaly—if severe, probability of anemia, purpura, jaundice, edema, hypoalbuminemia
3. *Rash*
   - Maculopapular, papular, and bullous eruptions may all appear together
   - Occasionally papular lesions may coalesce to form condyloma latum

Diagnosis

The diagnosis of maternal syphilis is based on the type of lesions present. The test of choice for primary infection is a dark field examination of secretions from the chancre. To perform this test, it is necessary to remove the exudate from the chancre and place it on a glass slide, add saline, and examine it with dark field microscope for the presence of the spirochete. This technique is also applicable for secondary lesions.

Serologic tests are necessary to confirm the diagnosis in patients with secondary and latent syphilis. The VDRL and RPR tests are used for rapid screening. These tests are accurate in pregnancy and their false positive and false negative rates are no different than those in the nonpregnant status. The FTA-ABS test and the MHA-TP tests are used to verify a positive screening test.

False positives in the screening tests are a significant problem. Their incidence is directly related to the prevalence of syphilis in the population: the lower the risk of syphilis, the higher the rate of false positives. Box 5-6 lists some causes of false positive VDRL results. Women who have persistent unexplained false positive VDRL results are at high risk for antiphospholipid antibody syndrome.

BOX 5-6

Frequent causes of false positive syphilis tests (RPR and VDRL)

- Autoimmune disease (antiphospholipid antibody syndrome)
- Febrile illness
- Intravenous drug abuse
- Immunization
- Laboratory error

BOX 5-7

Center for Disease Control and Prevention's recommendations for the treatment of syphilis in pregnant patients not allergic to penicillin

Early latent syphilis (less than 1 year duration)

- Benzathine penicillin G, 2.4 million units IM in a single dose

Late latent syphilis (more than 1 year duration) or latent syphilis of unknown duration

- Benzathine penicillin G, 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-week intervals

Neurosyphilis

- Procaine penicillin G, 2.4 million units IM once daily plus probenecid, 500 mg orally four times daily, both for 10–14 days
  Or
- Aqueous crystalline penicillin G, 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion for 10–14 days

Patients with secondary, latent, and tertiary syphilis need cerebrospinal fluid examination to rule out CNS infection. It has been shown that 40% of patients with untreated secondary and latent syphilis have asymptomatic neurosyphilis and need more intensive therapy for a cure (Lukehart et al., 1988).

Treatment

Box 5-7 shows the treatment guidelines recommended by the CDC (2006). These guidelines are based on the use of penicillin and should not be used in patients allergic to this antibiotic. Unfortunately, there are occasional treatment failures with these guidelines and they must be viewed as a minimum treatment that may be modified according to the specific circumstances of each individual patient.

Other antibiotics including erythromycin, tetracycline, and azithromycin have been used to treat syphilis. A 14-day course of doxycycline or tetracycline has been used for the treatment of early syphilis, but they are not as effective as penicillin. Azithromycin, in a single 2 g oral dose or as two 2 g oral doses given 1 week apart has been tried successfully in the treatment of subjects with primary and latent syphilis (Hook et al., 2002; Riedner et al., 2005). However, azithromycin treatment failure and resistance have been reported (Lukehart et al., 2004).

BOX 5-8

Penicillin desensitization protocol

Dose number	Phenoxymethyl penicillin suspension (units/ml)	Penicillin amount (units)	Cumulative dose (units)
1	1000	100	100
2	1000	200	300
3	1000	400	700
4	1000	800	1500
5	1000	1600	3100
6	1000	3200	6300
7	1000	6400	12700
8	10000	12000	24700
9	10000	24000	48700
10	10000	48000	96700
11	80000	80000	176700
12	80000	160000	336700
13	80000	320000	656700
14	80000	640000	1296700

Observe for 30 minutes before administration of parenteral penicillin; interval between doses: 15 minutes; elapsed time: 3 hours 45 minutes.
From Wendel GD. Early and congenital syphilis. Obstet Gynecol Clin North Am 1989; 16: 479–94.

BOX 5-9

Syphilis treatment in patients allergic to penicillin

Recommended treatment

- Desensitization followed by appropriate penicillin dosage for stage of syphilis

Alternative treatments

- Erythromycin, 500 mg four times daily, orally, for 15 days (early syphilis)
- Tetracycline, 500 mg four times daily, orally, for 15 days (early syphilis)
- Nonpenicillin therapy for disease of greater than 1-year duration is not recommended

From Wendel GD. Gestational and congenital syphilis. Clin Perinatol 1988; 15: 287–303.

Management of the Penicillin-Sensitive Patient

The penicillin-sensitive pregnant woman poses a major dilemma in intrauterine therapeutics. Maternal and fetal toxicity, poor placental transmission, and low fetal tissue penetration make undesirable during pregnancy treatments that otherwise will be adequate outside of pregnancy. At present there is no drug that can be substituted in pregnant women allergic to penicillin. The best approach is to perform skin testing to document serious allergy followed by desensitization using established protocols. Oral desensitization is safer and easy to perform (Box 5-8). Other therapeutic options for pregnant women with documented allergy to penicillin are shown in Box 5-9. Any infant born to a

mother who receives one of these alternatives is suspect and should be treated with a full course of penicillin.

Serologic Follow-up

Serologic follow-up is important to identify therapeutic success and detect reinfection. Most commonly, the FTA-ABS test will remain positive for the lifetime of the patient, while reaction to the VDRL test progressively declines and becomes negative. Serologic evidence of adequately treated syphilis in patients with early syphilis is demonstrated by at least a fourfold decrease in VDRL or RPR titers. If the disease has entered the latent phase before treatment, a large percentage of patients may never attain a completely negative VDRL result. In these cases the evidence of adequate treatment will be a stable or declining RPR or VDRL titers of less than or equal to 1:4.

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) is the most common congenital infection and the most important infectious cause of mental retardation and congenital deafness in USA. CMV affects 1–2% of all pregnancies. About 10% of infected babies (1 per 1000 births) will be symptomatic at birth and 5–25% of them may have sequelae, particularly deafness, later in life. Usually, CMV is acquired in the infant years and only 10–15% acquire the infection in the perinatal period. The highest infection rate occurs during the 2nd and 3rd year of life when as many as 50% of children become infected. Another period of seroconversion occurs in the adolescent years.

The Virus

CMV is an icosahedric, enveloped, double-stranded DNA virus, member of the herpes family. Histologic evaluation of cells infected with CMV reveals large intranuclear inclusions, leading to the alternate name, cytomegalic inclusion disease. Similar to other members of the herpes virus family, CMV has the ability of becoming latent following an acute attack and to reactivate at a later time. A special feature of the CMV virus is the persistence of viral shedding. Children shed the virus for years and adults for months following infection. Replication of the virus is slow, taking 48–72 hours. The viral particles are assembled in the nucleus of the infected cell in a rather inefficient manner and the result is that infected cells contain more incomplete than complete viruses, making the yield of conventional cultures low.

Transmission

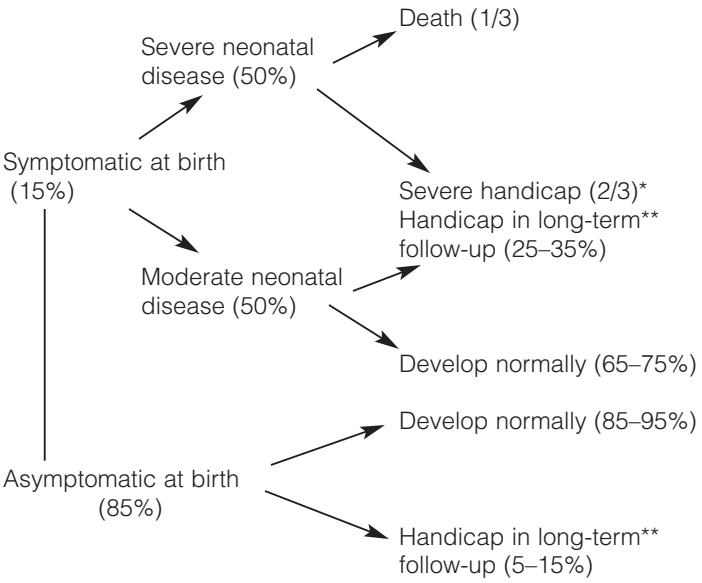
The CMV virus is excreted in urine, semen, cervical secretions, and saliva. The route of transmission therefore may be sexual, respiratory, or by contact with infected urine or saliva. The risk of primary CMV infection in seronegative women during pregnancy is approximately 1%. The most common source of maternal infection is children attending day-care centers (Pass et al., 1987). This risk increases with the presence of high-risk factors such as age less than 25 years, White race, upper socioeconomic status, promiscuity, and exposure to young children at home or at work. Patients with primary infections may show a mononucleosis-like syndrome of malaise, lymphadenopathy, and hepatosplenomegaly. However, fatigue is the most impressive symptom. Many patients are asymptomatic during primary and recurrent infections.

A primary maternal infection in any trimester has the potential for congenital transmission, which appears to occur transplacentally. Primary maternal infection in any trimester can lead to fetal infection but the more severely affected infants are usually born to mothers who develop infections during the second rather than the third trimester. CMV infection can be acquired at the time of vaginal delivery. This is not surprising because viral shedding from the cervix increases from 5 to 15% of the time in the nonpregnant status to as much as 28% at some point in gestation. Another common route of infection is breast-feeding. The virus is found in the breast milk of 25.7% of women with serologic evidence of CMV infection, and breast-feeding may account for the frequent seroconversion that occurs during infancy. Another potential but rare source of infection is by introduction of the virus into the fetal blood stream or the amniotic fluid during intrauterine transfusion or amniocentesis.

There is variation in the frequency and severity of the congenital infection depending on the nature of the maternal infection. When the maternal infection is primary, 30–40% of the neonates will be infected and 10% of them will exhibit overt CMV disease (Stagno and Whithley, 1985). The risk is less when the infection is recurrent and only 2–3% of the babies will be infected. Maternal immunity reduces the virulence of the fetal infection but does not protect 100% of the neonates (Boppana et al., 2001). However, there is no report of severe congenital infection in women seropositive for CMV before pregnancy.

Severe Congenital Infection

Infants born with severe congenital infection often exhibit hepatosplenomegaly, thrombocytopenia with petechiae and purpura, hepatitis associated with icterus, pneumonitis, and chorioretinitis. Abnormalities that result from faulty neurologic development include microcephaly, optic atrophy, aplasia of various parts of the brain, and microphthalmia. The incidence of fetal growth retardation is 30–40%. The presence of intracranial calcifications is an indication that the infant will have at least moderate to severe retardation. Half of infants with severe congenital



*Cerebral palsy and mental retardation
**Hearing loss, speech, and learning disabilities

Figure 5-1. Perinatal outcome of women with primary CMV infection during pregnancy.

infection will die in the neonatal period. Most asymptomatic infected newborns will be undetected.

Late Sequelae

Follow-up studies of infants with congenital CMV infections indicate that the most significant sequelae are the result of CNS infection. Auditory deficiencies are the most common handicap affecting 25–50% of congenitally infected newborns. Mental retardation affects 93% of newborns with severe infection and 20% of those who are asymptomatic at birth. Visual difficulties affect 25% of newborns with symptomatic infection and include chorioretinitis, optic neuritis, optic atrophy, cataracts, and microphthalmia. Bilateral hearing loss is present in approximately 10% of infected infants. A few of the infected children have profound deafness. Figure 5-1 summarizes the perinatal outcome of primary and secondary CMV infection during pregnancy. Overall, 3% of infected fetuses will die, 6% will survive with severe handicaps, 10% will survive with moderate handicaps, and 80% will develop normally.

Diagnosis

Primary CMV during pregnancy is asymptomatic or is confused with symptoms of a common cold. For that reason, most cases that occur during pregnancy are detected by the presence of IgM antibodies in maternal serum. Seroconversion from no antibodies to positive IgM antibodies is rarely documented during pregnancy. Since CMV IgM antibodies may persist for 6–9 months following the primary infection, the most common serologic finding in relatively recent CMV infections is a mix of IgM and IgG antibodies. Recurrent infections are characterized by the absence of IgM antibodies and at least a fourfold increase in IgG titer.

Due to the asymptomatic nature of the primary infection and the persistency of CMV IgM antibodies in the serum, it is frequently impossible to determine when the infection occurred. This is important because most of the time the abnormal serology is found in the second trimester of pregnancy and patients want to know if the primary infection happened before or after they became pregnant. In these cases it is necessary to find if the virus is present or not in the amniotic fluid. The gold standard for the diagnosis of congenital CMV infection is a positive amniotic fluid viral culture. The virus can be cultured by conventional techniques or by the shell vial method. In the latter method the amniotic fluid sample is inoculated into vials containing coverslips seeded with tissue culture cells. After centrifugation and incubation for 24–48 hours, the coverslip is stained with fluorescein-tagged monoclonal antibodies to CMV antigens. The accuracy of amniotic fluid testing improves when the amniotic fluid sample is obtained after 21 weeks in asymptomatic women or after a 7-week interval between maternal infection and amniocentesis (Liesnard et al., 2000). Cordocentesis is not justified in these cases because fetal blood cultures and CMV-specific IgM are frequently negative in umbilical blood samples.

The presence of the virus in the amniotic fluid can also be assessed by PCR. Initial studies with this technique demonstrated a small number of false negatives and false positive results. Recent studies (Guerra et al., 2000) indicate that a quantitative PCR reaction showing the presence of $\geq 10^3$ CMV genome equivalents predicted mother–fetus infection 100% of the time. The presence of $\geq 10^5$ CMV genome equivalents predicted symptomatic neonatal infection. Another study (Liesnard et al., 2000) compared the accuracy of amniotic fluid cultures, PCR, fetal blood for CMV IgM, and PCR and repeated ultrasound examinations. The global sensitivity of these tests to detect fetal infection was 80%. The sensitivity and specificity of amniotic fluid PCR were 78 (43 of 44 cases) and 100%, respectively. In 3.3% (8 of 237 cases) the PCR was positive in the amniotic fluid but the viral culture was negative. Similar overall sensitivity and specificity (78 and 100%, respectively) was found in another study (Ahmad-Zalmai et al., 2001). Determination of IgM antibodies to the 70-kd heat shock protein in fetal serum (Gerber et al., 2002) and anticytomegalovirus IgG avidity (Bodeus et al., 2002) are techniques that have been used in attempts to improve the accuracy of prenatal diagnosis of CMV infection without convincing results.

Ultrasound has poor sensitivity and specificity for the diagnosis of congenital CMV infection. Hyperechogenic

bowel, intracranial calcifications, microcephaly, fetal growth restriction are suggestive of severe congenital CMV infection. Positive sonographic findings are limited to fetuses with severe syndromes.

Prevention

There is no vaccination available for CMV. The only preventative measure available is to investigate the CMV immunity of new employees of high-risk places such as mental institutions, NICUs, dialysis units, and day-care centers. Those who are not immune should be informed of the high risk of acquiring CMV and the effects of the infection in pregnancy so that they can make a decision about an occupational change.

Treatment

The antiviral agent ganciclovir is a potent inhibitor of CMV replication with potential use in congenital CMV infection. This medication is available only for intravenous administration and has significant hematologic toxicity. The only approved indication for ganciclovir is in the treatment of CMV retinitis in immunocompromised hosts. There are no published trials on the use of this drug during pregnancy. Acyclovir is not useful because the virus does not induce its own thymidine kinase.

CMV Infection: Indian Experience

Broor et al. (1991) in an extensive study of 249 infants suspected of congenital infections at the All India Institute of Medical Sciences (AIIMS), New Delhi reported the detection of CMV specific IgM antibodies in 12% of these infants. Many of these infants displayed hepatosplenomegaly and developmental delays. In a more recent survey of 1300 newborns by Deorari et al., (2000) at AIIMS, the incidence of detection of CMV specific IgM antibodies was 0.6% and in a study (2004) at AIIMS by Broor et al. on the saliva of 550 newborns, CMV was detected by PCR in 7 out of 550 newborns (1.4%).

RUBELLA

Rubella was considered an inconsequential disease until 1941 when the association between maternal rubella and congenital cataracts was described. In 1962 the virus was cultivated in cell culture and in 1969 the first vaccine was licensed in USA. The history of neonatal rubella infection is similar to the history of Rh isoimmunization. In a relatively short time the cause of the disease was identified, the pathogenesis explained, a preventive measure created, and public health measures markedly reduced the incidence of the disease. In USA in 1989 the CDC started a program aimed to eliminate rubella. In 2001 less than 100 cases were reported and in 2004 fewer than 10. This led to the CDC to declare in March 2005 that rubella had been eliminated from this country. The situation is different in the developing world and the incidence of rubella is particularly high in Latin America and outbreaks still occur in Eastern Europe and the Russian Federation. The proportion of rubella-susceptible women of childbearing age varies from country to country. In Turkey 15% of women between 20 and 29 years of age have negative titers, 16.5 in the Russian Federation, and 23% in Nigeria.

Signs and Symptoms

The wild rubella virus is highly contagious, with only minimal contact necessary for transmission. Rubella occurs predominantly in young children and adolescents, most commonly in springtime. Rubella causes a usually mild exanthema in children (fever, malaise, and lymphadenopathy) and a somewhat more severe form of the illness in young adults. A facial rash, postauricular adenopathy, flu-like symptoms, and arthralgia or arthritis are characteristic of the condition. Arthralgia and arthritis occur largely in women and commonly involve the smaller joints. Transmission usually occurs by contact with nasopharyngeal secretions.

Rubella exhibits a typical time relationship between clinical signs, virus shedding, and antibody development that is important in the evaluation of potential exposures. The virus enters through the upper respiratory tract, multiplies, invades the cervical lymphatic nodes, and after 7–10 days enters the bloodstream and has widespread dissemination. The viremia continues until antibodies appear, generally in another 7 days. The virus is present in blood for several days before the facial rash appears and is shed from the nasopharynx after the appearance of the rash. The total incubation time (exposure to symptoms) is 14–21 days, most commonly 16–18 days. Infected individuals may shed the virus for up to 2 weeks before the occurrence of the rash. Viral shedding decreases rapidly after the rash probably because of the immune response to the infection.

Immunity

IgM appears shortly before the onset of symptoms, peaks approximately 1 week later, and disappears approximately 1–2 months after the onset of the disease. Acquired immunity is lifelong. However, rubella may occur again after natural infection and after vaccination. Second infections occurring during pregnancy are not associated with congenital infections.

Congenital Rubella

Rubella is a teratogenic virus. Most of the information about congenital rubella syndrome (CRS) is a product of

observations made during the US rubella epidemic of 1964. This epidemic made it possible to perform a large amount of clinical, serologic, and virologic research on this congenital infection.

Both clinically apparent and totally silent maternal infection can result in fetal infection. The fetus is at risk of CRS only during a primary infection. The possibilities of fetal infection are 61% when maternal transmission occurs during the first 4 postconception weeks, decrease to 26% during weeks 5–8, and further decrease to 8% during weeks 9–12. After 12 weeks the risk of congenital infection is less than 5%. Therefore, the fetal consequences of first-trimester rubella may be no infection, asymptomatic infection with no clinical consequence, single-organ involvement (typically the ear), or multiple-organ involvement with mild to severe damage. Infection in the first weeks of gestation is associated with a doubling of the spontaneous abortion rate.

The most common abnormalities associated with first-trimester infection are hearing loss in 60–75%, eye defects in 50–90%, heart disease in 40–85%, and psychomotor retardation in 25–40% of affected infants. Other abnormalities are fetal and neonatal growth retardation and hepatosplenomegaly. Less frequently found are thrombocytopenia, meningoencephalitis, radiolucency of the long bones, and myocardial necrosis. Rarely found are microcephaly, brain calcifications, and hepatitis. Late-onset features appearing after 3–12 months include interstitial pneumonitis, chronic rubella-like rash, recurrent infections, hypogammaglobulinemia, chronic diarrhea, diabetes mellitus, and progressive CNS deterioration.

The late sequelae of rubella are significant. Fifty percent of affected infants will attend schools for the deaf and 25% will require special schooling because of hearing problems. Several will develop diabetes secondary to pancreatic infection and some will develop subacute sclerosing panencephalitis.

Diagnosis

The cornerstone for the assessment of maternal immunity is serologic testing. The most widely used test is the hemagglutination-inhibition (HI) test. In this test the presence of rubella antibodies impedes the agglutination of chick red cells by rubella virus. The HI is time consuming, technically complex, and is being rapidly replaced by other techniques that are faster and less dependent on adequate technique. Among the new methods we have solid-phase enzyme-linked immunosorbent assay (ELISA), passive agglutination test (PHA), immunofluorescent assay (IFA), radioimmunoassay (RAI), and radial immunodiffusion test. Demonstration of rubella antibodies by any of these techniques constitutes proof of immunity and demonstration of seroconversion implies recent infection.

Recent infection can be confirmed by using an EIA to detect rubella-specific IgM in the maternal serum. This is the most common method for the diagnosis of recent rubella infection. During pregnancy it is necessary to make a firm diagnosis and any woman with positive EIA should have the diagnosis confirmed by PCR detection of the virus or by demonstrating a fourfold increase in IgG antibody level (Terada et al., 2000). The reverse transcription polymerase chain reaction (RT-PCR) is an extremely sensitive test that can be used for the detection of the virus in CVS (chorionic villus sampling) specimens, amniotic fluid, or in fetal blood (Revello et al., 1997). Fetal blood is the less adequate specimen for diagnosis of fetal infection because it can only be used after 22 weeks. Before this gestational age the fetus does not synthesize a significant amount of IgM antibodies. The best specimens are amniotic fluid and CVS material, and there are suggestions that detection of the virus is better in CVS specimens (Tanemura et al., 1996).

Management

Every pregnant woman should have rubella immunity testing at her first prenatal visit. A history of prior infection or vaccination is often misleading because they may not have resulted in adequate immunization. The HI test is the most common screening test to assess immunity. A titer of 1:16 or 1:20 is conclusive evidence of immunity. Titers of 1:8 or 1:10 are equivocal and more difficult to interpret. In a recent study up to 17% of these patients lacked antibodies when tested with RAI. False positive results are probably the result of incomplete removal of nonspecific inhibitors present in all human sera. Seronegative pregnant women should be counseled to avoid exposure to individuals with erythemas.

The most common problem faced by the obstetricians with respect to rubella infection is the evaluation of pregnant women exposed to an exanthematous illness. To evaluate a person seen 7 days or fewer after exposure, a sample is drawn for the HI test or, if available, the results of the test performed at the first prenatal visit are referred to. The titer may be as high as 1:256 in up to 15% of the normal immune population, and, if the test is obtained within 7 days after exposure, it does not indicate infection. If the patient is not immune (titer < 1:10) or the titer is high (>1:256), the HI test should be repeated 2–3 weeks later. If the second HI titer shows a similar value or an insignificant variation (less than two dilutions) in relation to the first sample, infection has not occurred. The repeat titer in 2–3 weeks should show at least a fourfold rise if an infection has occurred. Rubella-specific IgM antibody titers rise rapidly after a recent infection and disappear after 4–5 weeks. A positive rubella-specific IgM is the most specific test indicating recent rubella infection and should be done in every case where infection is suspected.

When the patient is seen 1–5 weeks after exposure or up to 3 weeks after the onset of a rash, serum HI and CF

(complement fixation) antibody levels should be obtained immediately and 2 weeks later. A fourfold increase in either antibody will be evidence of acute infection. Absence of CF antibody in both specimens will rule out acute infection. Stable, elevated positive titers for both HI and CF antibodies will require determination of rubella-specific IgM to confirm the diagnosis of infection.

Vaccination

In 1969 two rubella vaccines were licensed in USA, the HPV77-DE5 and the Cendenhill strain. HPV77 was the vaccine most commonly used until its replacement by RA 27/3 in 1979. RA 27/3 mimics natural rubella better and more consistently than the other vaccines and is presently the vaccine most commonly used in USA. The vaccine causes seroconversion in 95–98% of susceptible individuals and symptoms resembling mild rubella in 10–15% of recipients. Transient arthralgias and arthritis are particularly common in adult women receiving the vaccine; in those over 20 years of age, up to 20–30% may experience joint involvement. In view of the potential fetal effects of the vaccine, it is recommended that women of childbearing age avoid pregnancy for 28 days following vaccination.

The major problem with the earlier vaccines was that they were not as immunogenic as the natural virus. Several recent studies have shown absent HI antibody titers in long-term follow-up in an alarming 10–25% of individuals vaccinated with HPV77, whereas the RA 27/3 vaccine has had a serologic failure rate in 4–5 years of follow-up of only 3%. However, there is some evidence that patients with absent titers after vaccination still have some protection against viremia. Their serologic response to reimmunization resembles a "booster" response more closely than a primary one.

Selective immunization of women of childbearing age has been difficult and incomplete at best. Several studies have shown that, even when physicians obtain routine serologic tests of women, the results are rarely acted upon. Just as prenatal serologic testing has become commonplace in USA, so should postnatal immunization of all susceptible patients. The CDC, the American Academy of Pediatrics (AAP), and American College of Obstetricians and Gynecologists (ACOG) recommend that pregnant women seronegative for rubella should receive MMR (measles, rubella, and mumps containing vaccine) postpartum for protection against these three infections (Reef et al., 2002; ACOG, 2003). It has been shown that 9.4% of women in USA are susceptible to rubella, 16.5% to rubeola (measles), and 16.3% to mumps (Haas et al., 2005). The newly vaccinated woman is not contagious to other pregnant women in the hospital, nor is her baby at risk even if she breastfeeds. Despite extensive testing, there is no documentation of spread of rubella vaccine virus from a vaccinated person to a susceptible contact. Therefore it is not necessary to vaccinate susceptible household members of a pregnant woman vaccinated after delivery.

Rubella vaccine is contraindicated in pregnancy, as are the other live-attenuated vaccines, since the vaccine virus crosses the placenta (CDC, 2001). Occasionally, pregnant women have received the vaccine and the risk of fetal infection is not nearly as great as that with the wild virus. In a report of five cases the virus was transmitted in only one case but the newborn did not show evidence of clinical disease (Hoffman et al., 2000). The CDC estimates that the maximum risk of fetal infection after vaccination is between 3 and 5%. There are no reported live births with the CRS after immunization of the mother during pregnancy with the HPV77, Cendenhill, or RA 27/3 vaccines.

The role of immune globulin for exposed first-trimester mothers remains controversial. Some investigators recommend its use in infected patients who refuse termination of pregnancy. However, the CDC does not recommend its use. Preparations of immune globulin vary greatly in their rubella antibody content and, to be effective, the immune globulin needs to be given at the time of exposure before viremia occurs. Thus, immune globulin is an uncertain option of controversial benefit that should be offered only to a small number of women in special circumstances.

Rubella Epidemiology: Indian Experience

In India, three types of epidemiological information on rubella are available. (a) Incidence of seropositivity in pregnant women and in young girls. (b) Seropositivity among infants with congenital malformations. (c) Information on congenital cataracts and eye defects (Maria and Deorari, 2004; Seth et al., 1971; Seth et al., 1985; Shanmugham et al., 1982).

Table 5-1 displays wide differences in rubella immunity in different parts of the country. Until universal and

Table 5-1. Incidence of seropositivity in population surveys

Authors	Place and year	Prevalence
Seth et al.	North India three cities; 1985	80% seropositive (rubella IgG)
Yadav et al.	New Delhi; 1995	55% seropositive (rubella IgG)
Chakraborty et al	Kolkata; 1973	56% seropositive (rubella IgG)
Bhaskaram et al.	Hyderabad; 1991	95% seropositive (rubella IgG)
Verma and Gulati	Faridabad; 2004	85% seropositive (rubella IgG)
Shanmugham et al.	Kerala state; 1982	64% seropositive (rubella IgG)

compulsory immunization of all adolescent girls in India is not achieved, clinicians will continue to face the consequences and ravages of rubella infections in pregnancy.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

The human immunodeficiency virus (HIV) is the cause of the acquired immune deficiency syndrome (AIDS)—a condition that affects hundreds of thousands of individuals in USA and millions more throughout the world. HIV is infecting a growing number of women in the reproductive age and as a consequence the number of infants born to HIV-infected mothers is also rapidly increasing.

There is a significant difference in the incidence, progression of HIV infection, and use of therapeutic agents between industrialized and underdeveloped countries. In USA the number of new cases of HIV infection has decreased dramatically, advances in therapy have allowed control in the progression of the disease for long periods of time, and the rate of mother-to-child transmission and opportunistic infections has also decreased. In contrast, in the third world the number of deaths and orphans and the cases of vertical transmission during pregnancy increase day after day. The advances in therapy have no impact in the poorest countries due to lack of accessibility of these drugs. This is a terrible situation that requires a global effort from the industrialized nations to avoid a tragedy of cataclysmic proportions.

Virology

There are five known human retroviruses (HIV-1, HIV-2, HIV-I, HIV-II, and HIV-IV) and three of them are associated with human disease. HIV-1 and HIV-2 cause AIDS and HIV-I is also the causal agent of T cell leukemia/lymphoma. HIV-1, the most common cause of AIDS in USA has an envelope formed by three glycoproteins (gp160, gp120, and gp41), surrounding a core that contains other proteins (p55, p40, p24, p17), reverse transcriptase, and endonucleases.

Attachment of the virus to the host cell is a critically important step in the mechanism of infection. The virus only infects susceptible cells that express in their surface a glycoprotein called CD4 which is recognized by the glycoprotein gp120 that is present in the viral envelope. The best known susceptible cell in humans is the CD4 or T4 helper–inducer T lymphocyte. Invasion and eventual destruction of these cells by the HIV-1 virus will cause the profound alteration in the immune system that is characteristic of AIDS.

Once inside the cell, retroviruses follow a unique reproductive cycle that involves reverse transcription of their RNA into DNA, incorporation of the newly synthesized DNA into a host cell DNA, transcription of the viral DNA into RNAs, and translation of the RNA into viral components. The viral DNA may remain incorporated into the host cell DNA for prolonged latent periods until viral synthesis is activated. It is unclear what the conditions are that initiate viral activation.

Maternal Infection

Maternal HIV is acquired primarily by sexual contact or by parenteral exposure to blood or blood products. Most sexual transmission is the result of receptive vaginal or anal intercourse with infected partners. Transmission by exposure to blood or blood products is usually the result of sharing needles or syringes between intravenous drug abusers. Rarely, maternal infection results from the administration of blood or blood products, especially if they were received before April 1985 when individuals from high-risk groups were not excluded as donors. Women account for approximately 10% of AIDS cases. A large majority of them are Black or Hispanic and are between 15 and 35 years of age. Most of the women are intravenous drug abusers, have multiple sexual partners, and have intercourse with partners at high risk (Box 5-10).

The initial infection with HIV is asymptomatic. Serologic evidence that infection has occurred may be obtained 2–8 weeks after the initial infection but in some cases it takes up to 6 months before an antibody response is present. Infected individuals undergo a prolonged period without symptoms during which they are shedding virus into most body fluids and are infective. Most pregnant women with HIV infection are in this asymptomatic carrier phase. At some point in the evolution of the disease, the infected individuals develop symptoms and signs called AIDS-related complex or ARC. AIDS-related complex is characterized by generalized lymph node enlargement, fever, night sweats, weight loss and unusual recurrent infections such as herpes or candidiasis. ARC is followed by the final stage of the disease, or AIDS, a condition characterized by severe dysfunction of the immune system. Patients with AIDS develop a series of systemic or local infections by opportunistic organisms such as candidiasis, CMV, herpes, histoplasma, cryptococcus, and pneumocystis carinii or develop Kaposi's sarcoma, lymphoma of the brain, or multiple recurrent bacterial infections.

BOX 5-10

Individuals at high risk for HIV infection

- Prostitutes
- IV drug abusers
- Women whose partners are:
  - Known HIV positive
  - IV drug abusers
  - Hemophiliacs
- African or Haitian immigrants after 1975
- Women whose partners have had:
  - Homosexual experiences
  - Blood transfusion between 1977 and 1985

Prospective studies have demonstrated that pregnancy does not affect the progression or the survival of HIV-infected women (French and Brocklehurst, 1998). On the other hand, there is an ongoing discussion regarding the effects of HIV infection on pregnancy outcome. The main associations of HIV are with preterm birth and fetal growth restriction. However, there are multiple confounding variables such as alcohol and drug abuse, poor nutrition, and advanced maternal disease that diminish the strength of this association and generate doubts about the existence of a cause–effect relationship.

Diagnosis

The diagnosis of HIV infection is serologic, by virus culture, or by detection of viral DNA or RNA using PCR. The screening procedure is an ELISA test that is extremely sensitive, specific, inexpensive, and easy to perform. The ELISA test may produce false positive results and all positive tests should be followed by Western blot analysis. Western blot detects antibodies against p24, p31, gp41, and gp160. The presence of antibodies against these structural envelope proteins is a reliable indication of infection. Results of the Western blot are positive, negative, or undetermined. A positive test is indicative of infection. The probability of a false positive diagnosis is almost nonexistent if two ELISA and one Western blot are positive. A negative test rules out infection. Most patients with indeterminate test results are not infected with HIV but a viral load test or repeating the test later in pregnancy is recommended. Once the presence of infection has been demonstrated, the following step is the determination of the CD4 cell count and the viral load, which are complementary methods of evaluating HIV infection. The principal determinant of the CD4 count is the duration of the disease while the viral load indicates the likelihood of progression. These tests should be obtained as early in pregnancy as possible and every month thereafter. Viral cultures are rarely used for diagnosis of HIV infection. Cultures are labor intensive, expensive, and less sensitive than serologic testing. PCR is a very sensitive technique that has the potential to become the test of choice for the diagnosis of HIV infection.

Data from several studies indicate that 40–85% of infants infected with HIV are born to women with unknown HIV status and rapid testing can be used for identification of infected women who arrive to labor and delivery with undocumented HIV status. The rapid HIV test result is available within hours and has a sensitivity and specificity close to 100%. The rapid test can be processed in the laboratory when the specimen is plasma or serum or in the labor and delivery suite when the specimen is whole blood. A negative rapid HIV test result is definite and indicates no infection. A positive test requires confirmation by Western blot and antiretroviral prophylaxis is started without waiting for the results of the confirmatory test (CDC, 2004).

Fetal Transmission

Approximately 24% of infants born to HIV-infected mothers will demonstrate the presence of the disease by 1 year of age. The virus is excreted in breast milk and breast-feeding is contraindicated in HIV infected women. In non-breast-feeding mothers 60–80% of the transmission occurs during labor and delivery and the rest antepartum.

Significant effort has been directed to the identification of factors predictive of fetal infection. The most important are maternal and obstetrical factors. The outstanding maternal factor is the severity of the disease that can be assessed immunologically by the number of CD4 cells or virologically by measuring the number of RNA copies. The presence of maternal antibodies against certain epitopes or against the principal-neutralizing domain of the envelope protein gp120 is predictive of the absence of newborn infection. There is a good correlation between the number of HIV RNA copies and the risk of vertical transmission. In untreated women the risk of vertical transmission is 0–10% if the viral load is < 1000 copies/ml, 17% with viral loads of 1000–10,000 copies/ml, and 33% if the viral load is greater than 10,000 copies/ml (Garcia et al., 1999). The guidelines to start therapy in pregnancy are a CD4 count < 400/mm^3 or a viral load > 1000 copies/ml using the PCR assay. This viral load is the threshold recommended by ACOG for the performance of cesarean delivery (ACOG, 2000). A CD4 count < 200/mm^3 is an indication for prophylactic treatment for opportunistic infections.

With respect to obstetrical factors the frequency of vertical transmission increases in relation to the duration of ruptured membranes (Landesman et al., 1996) and cesarean delivery has a protective effect (The International Perinatal HIV Group, 1999). An important factor associated with the frequency of vertical transmission is the use of maternal combination antiretroviral therapy. If the pregnant women is being treated with highly active antiretroviral therapy (HAART) or receives intrapartum treatment, the frequency of mother–infant transmission decreases drastically. HAART lowers the frequency of transmission irrespective of the maternal viral load, and when the viral load reaches undetectable levels vertical transmission is a rare event (Cooper et al., 2002). Antiretroviral therapy lowers the rate of vertical transmission among all women with HIV infection, 1% in cases with < 1000 RNA copies/ml, 6% with levels of 1000–10,000 RNA copies/ml, and 13% if the number of RNA copies is > 10,000 copies/ml (Cooper et al., 2002).

The majority of babies born to HIV-positive mothers have no physical signs of infection. A few of them may

exhibit the so-called HIV embryopathy characterized by growth retardation, microcephaly, and craniofacial abnormalities. All infants of HIV-infected mothers have positive HIV serology as a consequence of the passive transfer of maternal antibodies. Levels of these antibodies decline gradually and by 6 months of age most noninfected newborns will be seronegative. The presence of positive serology secondary to passive transmission of antibodies makes difficult the diagnosis of HIV infection in the newborns. In this situation viral cultures and PCR testing should be done to confirm or rule out infection.

Detection of HIV Infection During Pregnancy

One of the most important issues in the management of HIV infection during pregnancy is detection. The dismal prognosis of affected individuals and the fear of acquiring the disease have generated a demand for universal screening. The CDC recommendation (2006) is to have HIV testing in the first prenatal visit and offer the test later in pregnancy if the patient initially refuses. The recommended approach is the opt-out strategy in which the patient is informed that she will be tested for HIV infection as part of the routine battery of prenatal blood tests unless she declines. The opt-in approach consists of asking for specific informed consent, usually in writing, and is associated with a lesser degree of testing rates than those in the opt-in approach. The CDC (2006) and ACOG (2004) have recommended the opt-out approach. Irrespective of the type of approach to prenatal testing, a significant number of HIV infected pregnant women will not be tested because of lack of prenatal care or late prenatal care. To detect these cases it is necessary to use a rapid ELISA test in all untested women admitted in labor and follow any positive rapid test with ZDV treatment of mother and infant. If the confirmatory test is negative, the treatment of the infant will be discontinued.

Antepartum Care

The care of pregnant HIV-infected women is a complex task that requires a multidisciplinary approach. Surveillance of the infection and selection of treatment is a task for the infectious disease specialist or for the physician dedicated to the treatment of HIV. Many other aspects of the care of these patients will be provided by social workers, nutritionists, pediatric and obstetric educators, and many other health care providers. The guidelines provided in this book are mainly for obstetricians working in underdeveloped countries where the availability of teams of health care workers devoted exclusively to the care of these patients is not available.

One important task for the obstetrician is to advise these patients about the option of abortion if the gestational age is less than 22 weeks. If the patient decides to continue with the pregnancy, her antepartum management should include the measures described in Box 5-11. The evolution of the disease during pregnancy is followed with periodic assessments of the viral load and the CD4 cell count, usually every month. Drug therapy is not different from that provided to nonpregnant individuals with HIV infection with the exception of the threshold to initiate therapy which is lower during pregnancy. Once the threshold, CD4 count < 500/mm^3 or viral load >10,000 copies/ml, is exceeded the standard treatment is HAART. There are a large number of HAART regimens using combinations of nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors (Box 5-12). One of

BOX 5-11

Antepartum management of the HIV-infected patient

- Evaluation for other sexually transmitted diseases
- Serial ultrasounds to follow fetal growth
- Weekly nonstress testing after 32 weeks
- Measurement of CD4 cells every trimester
- If the CD4 cell count is greater than 500, regular obstetrical care
- If the CD4 cell count is less than 500, start therapy with azidothymidine (AZT), 100 mg five times daily
- If the CD4 count is less than 200, start prophylaxis for pneumocystis carinii infection, using trimethoprim-sulfamethoxazole double-strength two tablets twice daily, three times every week
- Obtain infectious disease consultation
- Coordinate participation in patient's care of other services such as nutrition, pediatrics, social services, etc.

BOX 5-12

Antiretroviral drugs

Nucleoside and nucleotide analogue reverse transcriptase inhibitors

- Zidovudine (AZT)
- Zalcitabine (HIVID)
- Didanosine (Videx)
- Stavudine (Zerit)
- Lamivudine (Epivir)
- Abacavir (Ziagen)
- Tenofovir DF (Viread)

Non-nucleoside reverse transcriptase inhibitors

- Nevirapine (Viramune)
- Delavirdine (Rescriptor)
- Efavirenz (Sustiva)

Protease inhibitors

- Indinavir (Crixivan)
- Ritonavir (Norvir)
- Saquinavir (Fortovase)
- Nelfinavir (Viracept)
- Amprenavir (Agenerase)
- Lopinavir/Ritonavir (Kaletra)

the principles governing treatment during pregnancy is to include ZDV as a component of the HAART regimen whenever possible. Some of these drugs have overlapping toxicities, or decreased efficacy when used in combination, or potentially serious maternal or neonatal side effects such as lactic acidosis and mitochondrial toxicity. This is one of the many reasons why the decision regarding drugs selection should be in the hands of the HIV specialist. The use of antiretroviral agents as monotherapy is not recommended except when it is used to reduce perinatal transmission during labor.

Women with HIV infection should be scheduled for induction of labor or cesarean delivery at 38 weeks of gestation. The reason for this timing of delivery is to avoid rupture of the membranes or labor before delivery. Also, timed delivery is useful to determine in advance the patient's viral load and to be certain that intrapartum prophylaxis is accomplished.

Intrapartum Management

At the time of delivery, special precautions should be taken to avoid contact of the health care personnel with the body fluids of the HIV-infected patients. These measures are shown in Box 5-13. The pediatric service should be notified in advance so that they will be present at the time of delivery and for adequate follow-up of the infant.

The protective effect of cesarean section on vertical transmission has been demonstrated by several studies. The evidence is so strong that the ACOG (2000) recommended to discuss and advise cesarean delivery for women with viral loads > 1000 copies/ml. Patients should be informed that in the absence of treatment or cesarean delivery, the incidence of neonatal infection is approximately 25%. When ZDV treatment is used during delivery, the frequency of infection drops to 5–8% and when the care includes both ZDV therapy and cesarean delivery the frequency of neonatal infection is reduced to 2%. If the viral load is < 1000 copies/ml the incidence of neonatal infection is 2% irrespective of the type of delivery and these patients may choose between cesarean or vaginal delivery. For patients who chose vaginal delivery, it is recommended to avoid the use of fetal scalp electrodes to decrease the contact between fetal blood and vaginal secretions.

Intrapartum treatment with ZDV is of fundamental importance to decrease vertical transmission. The recommended treatment is ZDV 2 mg/kg IV over 1 hour, followed by continuous infusion of 1 mg/kg IV until delivery. The newborn treatment is oral ZDV, 2 mg/kg every 6 hours for the first 6 weeks of life.

BOX 5-13

Intrapartum measures for HIV-infected patients

- The health care personnel should use protective barriers including protective eyeglasses, impermeable gowns, and double gloves
- Handle blood, amniotic fluid, and other secretions and body fluids as if they were infected
- Proper handling of needles and scalpels
- The nasopharyngeal secretions of the neonate should be removed using wall suction with a device to keep the pressure below 140 mmHg. The oropharyngeal secretions should be removed with bulb or with wall suction

Postpartum Care

Universal precautions should continue in the postpartum period. The mother should be instructed to avoid breastfeeding. Medical and pediatric follow-up for mother and baby is extremely important.

HIV in Pregnancy: Indian Experience

Damania and Tank from India (2004) made a pertinent observation that HIV infections lowered patient's resistance to disease; they were prone to develop pulmonary infections. Tuberculosis and fungal infections far outnumber Pneumocystis carinii seen in the West; there is also a fear of catching malaria in poor tropical countries.

Patel et al., (2000) from Pune reported an incidence of 3.4% seropositivity for HIV in the pregnant population attending the prenatal clinic of a government hospital, of these 24.1% were teenagers and 20.7% had evidence of other STDs as well. PROM was reported in 24.2% and the incidence of fetal wastage exceeded 24%. The mean birth weights of babies born to HIV positive mothers was about 120 g lower than in normal controls. Abortion was induced in 14.7% patients. Most of these patients (about 70%) were detected only in the third trimester of pregnancy. Gopalan et al. from Chandigarh (2000) reported a low incidence of HIV of 0.036%. In her study she observed that 80% of the patients were young in the age groups of 21–30 years and more than 80% did not use contraceptives. Datey et al. (2003) in a multicentric ICMR study reported the highest incidence of 4.5% HIV in pregnancy from Mumbai compared to less than 1.0% in other centers. Madhivanan et al. from Chennai (2002) reporting on the profiles of HIV positive pregnant women reported that heterosexual contact was the main route of transmission. Housewives accounted for 88.0% of the afflicted. The incidence of opportunistic infections was 14.6% and lower genital tract infection was detected in 26.6%. Pregnancy termination was undertaken in 12%. Antiretroviral treatment was prescribed to 75.6%. Delivery was accomplished vaginally in 5% whereas cesarean section was performed in 34%. Follow-up of infants 6 months after birth revealed that 5% were seronegative, 17% were seropositive, two babies died and the rest were still under observation. Dave et al. (2002) from Indore documented that 33 out of 500 pregnant

women tested HIV positive . The age group of 25–34 was mainly affected; the mean age was 28.5 years. About 75–80% of women were infected through heterosexual contact. Husbands of 54% tested positive for HIV infection. Blood transfusion accounted for 3.6% cases. Other STDs were present in 45.4% patients. Dongaonkar et al. from Mumbai (2001) reported an incidence of HIV positive in 3.9% of the pregnancies with a vertical transmission incidence of 36.4%. Asha Dalal from Mumbai (2001) in a leading editorial on the subject made a plea for screening of all pregnant women for HIV prevalence, providing counseling in confidence, making available treatment at affordable costs, and observing universal precautions to protect the staff and all concerned in patient care whilst handling these patients. Although, ideally breast feeding is contraindicated, in poor and low resource countries this requires a critical reappraisal

GENITAL HERPES

Infection with herpes simplex virus (HSV) is the most frequent sexually transmitted disease in USA. About 1.6 million new cases of genital herpes occur every year, 22% of pregnant women are seropositive for HSV-2, and approximately 1500 cases of neonatal herpes occur every year. Approximately 80% of the cases of neonatal herpes are the result of vertical transmission during the passage of the fetus through the birth canal. Neonatal herpes is a devastating infection that affects the CNS in approximately 50% of the cases. More than 30% of newborns with CNS herpes infection will die and 40% of the survivors will have severe neurologic sequelae. The obstetrician has an important role in the prevention of neonatal herpes by identifying pregnant women at risk and preventing vertical transmission.

The Virus

HSV belongs to the herpes virus family, a large group of DNA viruses that includes at least three other human viruses: CMV, varicella-zoster, and Epstein-Barr virus. These viruses have the ability to persist throughout the life of their hosts, to produce recurrent infections, and to induce intranuclear inclusions in infected cells. There are two main antigenic types of HSV, HSV-1 and HSV-2. Although there is a 50% concordance in DNA sequences, several biologic and biochemical differences between HSV-1 and HSV-2 have been identified. Both types of HSV can affect the genital areas and both can lead to neonatal infections of equal severity. However, genital infections are predominantly by HSV-2 and approximately three-fourths of neonatal HSV infections are of type 2. HSV-1 infection is the most frequent cause of genital herpes among college-age population, and epidemiologic studies suggest that oral genital contact is the most important risk factor for its acquisition.

Maternal Infection

Clinical diagnosis of genital HSV infection during pregnancy is notoriously inaccurate because between 75 and 90% of HSV-2 infected persons are not aware of having the infection and approximately 70% of new HSV infections among pregnant women are asymptomatic or unrecognized (Brown et al., 2003). The other 30% have clinical symptoms that range from minimal lesions to severe presentations. The reason for this is that most sexual transmission occurs during episodes of subclinical reactivation in persons who are not aware of their infection. It is clear that selecting a population at risk of vertical transmission by relying on maternal symptoms or on the presence of visible lesions is completely inadequate.

Women with clinical manifestations of primary or recurrent infections show characteristic lesions in the external genitalia and have nonspecific manifestations of genital infection, including cervical inflammation, dysuria, hematuria, leukorrhea, and pelvic pain. However, approximately 43% of patients with positive cultures are asymptomatic at the time of diagnosis. Asymptomatic shedding occurs between 1 week and 3 months after an infection, most commonly from 1 to 3 weeks. Shedding tends to be longer with primary infections. The rate of asymptomatic shedding during pregnancy is between 0.2 and 7.4% and at the time of delivery between 0.1 and 1.4%.

Women with genital HSV infections during the first half of pregnancy have a 50% incidence of spontaneous abortions. The risk of abortion seems to be higher in those with primary infections. HSV has been isolated from abortus material but it is unclear if the increased abortion rate results from generalized maternal toxicity or whether it is related to the fetal infection. After 20 weeks of gestation, maternal infection is associated with an increased incidence of preterm delivery that is more apparent in women experiencing primary HSV infections. In the study of Nahamias et al. (1971) 35% of a group of women experiencing primary infections after 20 weeks of gestation delivered prematurely as compared to 14% of women of similar gestational age affected by recurrent infections.

Neonatal Infection

Newborns with herpes may have disseminated disease, CNS infection, or local infection in skin, eyes, or mouth. Babies with disseminated herpes infection usually present between 9 and 11 days of life with unspecific symptoms such as lethargy, irritability, and apnea. This is followed within 24 hours by seizures, coagulopathy, cardiovascular compromise, liver involvement, and death. The disseminated form of HSV infection in the neonate involves primarily

the liver and adrenal glands. Other organs frequently involved include the larynx, trachea, lungs, esophagus, stomach, intestines, spleen, and heart. If the infant does not die early from visceral involvement, CNS disease is often manifest. Skin, oral, or ocular lesions are often associated with disseminated disease. Encephalitis may occur as a part of disseminated herpetic infection or as the predominant manifestation. It is characterized by nonfocal, intractable seizures. Most of the survivors have neurologic sequelae. Almost 50% of newborns with neonatal herpes have disease localized to the skin, mouth, or eyes. Also, several cases have been reported in which pneumonia appearing between days 3 and 14 of life is the most prominent feature of the infection.

Hematogenous Transmission

Transplacental intrauterine herpes infections are infrequent. However, their occurrence has been well documented and these babies show skin lesions and scars at birth, microcephaly, microphthalmia, and hydranencephaly, as well as positive viral cultures.

Transmission at Delivery

The most important source of infection to the neonate is the mother's genital tract at the time of delivery. Passage through virus-containing maternal secretions during the second stage of labor allows HSV to enter the infant via the eyes, upper respiratory tract, scalp (especially if internal fetal monitoring devices were used), and umbilical cord. Prolonged rupture of the membranes has also been associated with neonatal infections, suggesting an ascending spread of infection.

When an infant is delivered vaginally from a mother affected by primary HSV genital infection, the risk of acquiring the infection is 40–60%. This risk is less than 5% if the mother is affected by a recurrent infection because in these cases the maternal immune response limits the infection and has a protective effect on the fetus.

The risk of neonatal infection in patients with active genital herpes at the time of delivery is markedly decreased if the infant is delivered by cesarean section. In the past, a period of 4 hours after rupture of the membranes was considered to be the threshold for performing cesarean section because it was thought that after 4 hours the possibilities of fetal infection were pretty significant and cesarean probably ineffective. However, a 4 hours' period after ruptured membranes does not necessarily mean that the fetus is infected and that cesarean will have no protective effect. Cesarean should be performed irrespective of the duration of ruptured membranes. The risk of acquiring HSV infection appears to be similar whether the infant is term or preterm. Transplacental acquired antibodies against HSV may protect the infant from disseminated HSV infection but do not protect against localized disease, which may be fatal.

Diagnosis

Viral isolation is the definitive means of diagnosis for HSV infections. Specimens are obtained from any active lesions as well as from the cervix and vagina. If not tested within a few hours, the specimen should be frozen at –70°C or in dry ice or stored in a Leibowitz–Emory transport medium. A tentative diagnosis can usually be obtained by the viral laboratory in 1–3 days. The sensitivity of viral cultures is low and declines with the stage of the lesions, being better at the beginning and worse at the end of the active infection.

PCR assays for HSV are more sensitive and are replacing viral cultures as the preferred means of diagnosis. Similarly to the viral cultures, PCR is of value only when the result is positive because viral shedding is intermittent and the sample may be obtained at a time when the virus is not present. The PCR and the viral culture need to be typed to determine if HSV-1 or HSV-2 is the cause of the infection.

Cytologic techniques are a readily available, rapid means of identifying HSV infections. Cell scrapings are obtained from the base of lesions as well as from the cervix; they are smeared, fixed in alcohol, and then stained with Papanicolaou stain. The typical morphologic findings include intranuclear inclusions and multinucleated giant cells. In skilled hands, cytologic techniques will identify 60–80% of HSV infections.

Serology is of fundamental importance for the assessment of pregnant women with or at risk of genital infection. The antibodies to HSV develop several days after the primary infection. The serologic assays usually differentiate between HSV-1 and HSV-2 antibodies. The presence of HSV-2 antibodies indicates a genital infection while HSV-1 antibodies may be present due to genital or extragenital, usually oral, infection. False negative HSV-2 serology may occur in early stages of a genital infection when antibodies have not developed. False positive results may occur but are extremely rare.

Virus culture, PCR, and cytology cannot differentiate between primary and recurrent HSV infection. A careful history of prior HSV infections, both genital and oral, and of exposure to the virus may be useful in this respect. Serology is more useful because antibodies to HSV develop weeks after the primary infection and therefore, a genital lesion with positive HSV-1 or HSV-2 viral cultures and absence of the corresponding antibody is consistent with primary infection. A lesion positive for HSV-1 or HSV-2 and positive serology for the corresponding antibody indicates that the infection is a reactivation.

Identification of Women at Risk of Vertical Transmission

The present recommendation for the identification of women at risk of HSV fetal/neonatal transmission is based on historical facts and physical findings. All women with a history of HSV genital infection are considered to be at risk and require viral suppressive therapy during the last 4 weeks of gestation. Also, it is recommended to perform cesarean section if the patient describes prodromal symptoms of herpes infection or a herpetic lesion is detected in the vulva, vagina, and cervix at the time of labor. These recommendations will probably change in the near future because they fail in identifying 70% of the women who will be shedding HSV-2 virus at the time of labor and have infants with HSV infection. Most patients with HSV-2 infections are asymptomatic and unaware of their infection and have asymptomatic viral shedding during pregnancy. To prevent neonatal infection it is therefore necessary to recognize before labor women with negative history who are at risk of genital HSV-2 infection and women who are infected and are unaware of their infection who may shed the virus in the peripartum period. To achieve this objective it is necessary to perform serologic screening of all asymptomatic pregnant women without history of herpes and their partners at the end of the second trimester of pregnancy. Approximately 22% of all pregnant women will have no antibodies to HSV-2 while their partner is positive for HSV-2 antibodies, indicating that the woman has an approximately 14% risk of developing primary genital HSV-2 infection and transmitting the virus to the fetus. A similar situation occurs if the couple is discordant for HSV-1 antibodies although the risk of genital infection in these cases is less, approximately 2.4% (Gardella et al., 2005). Concordant serology for HSV-2 or HSV-1 indicates no risk for primary infection although there is a risk for recurrent infection and asymptomatic shedding at the time of labor. Absence of antibodies in both members of the couple indicates no risk for primary infection as long as the relationship is monogamous (Box 5-14). Acquisition of HSV-2 infection is associated with the duration of the partnership and 63% of the infections will occur when the partnership is of less than 1 year. Acquisition of HSV-1 infection is associated with having a partner with a history of oral herpes (Gardella et al., 2005). The CDC recognizes that herpes serology is useful to diagnose people with unrecognized infection, manage sex partners, and confirm clinical diagnosis (CDC, 2006).

Serologic screening is not without problems. In many cases it will be impossible to obtain the serology of women's partner(s) and is possible that the woman has multiple partners with unknown and diverse serology. Other concerns are the high number of women who would require viral suppression, the possibility of an increase in the rate of cesarean deliveries, and the emotional consequences for the woman and her partner of revealing the presence of an asymptomatic infection (Urato and Caughey, 2006). Despite these concerns, serologic screening will select a group of women at risk of vertical transmission who presently are not identified and are the largest contributors to the problem of neonatal herpes.

BOX 5-14

Risk of genital HSV infection according to serologic findings

Mother		Partner		Risk
HSV-1	HSV-2	HSV-1	HSV-2	
(–)	(–)	(–)	(–)	No risk. No prophylaxis needed.
(+)	(–)	(+)	(–)	Risk for HSV-1 shedding. Avoid oral sex. Need prophylaxis.
(–)	(+)	(–)	(+)	Risk for HSV-2 shedding. Need prophylaxis.
(+)	(+)	(+)	(+)	Risk for HSV-1 and HSV-2 shedding. Need prophylaxis.
(–)	(–)	(+)	(–)	Risk for HSV-1 infection. Avoid oral sex. No prophylaxis unless seroconversion occurs.
(–)	(–)	(–)	(+)	Risk for HSV-2. Use condoms. No prophylaxis unless seroconversion occurs.
(+)	(+)	(+)	(+)	Risk for HSV-1 and HSV-2 shedding. Need prophylaxis.
(+)	(+)	(–)	(–)	Risk of paternal infection and HSV-1 and HSV-2 shedding. Need prophylaxis.
(+)	(+)	(–)	(+)	Risk for HSV-2 and HSV-1 shedding. Risk for HSV-1 infection. No oral sex. Need prophylaxis.

Antiviral Suppressive Therapy

Prevention of vertical transmission in women at risk (Box 5-15) is by means of viral suppressive therapy after 36 weeks of gestation. Acyclovir, valacyclovir, and famciclovir have all shown similar clinical efficacy in the prevention of genital infection and neonatal transmission in women at risk. Acyclovir is a synthetic purine nucleoside with high affinity for the viral enzyme thymidine kinase. After entering the infected cell, Acyclovir is phosphorylated by a thymidine kinase produced by the virus and converted to acyclovir-monophosphate. This is followed by two more phosphorylation steps carried out by host cell enzymes, which results in the formation of acyclovir-triphosphate. This compound is a substrate and a competitive inhibitor of the HSV DNA polymerase and effectively stops viral replication. Valacyclovir is a medication that is converted to acyclovir by the liver, resulting in greater bioavailability and

BOX 5-15

Women at risk for vertical transmission of HSV to the newborn and in need of antiviral prophylaxis after 36 weeks of gestation

- History of genital HSV infection
- Seronegative for HSV-2 and husband seropositive for HSV-2
- Seronegative for HSV-2 and husband's serology unknown
- Seropositive for HSV-2

BOX 5-16

Recommended doses for HSV antiviral suppression therapy

Acyclovir	400 mg orally two times daily from week 36 to delivery
Valacyclovir	500 mg orally once daily from week 36 to delivery
Famciclovir	250 mg orally twice daily from week 36 to delivery

longer half-life, requiring less frequent dosing. Famciclovir is a synthetic guanine derivative that is transformed into the active antiviral compound penciclovir. Similar to acyclovir penciclovir is phosphorylated by thymidine kinase and eventually transformed in a nucleotide triphosphate that inhibits viral DNA replication. All these compounds are Pregnancy Category B drugs. So far there is no evidence that they cause teratogenic effects in the fetus. The recommended doses for these medications are shown in Box 5-16. A systematic review of the literature clearly demonstrates the benefits of antiviral suppression therapy in women at risk (Sheffield et al., 2003).

Cesarean Delivery for Women with Genital HSV Lesions

The recommendation of the ACOG (1999) is to deliver by cesarean all women presenting in labor with herpetic genital lesions or with prodromal symptoms suggestive of genital herpes. The beneficial effect of cesarean has been demonstrated in prospective cohort studies (Brown et al., 2003) and is greater in the absence of ruptured membranes. As mentioned before, cesarean is justified even if the infected woman has ruptured membranes for more than 4 hours. Positive viral cultures or cytology are not necessary to proceed to cesarean delivery in women with suspected genital HSV lesions present at the time of labor, because the results of these tests are not available in time so as to allow proper clinical decisions. Women with no history of herpes genital infection or in suppressive antiviral therapy should be examined and if no herpetic lesions are present, they should be allowed to deliver vaginally.

There is considerable controversy regarding isolation policies for both mother and infant when the mother has genital HSV infection (Box 5-17). Also, there are no defined policies with respect to herpes labialis, which puts

BOX 5-17

Care of mothers with proven or clinically suspected genital HSV infection

- Mother should be in private room:
  - All personnel having direct contact with the patient or with contaminated articles should wear gown and gloves
  - Perineal pads and other genital dressings as well as bed linen should be handled as if infected (i.e., double-bagged)
- Mother may handle and feed her infant if:
  - She is out of bed and has washed her hands carefully. For mother–newborn contact this is preferable to wearing gloves
  - She puts a clean gown before the baby is brought to her from the nursery
- Mother may leave room after washing hands and view baby through nursery windows

BOX 5-18

Care of mother with active nongenital HSV infection

- Mother should be in a private room.
- All personnel having direct contact with patient or contaminated articles should wear gown and gloves.
- Dressings covering lesions and bed linen should be handled as if infected (i.e., double-bagged).
- Attempts should be made to expedite crusting of lesions by applying drying agents such as povidone iodine (Betadine), benzoin, or ethyl ether.
- Once lesions are crusted (generally 2–3 days), mother may handle infant as described for mother with genital HSV infection, except that she should wear a face mask.

infants at greater risk, since it is almost impossible for mothers and health care providers with "cold sores" to keep their hands from their face, which may transfer the virus from the hands to the baby (Box 5-18). In general, as long as the mother maintains scrupulous handwashing after personal hygiene care, there is no increased risk of transmission of genital or labial HSV to other patients or to the baby. In cases of both genital and nongenital infections, standard operating room technique should be used and proper cleaning of labor and delivery rooms should be there to prevent transmission of HSV infection in these areas.

Treatment

Primary and recurrent HSV infections can be successfully treated with acyclovir, valacyclovir, and famciclovir. The doses for these medications are shown in Box 5-19.

HSV Infection: Indian Experience

Deepika Deka (2004) from AIIMS, New Delhi (India) has extensive experience in the field of maternal fetal medicine.

BOX 5-19

Recommended doses of antiviral medications for the treatment of primary and recurrent HSV infections during pregnancy

Primary infection	
Acyclovir	400 mg orally three times a day for 7–14 days
Valacyclovir	1 g orally two times a day for 7–14 days
Famciclovir	250 mg orally three times a day for 7–14 days
Recurrent infection	
Acyclovir	400 mg orally three times a day for 5 days
Valacyclovir	500 mg orally twice a day for 5 days
Famciclovir	125 mg orally twice a day for 5 days

She mentions that congenital HSV infection is mainly acquired intrapartum (85–90%) or postnatally. Fetal infection in utero is rare. However, it can lead to multiple fetal malformations like microcephaly, microphthalmia, intracerebral calcification, hydroencephaly, and hepatosplenomegaly. About 50% women with primary genital herpes in the first half of pregnancy abort whilst infection in the second half can lead to preterm labor (35%) and intrauterine growth restriction (IUGR). Since all organs are susceptible to infection, multiple abnormalities can arise. Clinical markers of HSV include abortion, preterm labor, stillbirth is rare, head abnormalities, and hepatosplenomegaly. Ultrasound detection of organ system abnormalities and testing of amniotic fluid and fetal blood for ELISA IgM antibodies to HSV may hold the clue to diagnosis. Obstetricians caring for pregnant women should suspect maternal herpes on the basis of history or on the basis of clinical evidence of the presence of painful clusters of tiny vesicles with surrounding erythema which rupture and subsequently appear as shallow and eroded ulcers persisting for 1–3 weeks. Viral shedding occurs at the same time. Recurrences are common, but with passage of time these become milder and last for shorter duration of time. Maternal manifestations of herpes should be looked for in every suspected subject—inspection of the genitals and perineum and speculum examination may often reveal the presence of suspicious lesions. Diagnostic tests include (a) maternal serum for ELISA IgG and IgM testing for HSV-1 and HSV-2, (b) culture of exfoliated cells from fluid from the vesicles, and (c) staining of smear (Papanicoulaou/Tzanck training) from the fluid from vesicle reveals presence of multinucleated giant cells implicating the presence of virus. Early diagnosis and treatment of the mother in the third trimester of pregnancy improves neonatal prognosis. Elective cesarean section is very effective in prevention of neonatal HSV in the presence of active herpes simplex.

VARICELLA

Varicella (chicken pox) is a highly contagious disease of children that may occur during pregnancy and cause significant maternal and fetal morbidity and mortality. Since varicella is a common infection in children and confers a lifelong immunity, it is not surprising that approximately 95% of women in the reproductive age in USA are immune. Therefore, the incidence of varicella in pregnant women is low, approximately 1–5 per 10,000.

The Virus

The varicella-zoster virus is a member of the herpes virus family. It measures approximately 200 nm in diameter, is enveloped, and its genetic material is double-stranded DNA.

Transmission

Varicella virus is usually transmitted by the respiratory route. It can also be transmitted from pregnant women to their fetuses by the hematogenous transplacental route.

Maternal Infection

The incubation period of varicella is, on average, 11 days. The first symptoms are fever, malaise, myalgias, and headaches. These symptoms are followed within 1 day by the onset of a maculopapular rash in the skin and mucosal membranes that rapidly transforms into vesicles which are extremely pruritic. The vesicles progress rapidly to pustules and then to scabs. Characteristically, new crops appear for 3–4 days and all stages of the cutaneous lesion are present concurrently. All skin lesions crust by day 10 after the onset of the rash. The disease is self-limited and if there are no complications the process ends in 2–4 weeks.

Varicella infection is more severe in adults than in children. When varicella occurs in pregnancy, maternal morbidity and mortality are increased and there are potentially severe fetal complications. The most serious maternal complication is the development of pneumonia—a problem that affects approximately 10–20% of pregnant patients with varicella. Pneumonia usually occurs 1 or 2 days after the appearance of the cutaneous lesions. The initial symptoms are shortness of breath, pleuritic pain, and cough. The chest x-ray will show characteristic pneumonic infiltrates. Many patients develop severe adult respiratory distress syndrome (ARDS) and the mortality varies between 10 and 35%. Another serious, albeit rare, maternal complication is encephalitis. Preterm labor affects approximately 35% of mothers with varicella. Herpes zoster is a common long-term sequelae.

Fetal Infection

The literature distinguishes three types of fetal varicella infection: varicella embryopathy, congenital varicella, and neonatal varicella. *Varicella embryopathy* is a severe form of the disease characterized by limb hypoplasia and CNS

involvement, which was thought to occur when the onset of maternal infection was before 20 weeks of gestation. *Congenital varicella* was a term used to describe the fetal effects of infection occurring between 20 weeks and term and neonatal disease was the term used to distinguish the newborn condition when the maternal infection takes place around the time of delivery. This division is artificial since the characteristic features of the "embryopathy" can also be seen when the infection occurs after 20 weeks. Also, many cases of neonatal varicella are the product of fetal or congenital infection manifesting after the birth of the infant. However, the classification into three types gives the physician and the parents some indication of the gestational age when the infection occurred.

When fetal disease occurs within the first 15 weeks of gestation, approximately 2–10% of newborns will have low birth weight, ophthalmologic lesions, neurologic symptoms, limb hypoplasia, skin scars, and psychomotor retardation. When the infection is acquired after 20 weeks of gestation, the manifestations of congenital varicella have a wide spectrum that varies between lesions similar to those found in typical varicella embryopathy and benign skin scarring lesions. The latter are typical of fetuses that develop varicella "in utero" which are healed at the time of birth. These babies are carriers of the virus and will develop herpes zoster during childhood. When the mother acquires varicella late in the third trimester of pregnancy, approximately 25–50% of the newborns will develop a severe form of varicella with a 30% mortality rate. Neonatal varicella is characterized by pneumonitis, hepatitis, and disseminated intravascular coagulation. The severity of the neonatal infection is inversely related to the concentration of maternal antibodies present in the newborn circulation. The mother will start to produce and transfer to the fetus protective antibodies approximately 5 days after the onset of her disease. Thus, babies born 5 days or more from the beginning of the maternal disease will be protected. Babies that develop neonatal varicella between birth and 5 days of age will also be protected. In contrast, mortality will be elevated if the neonatal rash appears between days 5 and 10 (Box 5-20). Neonatal infection after day 10 is usually mild.

BOX 5-20

Deaths from congenital varicella in relation to date of onset of rash in mother or neonate

	Deaths	Neonatal cases (%)	Neonatal mortality (%)
Day of onset of rash in neonate			
0–4	0	22	0
5–10	4	19	21
Onset of maternal rash, days antepartum			
> 5	0	23	0
0–4	4	13	31

From Gershon AA. Chickenpox, measles and mumps. In: Remington JS, Klein JO, eds. Infection Diseases of the Fetus and Newborn Infant. Philadelphia: WB Saunders, 1990: 413, Table 11–8.

Diagnosis

The diagnosis of maternal varicella is primarily clinical. However, the presence of the disease may be documented by viral culture or serologic seroconversion. The main serologic tests are the FAMA (fluorescent antibody to membrane antigen), the EIA, and the CF.

Management

The most common obstetrical problem related to varicella is the patient who does not know whether or not she had varicella during childhood and has been exposed to a child with varicella. In these cases, the woman's immunity should be assessed with a FAMA test. If the patient is immune, no treatment will be necessary. If the patient is not immune, she should be treated with varicella-zoster immune globulin (VZIG), in a single dose, intramuscularly, ideally no later than 96 hours postexposure. VZIG comes in vials containing 125 units per vial in approximately 1.25 ml volume. The recommended dose is 125 units per each 10 kg body weight up to a maximum of 625 units. The medication is only 50% effective in preventing the development of the disease. Due to the high failure index, some recommend increasing the dose to 250 units per kg. Varicella vaccine should not be given during pregnancy.

Pregnant women with varicella require special attention because they are prone to have a difficult disease course and to develop serious complications. The biggest fear is the development of pneumonia. If this occurs the patient should be admitted to the hospital. To avoid nosocomial spread of the infection the patient should be in respiratory isolation and her care should be provided only by individuals with known varicella immunity. Treatment should start immediately using acyclovir 500 mg/m^2 (10–15 mg/kg) IV every 8 hours, for 7 days. Acyclovir has not been show to avoid or improve the fetal effects of varicella. Mechanical ventilation should be used aggressively if necessary. Another antiviral drug that may be used in pregnant patients with varicella is vidarabine (ARA-A) in doses of 10 ml/kg over a 12-hour period every day for 5 days.

Pregnant patients with varicella should be monitored for uterine contractions and treated with tocolytic agents if they develop excessive uterine activity. The objective of the treatment is to delay delivery for at least 5 days after the onset of maternal symptoms so that the fetus has the protection of passively transmitted maternal antibodies.

Although the present recommendation is to give acyclovir only if pneumonia, encephalitis, or other complications develop, an argument can be made about the potential

advantages of giving acyclovir to *all* pregnant women who develop varicella at any time during pregnancy. Studies are necessary to determine if the course of maternal and fetal disease is modified and complications are avoided by giving acyclovir before those appear.

In India, chicken pox is a common childhood infection and generally mild in clinical manifestation. Hence most children suffer from it and acquire immunity before reaching adulthood. Presently there is an increasing trend towards seeking active immunization against varicella, therefore the incidence of encountering varicella during pregnancy in future will be diminished.

VIRAL HEPATITIS

Viral hepatitis is an infection that may have serious implications during pregnancy. There are at least five different types of viral hepatitis: A, B, D, C, and E. All hepatitis viruses except B are RNA viruses. Hepatitis A is not transmitted vertically to the fetus. Hepatitis B and C may be transmitted vertically to the fetus and are the main concern to the obstetrician. Hepatitis D is a defective RNA virus that requires concomitant infection with hepatitis B. Hepatitis E has similar characteristics to hepatitis A but is a more serious condition predominant in countries with poor sanitary conditions. It is spread by contaminated water supplies and has caused large epidemics of acute viral hepatitis in developing countries, with significant mortality in pregnant women.

Hepatitis A

Hepatitis A is uncommonly diagnosed during pregnancy because signs and symptoms are unspecific and the majority of infected individuals are asymptomatic. The virus is nonteratogenic and there is no evidence of vertical transmission. The infection may cause an increased frequency of preterm birth. The diagnosis is made by determination of specific anti-hepatitis A virus IgM. Treatment consists of bed rest and adequate nutrition.

Hepatitis B

The hepatitis B virus (HBV) is the cause of 40–45% of all cases of hepatitis found in USA. It occurs "de novo" in approximately 1 or 2 of every 1000 pregnancies while the frequency of chronic infection is between 5 and 15 per 1000. As a result, approximately 20,000 newborns are delivered to mothers seropositive for hepatitis B surface antigen (HBsAg). Fortunately, with the introduction of immunoprophylaxis only a minority of these newborns become chronically infected.

The HBV or Dane particle is a virus with a diameter of 42 nm, formed by a nucleocapsid containing the core antigen (HBcAg) surrounded by inner and outer envelopes. The genetic material of HBV is a long circular DNA molecule that is partially double stranded. The surface antigen (HBsAg) and the e antigen (HBeAg), which is a soluble polypeptide, are part of the viral envelope. The HBsAg is the marker of ongoing HBV infection and is found not only in the intact virion but also in incomplete viral surface capsule particles devoid of DNA. HBsAg usually disappears during the convalescent phase of the disease and its persistency indicates chronic infection. The HBeAg is a marker of infectivity and viral replication.

Transmission

HBV is highly infectious and can be transmitted by infected blood or blood products, by saliva, and by sexual intercourse. Chronic infection follows acute hepatitis B in about 10% of the cases. There are certain groups of individuals who are at high risk of being chronic carriers of HBV (Box 5-21). In some places around the world with high prevalence of HBV infection, perinatal transmission from chronic carriers is responsible for 35–50% of all new infections.

BOX 5-21

Individuals at high risk of being hepatitis B chronic carriers

- Intravenous drug abusers
- Individuals who work in hemodialysis units
- Household contacts of HBV carriers
- Immigrants from Asia, Pacific Basin, Alaskan Eskimos, sub-Saharan Africans, Caribbean, Central and South America
- Clients or staff of institutes for mentally retarded
- Prostitutes
- Sexual partners of IV drug users, hemophiliacs, bisexual individuals
- Multiple blood transfusion recipients
- Individuals with acute or chronic liver disease
- Professional exposure to blood or blood products

Maternal Infection

Pregnant women may be affected by acute HBV infection or have chronic infections. The acute infection is manifested by flu-like symptoms in approximately 25% of the patients and is asymptomatic in the rest. The majority of patients do not develop jaundice and fever is uncommon. Approximately 90% of individuals have spontaneous complete resolution of the acute infection, fewer than 1% would die of fulminant hepatitis, and 5–10% would become chronic carriers manifested by the continuous presence of HBsAg in their serum.

Seven of each 10 chronic HBV carriers have chronic persistent hepatitis (CPH) and the other 3 have chronic active hepatitis (CAH). In individuals with CPH the disease does not progress and liver enzymes are normal. Patients with CAH follow a different course and frequently develop

cirrhosis, hepatic failure, and primary hepatocellular carcinoma. About 50% of CAH patients of Mediterranean origin are simultaneously infected with the delta virus agent of hepatitis D, suffer recurrent attacks of acute hepatitis, and die of cirrhosis and liver failure.

Diagnosis

The diagnosis of acute HBV infection is made by the presence of HBsAg early in the course of the disease, followed by the appearance of antibodies against the core (anti-HBc), the e (anti-HBe), and the surface (anti-HBs) antigens. The liver enzymes will be elevated during the initial phase of the disease. The diagnosis of chronic carriers is more complex. Their serology marker is a persistence of HBsAg more than 6 months after the initial infection. The presence of a positive HBeAg indicates a highly infectious carrier. The presence of anti-HBc is a marker for prior disease. The presence of anti-HBe antibody and the absence of HBV DNA in the patient's serum indicate an end of the active liver disease even if the HBsAg is still positive. Approximately 10–40% of chronic HBV carriers with positive HBsAg have detectable anti-HBs antibodies. In these cases the antibodies are probably against a different viral genome that may have as little as a single amino acid substitution in the surface antigen.

Screening

All pregnant women should be screened for HBV infection. Selective screening of high-risk groups has failed to identify a high number of infected individuals. Screening is usually performed during the first prenatal visit and should be repeated during the third trimester in high-risk patients. The screening test is a determination of HBsAg.

Neonatal Transmission

Most newborn infections are the result of vertical transmission from chronic carriers or follow an acute infection in the last trimester of pregnancy. Mothers with acute infection during the first and second trimesters transmit the infection to approximately 10% of their newborns. When the acute infection occurs in the third trimester, 80–90% of the newborns will be infected. The higher risk for vertical transmission is from chronic carriers with positive HBeAg. These patients are highly infective and as many as 90% of their newborns will be infected. HBe antibodies are not protective and women with positive anti-HBe have a 25% probability of transmitting the infection. If the HBe antigen and the HBe antibody are negative the probability of neonatal infection goes down to 10%.

Transplacental infection of the fetus is rare and viral DNA is rarely found in the amniotic fluid and cord blood (Towers et al., 2001). Most neonatal infections are the result of contact with infected maternal blood and vaginal secretions during parturition or acquired during breast-feeding. Infected newborns are usually asymptomatic but, if they are untreated, approximately 85% will develop chronic infection. Infants born to HBsAg positive mothers do not need to be isolated at birth. However, the mother's secretions should be considered potentially infected and managed with universal precautions. Breast-feeding should be discouraged.

Prevention of Neonatal Infection

Neonatal infection can be prevented by generalized screening of the overall obstetrical population and administration of hepatitis B immunoglobulin and hepatitis B recombinant vaccine to newborns of women positive for HBsAg. The current recommendation is to administer HBV immune globulin (0.5 ml intramuscularly) to the newborn within 12 hours of birth followed by the first dose of hepatitis B vaccine (0.5 ml intramuscularly) within 12 hours of birth and then 1 and 6 months later. The efficacy of combined passive and active immunization in preventing perinatal transmission of HBV ranges between 85 and 95%. The efficacy of the treatment is not decreased by subsequent breast-feeding (Hill et al., 2002). Vaccination for HBV infection can be performed during pregnancy and is advisable in seronegative women at high risk for infection. The currently available vaccines are highly immunogenic and are prepared from yeast cultures using recombinant DNA technology.

Thee use of cesarean delivery for the prevention of neonatal infection in HBV carriers is controversial. Some studies have shown no advantage of cesarean delivery while others have shown a reduction in neonatal infection from 24.9% in infants delivered vaginally to 10.0% in infants delivered by cesarean (Lee et al., 1988).

Hepatitis C

Hepatitis C is a condition that affects approximately 1.0–5% of all pregnancies and is more frequent in women with HIV infection. It was previously recognized as non-A, non-B hepatitis and is predominantly acquired through transfusion of blood and blood products although it is also transmitted by sexual intercourse and by vertical transmission during pregnancy. The risk factors for the acquisition of hepatitis C are similar as for hepatitis B but chronic infection following hepatitis B affects 10% of the cases while chronic liver disease follows hepatitis C in more than 50% of the cases.

The majority of hepatitis C virus (HCV) infections are asymptomatic. Most of the times the diagnosis is made during pregnancy due to elevated transaminases found in a laboratory metabolic profile test ordered because of reasons unrelated to liver disease. Further testing to explain

this finding usually demonstrates seropositivity for anti-HCV antibodies, which is the marker of chronic HCV infection. The presence of antibodies to HBV is not indicative of protection, and HCV antibodies usually coexist with a variable amount of HCV viral RNA.

Hepatitis C is transmitted vertically to the fetus by contact with infected maternal blood and vaginal secretions, similarly to the mechanism of transmission of hepatitis B. The rate of transmission is approximately 3–6% but this risk is much higher if the mother is also infected with HIV. The risk of vertical transmission correlates with the HCV RNA viral load of the mother (Ohto et al., 1994). HCV is rarely transmitted by breast-feeding and present recommendations do not advise against breast-feeding for HCV-positive mothers. The role of cesarean delivery for the prevention of vertical transmission has not been clearly demonstrated.

There is no effective treatment available to treat HCV infections in mothers and newborns. For this reason, routine HCV screening is not recommended at the present time. The development of effective treatments and methods to interrupt the transmission of the virus from mother to fetus will certainly modify the current approach to this infection.

Viral Hepatitis: Indian Experience

In India, hepatitis B virus remains a major concern with an incidence of HBsAg positivity of 4–6% (Raut, 2007). HEV is the main cause of non-A, non-B hepatitis, whilst HCV is not an important cause of acute viral disease (Kar et al., 1997). Infective hepatitis is endemic to our country and assumes epidemic proportions particularly during the rainy season when contamination of drinking water sources is highest. It is transmitted by the feco-oral route. In multiple Indian studies on the prevalence of HBsAg, the following results have been reported (see Table 5-2).

Poor sanitary and hygienic conditions, overcrowding, illiteracy, and poverty help to perpetuate the conditions favoring its spread. Viral hepatitis is an important cause of maternal mortality in India, accounting for 0.8–29.4% maternal deaths in various parts of India (Mathai, 1996). The mortality is 3.5 fold higher during pregnancy (an immunocompromised state) than in nonpregnant women.

Various workers analyzing the problem of hepatitis complicating pregnancy have reported wide variations in maternal mortality from the disease in India (Table 5-3).

Table 5-2. Prevalence rates of HBsAg during pregnancy in India

Authors	Year	Prevalence rates
Mittal et al.	1996	HBsAg positive in 6.34% (micro-ELISA) HBeAg positive in 18% of above
Gill et al.	1996	HBsAg positive in 5.0% (ELISA) HBeAg positive in 12% of above
Ahmad et al.	2001	HBsAg positive in 9.0%
Sharma et al.	1996	HBsAg positive in 10% mothers and 5% newborn-cord blood. Transplacental transmission is 50%. Anti-HBc present in 75% of positive mothers—of these 58% neonates acquired HBsAg infection. Eighty eight percent of babies born to HBsAG positive mothers were healthy.
Gupta et al.	1992	Risk of acquiring infection in infants born to HBsAg positive mothers was 17.1%. The infant risk in HBeAg positive mothers was 73.3% and only 9.0% in HBeAg negative mothers.

Table 5-3. Maternal mortality due to viral hepatitis in India

Authors	Years	Maternal mortality (%)
Patel et al.	1994–1997	3.6
Doke and Salunkhe	1987–1990	24.0
Roy et al.	1990–1998	4.8
Shankar and Seetharam	1988–1997	12.4
Sharma	1987–1996	5.4
Kulkarni and Huilgol	1988–1997	9.4
Khare	1985–2000	25.0
Bedi et al.	1991–1996	7.1

PARVOVIRUS B19 INFECTION

Parvovirus B19 is a single-stranded DNA virus that requires rapidly dividing cells for replication. Parvoviruses are small (20–25 nm), nonenveloped, and structurally simple, being able to code for only a few proteins. Parvovirus B19 infection is the cause of up to 27% of all cases of nonimmunological fetal hydrops (Hall, 1994). In children, parvovirus is the cause of erythema infectiosum, or fifth disease, a condition characterized by diffuse erythema of the cheeks (slapped-cheek disease) which usually affects elementary school children. The organism is also responsible for arthralgias in the adult and may have a role in the development of rheumatoid arthritis. Also, it causes an aplastic anemic crisis in patients with sickle cell disease and other hemolytic anemias and is a cause of chronic anemia in immunologically deficient patients.

Maternal Infection

Approximately 50% of women of childbearing age are seronegative for parvovirus B19 and susceptible to infection during pregnancy. Infection occurs in 0.25–6.00% of susceptible pregnancies and in the majority of pregnancies

in which seroconversion occurs, there is no vertical transmission to the fetus. The virus can be transmitted to pregnant women in several ways including parenterally and through plates and eating utensils, but the primary mechanism is person to person via the oropharyngeal route. Maternal infection is usually asymptomatic. A few patients will complain of arthralgias, rash, and low-grade fever. Maternal infection results in a miscarriage rate of approximately 10% before 20 weeks of gestation and in an increased frequency of stillbirths.

The risk of becoming infected is related to the following: mother's occupation, individuals working in school cafeterias and day-care centers, and school teachers having the highest infection rate. The risk of infection for susceptible seronegative individuals during a school outbreak of erythema infectiosum is approximately 6% for women in the community, 20% for teachers, 30% for day-care personnel, and 50% for school cafeteria workers. For susceptible teachers the rate of infection will be increased if the school children are younger or if they are exposed to a large number of children with the disease.

Fetal Transmission

The frequency of fetal transmission of parvovirus infection is approximately 25% but in only one-third of these cases will the fetus be infected, and there is evidence that infected fetuses may tolerate the disease and be born without sequelae. Approximately 80–85% of infected women will therefore go to term and deliver normal newborns. The rate of fetal loss is higher when the infection occurs in the first 20 weeks of pregnancy. Of the fetal losses, only 9% have positive virologic findings.

Fetal infection is characterized by nonimmunologic fetal hydrops. These fetuses have ascites, pleural and pericardial effusions, and subcutaneous edema. Parvovirus B19 has a high affinity for the human bone marrow and replicates only in erythroid progenitor cells, and the destruction of these cells causes aplastic anemia and is the main cause of the fetal hydrops. Fetal cardiac cells also contain receptors for the parvovirus B19 and may become infected, resulting in myocarditis and congestive heart failure, which will aggravate the fetal hydrops.

Diagnosis

Parvovirus B19 does not grow in cell cultures and the diagnosis of the infection is based in detecting maternal IgG and IgM antibodies or viral DNA by PCR in maternal serum, amniotic fluid, or fetal blood (Zerbini et al., 1996). PCR in the amniotic fluid is the most commonly used diagnostic test but detection of parvovirus DNA in umbilical cord blood is also a very sensitive method.

Management

The most common problem that the obstetrician faces in relation to parvovirus B19 infection is the assessment of infection risk in pregnant women who actually or potentially have been exposed to affected children during an outburst of fifth disease. The overall probability of infection in these cases depends on the prevalence of seronegativity in the reproductive age population (50%), occupational risk for infection (20% for teachers, 30% for day-care center personnel), and the risk of fetal infection if the mother develops the disease (10%). For a school teacher it is $0.5 \times 0.2 \times 0.1 = 1.0\%$.

To further assess the risk of fetal infection it is necessary to determine parvovirus B19-specific IgG and IgM antibodies. If the mother has positive IgG and negative IgM antibodies, she is immune and will not develop infection. If the mother has negative IgG and IgM antibodies, she is at risk and since the incubation period of parvovirus is between 4 and 14 days, she needs follow-up with IgM determinations in 1, 2, and perhaps 3 weeks. Persistence of seronegativity indicates that the exposure did not result in maternal infection. Acute infection is demonstrated by the presence of IgM antibodies.

A maternal infection documented by the presence of parvovirus IgM requires weekly evaluation of the fetus for the possibility of fetal anemia and fetal hydrops. In most cases hydrops will develop between 6 and 8 weeks' post-transmission. However, since there are cases reported as far as 12 weeks post-transmission, most patients are evaluated weekly for 12 weeks. Doppler ultrasound assessment of the middle cerebral artery peak velocity (MCA PV) is the method of choice to assess the possibility of fetal anemia (Cosmi et al., 2002). In the absence of increased MCA PV, expectant management is continued. Elevation of the MCA PV above the 95th percentile for the gestational age is a sensitive index of fetal anemia that usually precedes the development of hydrops and is an indication for intrauterine blood transfusion. Intrauterine transfusion has a survival rate of 82%, which is clearly better than the 55% achieved with expectant management (Von Kaisenberg and Jonat, 2001).

TOXOPLASMOSIS

Approximately 400–4000 infants born in USA every year are congenitally infected with toxoplasmosis (Jones et al., 2001). Most of these infants are asymptomatic during the neonatal period but the manifestations of the infection may become apparent in the second or third decade of life. Early treatment—maternal or neonatal—may reduce the severity of congenital toxoplasmosis. The main challenge with this condition is in the early diagnosis of infected women and fetuses.

The Parasite

Toxoplasma gondii exists in three forms: the trophozoite, the tissue cyst, and the oocyst. The trophozoite requires an intracellular habitat to survive and multiply. Reproduction is endogenous by internal budding. During the acute phase of an infection the trophozoite invades virtually every type of cell, especially muscle, liver, and the central nervous tissue. After entering the cells the organisms multiply until the cell's cytoplasm is so filled that the cell is disrupted. The second form of the parasite, the tissue cyst, is formed within the host cell as early as the 8th day of an acute infection and probably persists throughout the life of the host. The skeleton, heart muscles, and brain are the most common sites for latent infections.

The oocysts are produced in the small intestine of cats. Once shed, the oocyst sporulates in 1–5 days and becomes infectious. Under appropriate conditions (warm, moist soil), the oocysts may remain infectious for more than 1 year. Humans may become infected by inadvertently ingesting the oocytes present in cat litter, the soil, unwashed fruits and vegetables, or food contaminated via insect vectors. In addition, humans may become infected by eating raw or uncooked meat from cows, pork, lambs, and wild game that have ingested the parasite from the soil and transplacentally from a mother having acute infection. Tissue cysts and oocysts are resistant to stomach and small bowel digestion but all forms of the parasite are destroyed by adequate freezing and heating.

Maternal Infection

Transmission of *Toxoplasma* to humans usually occurs through the ingestion of undercooked meat (pork or lamb and occasionally beef) and through other foods contaminated with oocysts. Isolated cases have been transmitted by the transfusion of whole blood. Most maternal infections with *Toxoplasma* are mild or asymptomatic. The most common clinical signs are adenopathy and fatigue without fever. The lymphatic nodes most often involved are the cervical, suboccipital, supraclavicular, axillary, and inguinal. The adenopathy may be localized in one node or diffuse. Retroperitoneal and mesenteric nodes may also be involved, as well as the spleen and liver. Occasionally there may be a fever or exanthema. Chorioretinitis is a late manifestation of the disease and rarely occurs in the acute infection.

Congenital Transmission

One major obstetric concern is the congenital transmission of the parasite. With very rare exceptions, congenital transplacental transmission occurs only during acute maternal infection. Unfortunately, the majority of acute toxoplasma infections are asymptomatic and only a few patients complain of lymphadenopathy, fever, malaise , myalgias, or other symptoms. The relative risk of acquiring toxoplasmosis during pregnancy is related, in part, to the overall incidence of the disease in each community. In USA 13–67% of the overall population have positive toxoplasma IgG, indicating immunity and no risk of acute infection. Studies of pregnant women in USA have shown an overall incidence of positive toxoplasma antibodies of 31%. The incidence is much higher in countries like France and Austria and in areas of Latin America.

Studies, uniformly, have shown that when acute maternal infection occurs, toxoplasmosis is transmitted to the fetus in less than 50% of the cases. When the acute infection occurs at conception or during the first 2 months of gestation, vertical transmission is rare. During this time the placenta appears to be a more effective "barrier" to fetal infection than later in gestation and provides nearly 80% protection. When the acute infection occurs in the third trimester, vertical transmission is more common (60%) but the severity of the fetal infection is greater when it is acquired in early pregnancy. Multiple prospective studies on vertical transmission have been done in France where the incidence of toxoplasmosis is high and seroconversion during pregnancy is frequent. In one group of 183 women who seroconverted during pregnancy, there was an overall vertical transmission rate of 33–39%, resulting in 11 abortions, 7 stillborn or immediate newborn deaths, and 59 infants born with congenital toxoplasmosis (Desmonts and Couvreur, 1974). Nine of 59 infected infants were severely affected, 11 were mildly affected, and 39 had subclinical disease at birth. All the severely infected infants acquired their infections during the first two trimesters of pregnancy. Third-trimester transmission resulted only in subclinical infection. None of the infants of 195 mothers with elevated antibody titers suggesting infection before gestation were infected. Another study (Foulon et al., 1999) found a transmission rate of 44% with variation from 0% when the infection occurred before 5 weeks to 87% when the infection occurred at the end of the pregnancy.

Congenital Infection

Infants with congenital toxoplasmosis may be stillborn or obviously affected at birth. They may develop symptoms gradually in the first months of life or even later, or remain asymptomatic. The "classic triad" of congenital toxoplasmosis includes hydrocephalus, chorioretinitis, and intracranial calcifications. Many affected infants have other symptoms including hydrops fetalis or erythroblastosis, hepatosplenomegaly, and abnormal cerebrospinal fluid.

Newborns that are obviously affected at birth have a poor prognosis and 85% of them will be mentally retarded, 75% will have seizures, spasticity, or other major motor defects, 50% will have severe vision impairment, and 15% will have significant hearing impairment. Infected newborns that are asymptomatic at birth have a guarded prognosis and a high percentage of them will develop significant visual impairment, mental retardation, and other neurologic sequelae later in life (Koppe et al., 1986). In one study, 20 of 23 asymptomatic infants developed significant visual impairment, with 6 becoming blind in both eyes and 5 more becoming blind in one eye. The mean IQ in this group was 89.4, with 5 children having IQs below 80.

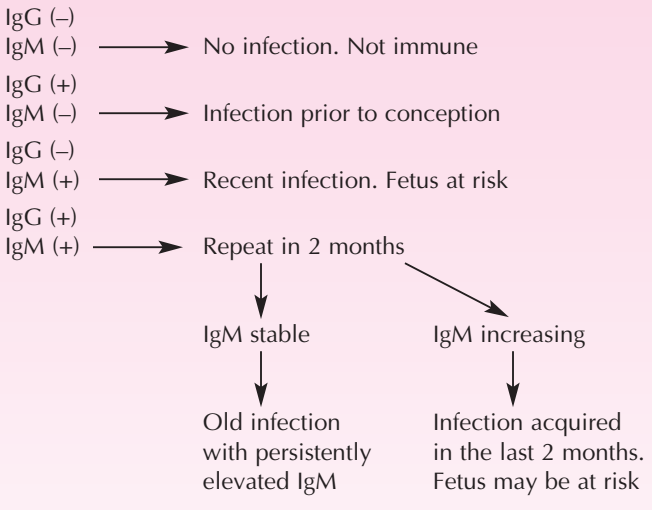
Toxoplasma cysts can be isolated from the myometrium, endometrium, and vaginal secretions of chronically infected women who have stable low antibody titers. Likewise, the organism has been isolated from aborted products of conception. Data indicate that although chronic toxoplasmosis is associated with abortion, it is not a common event.

Diagnosis

The most common method to diagnose toxoplasmosis is by means of antibody detection, and there are several serologic tests available for the diagnosis. IgG and IgM antibodies generally appear 1–2 weeks after the initial infection. Toxoplasma-specific IgG in the absence of IgM indicates that the infection is chronic and occurred at least 1 year before the test. Toxoplasma-specific IgM in the absence of IgG is a marker of recent infection. However, toxoplasma-specific IgM antibody may persist at high levels several years following the initial infection and the presence of both IgG and IgM antibodies does not help to determine when the infection occurred. Box 5-22 is a guide to the interpretation of serologic tests in toxoplasmosis.

BOX 5-22

Interpretation of serologic findings in toxoplasmosis



The two tests used to confirm a positive toxoplasma IgM serology are the Sabin–Feldman dye test and the IgM-indirect fluorescent antibody (IgM-IFA) test. The Sabin-Feldman dye test rises relatively slowly following an acute infection, taking up to 2 months to attain maximum levels, which are generally greater than 300 IU/ml and may be as high as 3000 IU/ml or more. High titers persist for months to years. Low titers almost always persist for life. Unfortunately, the Sabin–Feldman test is only available in a few specialized laboratories in USA. The IgM-IFA test becomes positive early in the course of an infection. Titers in patients with an acute acquired infection vary widely, ranging from 1:10 to 1:1000. High titers persist for several years and their presence does not necessarily indicate recent primary infection. In most cases the test becomes negative 3–4 months after infection.

The most common situation faced by the obstetricians is to determine the possibility of fetal infection when a positive IgM antibody for *Toxoplasma* is found during pregnancy. The first thing to do is to confirm the test result by a reference laboratory. The reference laboratory will run additional tests to help in determining the time of infection including the Sabin–Feldman test, IgM-IFA test, IgM ELISA, IgA ELISA, IgE ELISA, and IgG avidity testing. This toxoplasma serologic profile has been useful in the counseling of infected pregnant women and has been shown to decrease the rate of unnecessary abortions by approximately 50% (Liesenfeld et al., 2001). IgG avidity is an important test because the strength of the antibody binding to the parasite increases approximately 5 months after the primary infection. In cases of positive IgG and IgM antibodies and unknown timing of infection, high avidity can rule out primary infection early in pregnancy in approximately 75% of the cases.

If the serologic evidence is suggestive of primary toxoplasma infection during pregnancy, the next step is to confirm or rule out fetal congenital infection. The most sensitive tests for congenital infection are the testing of fetal blood for toxoplasma-specific IgM after 20 weeks of gestation and the quantitative PCR in amniotic fluid (Romand et al., 2004). A large toxoplasma DNA load by PCR and infection before 20 weeks of gestation are predictive of a poor fetal/neonatal outcome. Additional methods to diagnose congenital infection are as follows: (a) isolation of *Toxoplasma* from the amniotic fluid or fetal blood; (b) mouse inoculation with fetal blood or amniotic fluid which will be positive in 64% of infected fetuses, results being available only after 4–5 weeks; (c) immunofluorescence of the parasite in chorionic villi in vitro cultures using monoclonal antibodies. With the use of multiple tests in fetal blood and amniotic fluid, the specificity of the antenatal diagnosis may reach 90%. Ultrasound may be also valuable in cases of severe fetal

infection by detecting lesions, especially hydrocephaly and microcephaly, in mothers with positive serology.

Treatment

The main objective of the treatment of toxoplasmosis during pregnancy is to decrease the incidence and the severity of congenital infection. To decrease the frequency of vertical transmission, most centers use a combination of pyrimethamine 25 mg daily and sulfadiazine 3 g daily for 3 weeks, alternating with 3-week treatment with spiramycin 3 g daily. Sulfadoxine 500 mg daily can be substituted for sulfadiazine. Folic acid 5 mg daily is added to the treatment to antagonize the antifolate effects of pyrimethamine, and pyrimethamine is not given during the first 12–14 weeks of pregnancy because of the fear of teratogenic effects on the fetus. With this treatment, a definite reduction is noticed in the incidence of sequelae, particularly severe sequelae in treated mothers (Foulon et al., 1999). Apparently, the sooner the treatment is started after infection, the less frequently severe sequelae are observed.

Spiramycin is used widely in Europe for the treatment of women who seroconvert during pregnancy. In USA this macrolide antibiotic is available only by request to the US Food and Drug Administration. It may have gastrointestinal and dermatological side effects on the mother.

Prevention

Ideally, prevention of congenital toxoplasmosis requires screening for the identification of women at risk and treatment if seroconversion occurs. Routine prenatal screening for toxoplasmosis is practiced and is effective in countries with a high frequency of seropositivity such as France and Austria. In USA approximately 38% of the overall obstetrical population is seropositive, meaning that approximately 60% of all pregnant women will require repeated serologic testing to detect seroconversion. Another problem is the difficulties in the interpretation of positive IgM antibodies in women who are seropositive. Finally, studies have demonstrated that it is possible to achieve a significant decrease in the frequency of maternal toxoplasmosis without serologic screening by educational programs directed to (a) avoid eating undercooked meat, (b) wearing gloves when working in the garden, and (c) by avoiding taking care of cats (Foulon, 1992). Heating meat thoroughly to 66°C (150 F) or having meat smoked or cured eliminates tissue cysts. Pregnant women should thoroughly wash their hands after handling raw meats. If at all possible, seronegative pregnant women should avoid handling cat litter or soil contaminated with cat feces. Cat litter should be flushed away daily. To destroy viable oocysts, the empty litter pan can be filled with nearly boiling water for 5 minutes daily. Gloves should be worn when working in contaminated soil, and hands should be washed carefully.

In USA serologic screening for toxoplasmosis is recommended only for women infected with immunodeficiency virus (HIV). However, experts are urging that regional screening programs be developed and that women at high risk for toxoplasmosis, such as women working in veterinary clinics, cat owners, raw and rare meat eaters, deserve serologic or IgM-IFA screening. Similarly, any woman who develops adenopathy during pregnancy should be screened and should have follow-up serologic testing.

Any woman who develops acute toxoplasmosis during pregnancy should be counseled including the possibility of legal abortion. Inasmuch as congenital toxoplasmosis is limited almost exclusively to women with acute infections, reassurances can be made regarding future pregnancies. It should be emphasized during counseling that the risk of fetal infection appears minimal if the mother's infection occurred during the first 2 months of gestation but the risk is significant later in gestation. Women with acute toxoplasmosis who do not elect to terminate their pregnancy or who are too far advanced for an abortion will benefit from treatment with spiramycin, pyrimethamine, and sulfadiazine. It is important to alert the pediatrician, so that evaluation of the infant and the results of treatment are begun shortly after birth.

Toxoplasmosis: Indian Experience

Serum antibody profile of human beings has been commonly used to assess the endemicity of toxoplasmosis in a community. The seroprevalence of antibodies in India has revealed wide variations from 4 to 57% (Prakash and Chowdhury,1968; Singh and Nautiyal, 1991). The IgG ELISA method is presently the most widely used screening test during pregnancy. IgM tests are used to determine acute toxoplasmosis infection in pregnancy. Toxoplasmosis is not implicated in recurrent abortions or repeated pregnancy loss. Hence a screening for toxoplasmosis is not indicated in women with "bad obstetric history." Women at risk for congenital toxoplasmosis are those who acquire infection during the course of pregnancy, so that they convert from a seronegative to a seropositive status. If this occurs in the first trimester of pregnancy, medical termination of pregnancy (MTP) is indicated and justified. However, if this occurs later in pregnancy, the patient should be prescribed spiramycin throughout pregnancy. Those who are already IgG positive before the start of pregnancy do not require treatment (Mittal and Kothari, 2004). Neonatal manifestations of congenital toxoplasmosis include chorioretinitis (macular), hydrocephalus, microcephaly, and stillbirth. The severity of fetal disease is inversely proportional to gestation age at which the fetal infection is acquired. Only 10% of infected newborns exhibit adverse outcomes. Predominant ill effects include CNS manifestations—microcephaly, hydrocephalus,

intracranial calcifications, and encephaloclastic CNS lesions (Kabra, 2004); significant hearing loss (Deka and Sarin, 2004); and eye lesions like microphthalmia, cataract, necrotizing chorioretinitis. About 50% suffer from visual impairment (Chawla and Garg, 2004).

Management

Management strategies include:

1. Screening all pregnant women for toxoplasmosis IgG at the first visit (preferably in the first trimester).
2. Seronegative women are susceptible to infection, they should be screened once again in each trimester.
3. Seropositive pregnant women are assessed for the evidence of active toxoplasmosis by serum toxoplasma specific IgM antibodies, IgG in paired sera 3 weeks apart to determine rising titers, or IgG avidity test.
4. All pregnant women with acute toxoplasmosis seroconversion during first trimester of pregnancy be counseled and advised to undergo MTP.
5. Women in advanced pregnancy be started on spiramycin therapy, followed by prenatal diagnosis and monthly ultrasonography surveillance.
6. In case of documented fetal infection, the options are termination of pregnancy or prenatal therapy with sulfadiazine-pyrimethamine combination. This helps to reduce the severity of the infection and the incidence of future sequelae (Malhotra and Kriplani, 2004).

MALARIA

Malaria has been known to the human race for over 3000 years. There are references to it in the ancient Indian text of *Atharvaveda* 1500 BC (Desai, 2002). It has been a major killer in tropical and subtropical countries of the world. The WHO (2000) report draws attention to the fact that malaria has resurged in 103 countries of the world. Estimates of mortality range between 64/1000 in Africa, 20/1000 in India, and 4/1000 in America. (Malaria has been eradicated from Europe.) Singh et al. (1999) reported resurgence of malaria in several parts of India (Orissa, Meghalaya, Mizoram, Tripura, Chhattisgarh, and Andhra Pradesh).

Malaria is a protozoal disease caused by the parasite belonging to the genus *Plasmodium*. It spreads through the bite of the mosquito, blood transfusion, and transplacental transfer from mother to fetus during pregnancy.

Etiology

The following causative organisms have been recognized: *P. vivax, P. falciparum, P. malariae,* and *P. ovale*. Of these *P. falciparum* is responsible for most of the deaths. Resistant strains are posing major clinical problems in controlling the disease.

Pathology

The organism invades the RBCs, these get damaged, and its hemoglobin is consumed by the growing parasite. The damaged red cells become sticky and adherent in *P. falciparum* infection. This results in sequestration in vital organs leading to a disturbance in the microcirculation, which in turn leads to disturbed metabolism. The spleen removes both the parasitized and damaged RBCs. Progressive splenomegaly occurs. Excessive hemolysis leads to progressive anemia.

Clinical Manifestations

Mother: The immunocompromised state of the mother renders her susceptible to malaria. The severity of the symptoms depends upon the species of malaria causing the attack and the maternal host resistance/immunity. A typical attack is characterized by three stages: the cold, the hot, and the sweating stage. These episodes recur at 24–48 hours intervals. Constitutional symptoms like vomiting, malaise, and headaches are not uncommon. In severe cases delirium sets in. Hemolytic jaundice and anemia are common. Cerebral malaria is a life-threatening condition requiring intensive care. In endemic areas it takes 5–10 years to develop immunity.

Fetus: Placental parasitization occurs in 15–60% of affected patients. Passive transfer of antibodies to the fetus occurs, hence congenital malaria is rare. Pregnant mothers living in nonendemic areas are particularly vulnerable. Covell (1950) has reported congenital malaria in such cases.

Diagnosis

The following tests are useful:

- Examination of thick and thin smears of blood films stained with Giemsa stain.
- Quantification of parasites on examination of blood smears.
- PCR based detection of plasmodium DNA in blood.
- Serological tests.

Effects of Malaria in Pregnancy

There is enhanced risk of abortion, preterm delivery, IUGR, intrauterine fetal demise, and maternal risk of anemia, jaundice, hypoglycemia, hyperpyrexia, and convulsions.

Effects of Pregnancy on Malaria

The immunocompromised status of the mother predisposes to an increased severity of the attacks, and recurrent attacks are common.

Complications

Hypoglycemia, dehydration, acidosis, anemia, renal failure, acute pulmonary edema, coagulopathy, convulsions, circulatory collapse, fluid and electrolyte imbalance, jaundice, and death.

Management

Prevention

Intensify malaria control programs, early detection clinics, prompt treatment, vector control, and mass chemoprophylaxis of pregnant mothers and children.

Treatment

This includes:

- Antimalarial medication
- Supportive medication—antipyretic analgesics
- Nursing care
- Vaccines, if available

INDIAN EXPERIENCE OF FETAL INFECTIONS

Congenital infections constitute an important etiological factor contributing to increased perinatal morbidity and mortality. Evaluation of the contribution of congenital infections to perinatal mortality in various Indian surveys revealed it to be responsible for early neonatal deaths in 5.7% of cases (Shinde, 2000), 19.6% of cases (Jotwani et al., 2001), and 10.7% of cases (Gaddi and Seetharam, 2001). The most common congenital infections are caused by bacterial, viral or protozoan organisms.

Bacterial Infections

In the West, the most prevalent bacterial infection affecting the parturient has been the group B hemolytic streptococci (GBS), however in India its prevalence has been much lower. The dominant organisms are *Escherichia coli, Staphylococcus aureus, Klebsiella, Proteus,* and *Pseudomonas aeruginosa*. Listeriosis in pregnancy can cause transplacental infection of the fetus leading to abortion, preterm birth, or stillbirth and brain damage in later life. Studies on the prevalence of perinatal listeriosis are few in India. Krishna et al. from Bombay (1966) isolated the organism in 14% of cases with bad obstetric history and Bhujwalla et al. from New Delhi (1973) isolated the organisms in 3% of high-risk pregnant patients. The T-strains of *Mycoplasma* and *Ureaplasma urealyticum* have been implicated in infection leading to birth of IUGR infants. Tuberculous infection of the placenta has been reported but it is rare. It can cause congenital tuberculosis. Latent gonococcal infection may lurk in the glands of the ectocervix and infect the fetus during its passage through the birth canal. In olden days, it was a known cause of ophthalmia neonatorum, but present-day effective therapy of gonorrhea and the routine practice of instilling antibacterial eye drops in the newborns have eradicated this once dreaded complication.

Viral Infections

Rubella infection by far has been the *Bette Noir* of congenital infections causing fetal malformations. Epidemiological studies in the decade of the seventies from New Delhi (Seth et al., 1971) and from Chandigarh (Pal et al., 1974) revealed that about 20% of adult women tested did not demonstrate immunity to rubella. The incidence of lack of immunity was much higher in rural areas around Delhi > 56% (Seth et al., 1971); Chakraborty (1973) also reported a high incidence of lack of immunity (54%) in rural areas around Calcutta. The above studies indicated that a sizeable population in India was susceptible to rubella infection. Later studies on the incidence of rubella in India revealed the following.

Table 5-4 shows that over the years the seropositivity rate in the Indian population, particularly in urban localities, has progressively increased thus lowering the possible susceptibility of acquiring rubella infection during pregnancy with its accompanying fetal hazards.

Manifestations of congenital rubella syndrome have been tabulated in Table 5-5.

The present-day drive of immunization of all school children against rubella has helped to control the susceptible population. All medical personnel in charge of women's health must endeavor to ensure rubella immunization amongst patients under their care. The risk of development of congenital fetal defects following rubella infection depends upon the stage of pregnancy when the infection is acquired; the risk of malformations is 50%

Table 5-4. Incidence of rubella in India

Source	Cohort	Seropositivity
Khare et al. (1987)	160 pregnant patients	50%
Khare et al. (1990)	100 young women (age group 19–29 years)	63%
Gray (1989)	374 deaf children	29%
Kishore et al. (1990)	17 pregnant women suspected of rubella	59%
Bhaskaram et al. (1991)	274 pairs of pregnant women and newborns 139 children aged 1–5 years	95%
Bhargava (1995)	442 pregnant women	85%

Table 5-5. Manifestations of congenital rubella syndrome

Frequency	Type	Manifestations
Common	Transient	IUGR, hepatosplenomegaly, thrombocytopenic purpura, lymphadenopathy, meningoencephalitis, pneumonia, blueberry muffin lesions, bony or EEG abnormalities.
	Permanent	IUGR, postnatal retardation, patent ductus arteriosus, pulmonary hypoplasia, cataract, microphthalmia, retinopathy, microcephaly, mental and motor retardation.
	Late onset	Deafness, language problems, motor and mentally slow, insulin-dependent diabetes mellitus
Uncommon	Transient	Hemolytic anemia, leucopenia, hepatitis, large anterior fontanelle, prematurity, myocarditis, myositis, nephritis, cloudy cornea, interstitial pneumonitis.
	Permanent	Atrial septal defect or ventricular septal defect, glaucoma, intracranial calcification, renal artery stenosis, thymic hypoplasia, tooth defective, T-O fistula, cleft palate, hand abnormalities, biliary atresia.
	Late onset	Coarctation of aorta, autism, progressive encephalitis, thyroiditis, precocious puberty, growth defect, eye defects like subretinal vascularization, keratoconus, lens absorption.

during the first trimester, 22% in the second trimester, and 6% in the third trimester. However, the risk of fetal IUGR development has been assessed to be much higher at 60-70%.(Vohra and Jain, 1986). Therapeutic abortion (MTP) should be advised to affected pregnant women if they show rising IgG titers or positive IgM titer.

Cytomegalovirus disease

Cytomegalovirus disease is widely prevalent in the Western countries. It affects 0.4–2.3% of neonates. In immunocompetent adults, CMV infection is often silent. Symptoms appear only in 1–5% of cases. These include low grade fever, malaise, arthralgia, and occasionally symptoms suggestive of pharyngitis with lymphadenopathy. The risk of acquiring infection during pregnancy is about 1.0%, however the risk of fetal transmission in affected patients is about 30–40%. CMV is a known and common cause of congenital infection and mental retardation. Transmission to adults is due to contact with young children or through blood transfusion or sexual contact. In 1972, Pal et al. documented the first two cases of CMV inclusion disease from the Indian subcontinent. It was also noted that a vast majority of women of child-bearing age in India are immune to CMV and thus fetal infections are rare.(Pal et al., 1972; Madhavan et al., 1974). During pregnancy, CMV infection often passes undetected in clinical practice. The highest risk is present during the second trimester. The most important clinical manifestations are microcephaly, mental retardation, chorioretinitis, optic atrophy, cerebral calcification, hydrocephalus, deafness, and hepatosplenomegaly. Almost 60–70% of affected infants demonstrate IUGR. No vaccine or antiviral drug of much use is presently available for treatment. Recently ganciclovir has been reported to be of use in the treatment of chorioretinitis, however further evaluation is necessary. Prevention measures are important—general cleanliness and hygiene, avoid contamination with urine, saliva, or blood of virus excreting infants.

Herpes simplex virus

About 1:7,500 live-born infants suffer from perinatal transmission of HSV. The HSV-2 virus is the common offender. Fetal infection can occur in one of three ways: (a) in-utero transplacental transfer, (b) ascending infection through the cervix, and (c) intrapartum through fetal contact with maternal lesions in her genital tract. Clinical manifestations in the infected infant vary from local infection of the skin, eye, or mouth to a fulminant and lethal generalized disease. The antiviral drugs (category C drugs)—acyclovir, valacyclovir, and famciclovir—have been used effectively to control the disease.

Other viruses

Several other viruses like variola, vaccinia, varicella, mumps, measles, and influenza, etc., are known to cause intrauterine infections. Although the risk of abortion is increased, however the risk of congenital malformations is negligible.

Human immunodeficiency virus

Perinatal transmission of HIV affects nearly 5,00,000 infants globally every year, most of them live in developing countries. Surveys from India reveal that 25 million births take place annually in India. Considering on the basis of conservative estimates that about 1–2% of pregnant women in India are afflicted with HIV and that the incidence of vertical (mother to fetus) transmission is about 30%, it can be safely estimated that about 75,000 to 1,50,000 HIV affected infants are added to our population annually (Damania and Tank, 2004). In India,

heterosexual transmission is the dominant route of transmission of HIV. A survey of public hospitals from all parts of the country suggests that the incidence of HIV during pregnancy ranges between 0.5 and 3.3% (Joshi and Prasada Rao, 1999). Gopalan et al. from Chandigarh in the year 2000 reported a very low incidence of 0.036% of HIV complicating pregnancy as compared to an incidence of 0.8% from Manipur and 2.5% from Mumbai. In contrast, a study from Pune by Patel et al. (2000) revealed the incidence of HIV in pregnancy to be 3.4%. Dave et al. (2002) from Indore reported HIV seropositivity in 6.5% of 500 women in the reproductive age and Datey et al. (2003) in an ICMR study covering five centers all over India reported the highest incidence of HIV in pregnancy from Mumbai of 4.5% in contrast to < 1.05% from all other centers in the country. In this study the incidence of premature rupture of membranes was recorded as 24.2%, fetal wastage was 24.2%, and the mean birth weight of babies born to affected mothers was 120 g less than in normal controls. The incidence of IUGR was 22.0%. Elective termination of pregnancy (MTP) was carried out in 14.7% of affected pregnancies.

HIV infection has no discernible effect on the rates of prematurity, low birth weights, premature rupture of membranes, or embryopathy (craniofacial dysmorphism).

It is indeed ironical that HIV infection (a harbinger of death) and pregnancy (the generation of a new life) should coexist and be so intertwined. World statistics show that a combination of antiviral medications and elective cesarean section helps to lower the incidence of vertical transmission of HIV to about 2% in nonbreastfed infants. In India, grinding poverty, poor sanitation, and lack of clean drinking water makes top feeding fraught with danger. The concept of breast feeding the infant is traditionally well accepted in our country, hence breast feeding with due care and retroviral therapy to the newborn seems to be a more rational alternative (Damania and Tank, 2004).

IMPORTANT POINTS

1. GBS colonize the genital tract of 10–35% women of childbearing age. Between 40 and 50% of infants born to women who are colonized at the time of delivery will also be colonized. Less than 1% of these colonized newborns will develop early-onset GBS septicemia. Thus, the overall risk for any newborn baby of developing early-onset GBS infection is approximately 1 in 1000.
2. The current approach for the prevention of early-onset GBS infection is based in screening for anogenital colonization of all pregnant women at 35–37 weeks' gestation except for those who have had GBS bacteriuria during the present pregnancy or have had a previous infant with invasive GBS disease because they are assumed to be colonized. All women with positive cultures, considered to be colonized, or with unknown GBS status and positive risk factors should receive intrapartum antibiotic prophylaxis. Screening is unnecessary in women who are planning an elective cesarean delivery.
3. The recommended treatment for intrapartum GBS prophylaxis is penicillin G (4 million units IV initial dose and then 2.5 million units IV every 4 hours until delivery or ampicillin 1 g IV every 6 hours until delivery). For women allergic to penicillin who are not at high risk for anaphylaxis, the antibiotic of choice is cefazolin (2 g IV initial dose, followed by 1 g IV every 8 hours until delivery). For women at high risk for penicillin anaphylaxis, the best choice is vancomycin 1 g IV every 12 hours until delivery. Erythromycin and clindamycin are poor choices for women allergic to penicillin due to their slow transfer through the placenta and the high frequency of GBS strains resistant to these antibiotics.
4. Traditionally neurosyphilis has been considered a manifestation of tertiary syphilis. However, CNS involvement can be demonstrated by cerebrospinal fluid analysis in a high number of patients with secondary and early latent syphilis.
5. Neonatal syphilis will occur more frequently and will be more severe in mothers with primary or secondary syphilis than in patients with latent syphilis. The severity of neonatal infection is also related to gestational age and fetal morbidity would be more severe if the infection occurs in the first and second rather than in the third trimester.
6. Approximately 25% of all pregnant women in USA are seronegative for CMV and their risk for primary infection is approximately 1%. Only 10% of the newborns from mothers with primary CMV infection will have severe congenital infection. Therefore, the risk for a pregnant woman of unknown CMV immunity to have a baby with overt CMV infection is 1 in 4000. The risk for the same woman of having a child asymptomatic at birth that will develop hearing problems as a consequence of congenital CMV infection is 1 in 1300.
7. Specific CMV IgM antibodies persist for several months following primary infection. Therefore, the presence of CMV IgM antibodies is not necessarily evidence of recent infection. The best evidence of primary maternal CMV infection is seroconversion or isolation of the virus from urine or blood. The diagnosis of fetal CMV infection requires viral culture of the amniotic fluid.

8. The best contribution of the obstetricians to the prevention of congenital rubella is postpartum vaccination of nonimmune patients.
9. The diagnosis of HIV infection can be made by serology, by viral culture, or by detection of viral RNA or DNA. The procedure most commonly used for screening purposes is the ELISA test. A positive ELISA requires confirmation by Western blot analysis.
10. HIV screening should be performed in the first prenatal visit. The recommended approach is the opt-out strategy in which the patient is informed that she will be tested for HIV as part of the routine battery of prenatal tests unless she declines. This approach results in a greater testing rate that the opt-in approach, when the patient is asked for specific informed consent for the test.
11. Herpes screening on the basis of maternal history and search for lesions at the time of labor is ineffective and misses 70% of the cases of neonatal herpes. A more reasonable approach is to obtain maternal and paternal HSV IgG and HSV IgM serology and give antepartum prophylaxis during the last 4 weeks of gestation to all women who have discordant serology with their partners.
12. Varicella (chicken pox) during pregnancy is rare. However, the potential maternal and fetal consequences of this disease are very serious. The maternal mortality when pneumonia complicates varicella during pregnancy is between 10 and 35%. The mortality rate of neonatal varicella is approximately 30%.
13. Pregnant women exposed to varicella should have their immunity evaluated with a FAMA test. If the patient is not immune she should be treated with VZIG.
14. Chronic carriers of hepatitis B are identified by the serologic persistence of HBsAg more than 6 months after the initial infection. The presence of the HBe antigen indicates a highly infectious carrier and the possibilities that the newborn will be infected are 90%.
15. The current recommendation to prevent neonatal hepatitis is to administer HBV immune globulin and hepatitis B vaccine within 12 hours of birth to every infant born to a mother with positive HBsAg.
16. The possibility of fetal parvovirus B19 infection developing in a school teacher following an outbreak of erythema infectiosum is approximately 5 in 1000. The probability for a pregnant woman who does not work at the school and is exposed to one child with the disease is approximately 1 in 1000.
17. Congenital transmission of toxoplasmosis occurs only during an acute infection. Transmission is lower in the first trimester (15%) than in the third (60%) but the severity of the fetal infection is greater when the infection occurs early in pregnancy.
18. Congenital toxoplasma infection can be diagnosed in more than 90% of the cases using a combination of tests in the amniotic fluid and in fetal blood obtained by cordocentesis.
19. Because of the low incidence of acute toxoplasmosis during pregnancy in USA and the unreliability of serologic tests, routine serologic screening for toxoplasmosis during pregnancy is not recommended. However, screening may be valuable in certain groups at risk such as women infected with HIV, raw-meat eaters, veterinary workers, and cat owners.

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6

Birth Asphyxia

CHAPTER OUTLINE

One of the worst outcomes of pregnancy is the delivery of an asphyxiated newborn. An asphyxiated newborn has no spontaneous respiration, is bradycardic, has poor or no muscle tone, does not cry, and requires immediate resuscitation to avoid death. Many of these newborns will have a complicated course in the neonatal intensive care unit and will require mechanical ventilation and treatment of multiple organ failure. The majority of them will recover without apparent deficits but some will develop neurological sequelae. This dreadful clinical picture is the result of an abnormality in the fetal gas exchange resulting in severe hypoxia and metabolic or mixed acidosis. In an effort to avoid this outcome, a large part of the current obstetrical practice consists of methods to detect, avoid, and treat fetal asphyxia.

DEFINITIONS

Hypoxia is a pathologic condition characterized by a decreased concentration of oxygen in the tissues and in the blood (hypoxemia).

Acidosis is a pathologic condition characterized by an increased concentration of H+ ions in the tissues and in the blood (acidemia).

Asphyxia. There is no universally accepted definition of asphyxia—a term that should be used exclusively to indicate those infants who have hypoxia and metabolic acidosis at birth (American College of Obstetricians and Gynecologists, 1998). Since invariably asphyxia is characterized by an alteration in the fetal gas exchange, most studies use umbilical artery blood gases to define birth asphyxia and several studies have determined normal reference values for this variable. The study by Yeomans et al. (1985) concluded that the lower normal limit (–2 SD) for umbilical artery pH was 7.18. A similar study in Finland (Ruth and Raivio, 1988) indicated that the lower normal limit (–2 SD) was 7.16. Thorp et al. (1989) found a lower normal limit of 7.10. Based on these studies, it is possible to conclude that abnormal fetal acidemia is present when the umbilical artery pH is < 7.14. However, the

majority of newborns with umbilical artery blood pH < 7.14 have an acidosis that is not clinically important and do not require extensive resuscitation. Goldaber et al. (1991) performed a study designed to clarify the umbilical artery pH threshold, below which major neonatal morbidity was significantly increased. They studied 3506 term, singleton newborns with umbilical artery pH < 7.20 and concluded that a pH < 7.0 was a more realistic threshold to characterize pathologic fetal acidemia. Therefore, the term birth asphyxia should be reserved for newborns with umbilical artery blood pH ≤ 7.0, base excess ≥ 12, and severe neonatal depression (Apgar score 0–3 for ≥ 5 minutes).

Hypoxic-ischemic encephalopathy (HIE). This term was designed to describe a constellation of neurological findings in term newborns thought to be characteristic of intrapartum asphyxia. However, further investigations have demonstrated that HIE lesions are not specific for intrapartum asphyxia. The use of this term is not recommended. It generates the distinct possibility of erroneously assigning a specific etiology (intrapartum asphyxia) to a newborn with neurological findings of a different origin.

Neonatal encephalopathy. This term should be used instead of HIE. It describes a syndrome of altered neurological function in the early days of life of a term infant without assuming a specific etiology. Neonatal encephalopathy is manifested by difficulties in initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and, often, seizures (Nelson and Leviton, 1991).

INCIDENCE

A precise assessment of the frequency of fetal asphyxia is difficult due to variations in the criteria used to define asphyxia and particularly because of the frequent confusion in the literature between asphyxia, neonatal encephalopathy, and HIE. The incidence of birth asphyxia is approximately 5.4–6.9 cases per 1000 term live births. Many more newborns (as many as 20%) exhibit abnormal pH, pO_2, and pCO_2 values at birth (Josten et al., 1987; Miller et al., 1990). In the study of Ruth and Raivio (1988) when a pH of 7.16 was used as threshold to define fetal acidemia, the incidence of this condition in a mixed population was 11%. However, the majority of term AGA (appropriate for gestational age) newborns with umbilical pH > 7.0 are vigorous or require minimal resuscitation and do not develop abnormalities during the neonatal period.

PATHOPHYSIOLOGY

The most common reason for an umbilical artery blood pH in the acidotic range is an alteration in CO_2 gas exchange (respiratory acidosis). The second most common reason is an alteration in the oxygen supply to the fetus (metabolic acidosis). Frequently the two problems occur simultaneously (mixed acidosis).

CO_2 Exchange and Respiratory Acidosis

The fetal acid-base balance depends on a bicarbonate buffer system which is not as efficient as it is in extrauterine life because the fetus cannot eliminate CO_2 into the atmosphere. Fetal CO_2 is eliminated by diffusion throughout the placenta as molecular CO_2 and is eventually disposed of by maternal respiration. The diffusion of CO_2 through the placenta is possible because of the existence of a CO_2 gradient between the fetal and the maternal circulations. Fetal pCO_2, measured in scalp blood, is 38–44 mmHg, whereas maternal pCO_2 is 18–24 mmHg.

Interferences with the ability to eliminate CO_2 (respiratory acidosis) are the most common cause of alterations of the fetal gas exchange. Typical examples are umbilical cord compression and severe maternal asthma. In such cases the initial biochemical alteration is an increase in fetal pCO_2 (≥75 mmHg) which is the hallmark of respiratory acidosis. The increase in pCO_2 causes an increase in fetal H+ ion concentration and a lowering of the pH. This happens because, as shown in Figure 6-1, any interference with CO_2 elimination causes a drive of the bicarbonate buffer equation toward the left with formation of H+ ions. As a result, pure respiratory acidosis will be characterized by a low pH, an increased pCO_2, and a minimally decreased buffer base. However, the characteristics of the fetal bicarbonate buffer equation determine that with persistency of the problem the buffer base will decrease further and the blood gases will reveal a mixed profile of respiratory and metabolic acidosis. Respiratory acidosis is usually transient and responds readily to neonatal resuscitation.

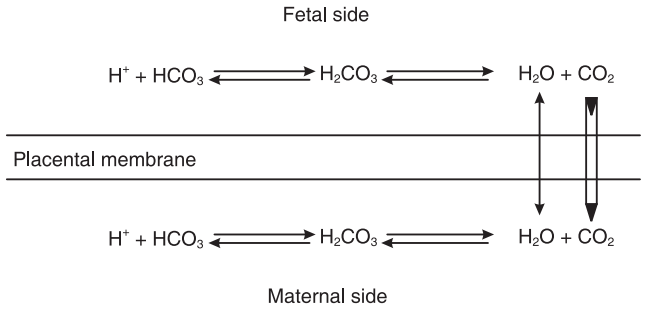

Figure. 6-1. Fetal bicarbonate buffer system. H+ ions produced in the intermediate metabolism of the fetus are transformed into CO_2. This CO_2 is transferred by a pressure gradient into the maternal circulation and eventually eliminated by the maternal lungs. The fetus is easily affected by conditions that impair CO_2 transfer to the placenta such as cord compression or interfere with maternal CO_2 elimination such as severe asthma.

O_2 Exchange and Metabolic Acidosis

Fetal hypoxia is another important cause of acidosis. A normal fetus requires 5–10 ml O_2/kg/minute to sustain normal growth, development, and a normal pH. A decrease in O_2 supply to the fetus may occur suddenly (abruptio placentae, hypertonic labor, maternal hypotension) but it may also be a chronic process. In both cases O_2 deficiency causes a switch to anaerobic metabolism with the generation of 2 moles of lactate and 2 moles of H+ ion per each mole of glucose. The H+ ions generated will reduce the concentration of buffer base (bicarbonate and protein), a phenomenon which is the marker of metabolic acidosis. Therefore, a characteristic profile of metabolic acidosis in its initial stage will be a low pH, a normal pCO_2, and a decreased buffer base. If the process continues, the excessive H+ ion will generate equimolar amounts of CO_2, driving the equation in Figure 6-1 toward the right, resulting in a profile of mixed metabolic and respiratory acidosis.

When fetal hypoxia is acute and severe such as in abruptio placentae, there is no time for adequate adaptation to the sudden decrease in pO_2, and the drop in pH will be fast and severe. If fetal hypoxia is chronic such as in cases of chronic placental insufficiency, the fetus will temporarily adapt to the situation. However, the inefficient generation of adenosine triphosphate (ATP) caused by chronic oxygen deprivation will affect the fetal growth, compromising the ability of the fetus to tolerate stressful situations.

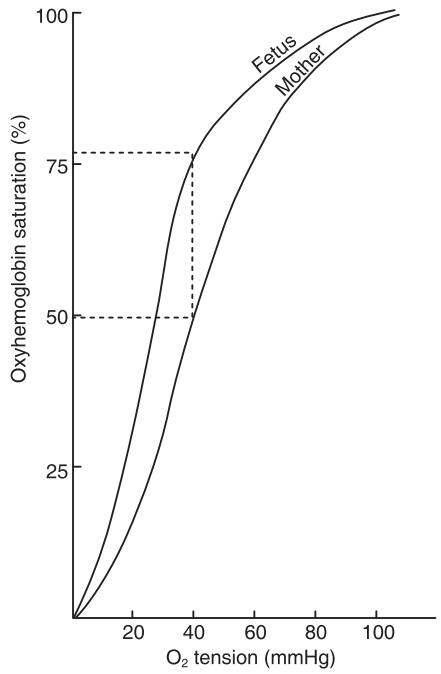

Figure. 6-2. Fetal and maternal oxyhemoglobin dissociation curves. The high oxygen affinity of fetal hemoglobin allows the fetus to have an adequate oxygen saturation at O_2 tensions that are inadequate to maintain a normal oxygen concentration in the maternal blood.

The fetus can effectively compensate for transient or mild deficiencies in oxygen supply because the high affinity for oxygen of fetal hemoglobin allows adequate oxygen saturation of the fetal blood despite significant decreases in maternal pO_2 (Figure 6-2). For example, at a maternal pO_2 of 40 mmHg the fetus is still capable of keeping about 75% of its hemoglobin saturated with oxygen. In contrast, the compensation for rises in pCO_2 is limited to improving the delivery of CO_2 to the placenta by increasing the heart rate. The rebound tachycardia seen after episodes of cord compression most probably represents such a mechanism of compensation.

In some cases, fetal acidosis is secondary to an interference with both fetal oxygenation and CO_2 elimination. In that situation the effects on the fetus are severe, and the metabolic events occur rapidly. A typical example of this situation is hypertonic labor in which both the availability of oxygen to the fetus and the ability to dispose of the fetal pCO_2 are compromised. The biochemical profile in this situation is that of a mixed respiratory and metabolic acidosis.

DIAGNOSIS

Fetal/neonatal asphyxia is frequently confused with some of its components such as a low Apgar score, neonatal depression, and neonatal encephalopathy—conditions that may be caused by fetal asphyxia but which may be the result of other conditions. This confusion in terminology is unfortunate and has a definite impact in the medical-legal area. To add to the confusion many lawyers and obstetricians use the term "fetal distress" as an equivalent to fetal asphyxia. The term "fetal distress" designates an unspecific state of fetal jeopardy that may or may not be caused by hypoxia. The term "fetal distress" should not be used as a diagnosis and should be replaced by a precise description of the findings, i.e., "severe variable decelerations," "mild fetal respiratory acidosis (pCO_2 76; pH 7.18)," etc.

It is important to adopt specific criteria for the diagnosis of asphyxia, to avoid the inclusion of newborns with mild or moderate degree of hypoxia and acidosis. These criteria are as follows:

1. Umbilical artery pH < 7.0 and base deficit ≤ 12 mmol/L
2. Neonatal depression manifested by an Apgar score 0–3 for 5 minutes or more

A diagnosis of neonatal asphyxia does not indicate whether the events leading to asphyxia happened during labor or before labor or whether or not the fetus

had chronic hypoxia for days or weeks before labor which became worse during labor. Later in this chapter we will discuss the criteria to differentiate antepartum from intrapartum asphyxia but first we will analyze in some detail the variables required for the diagnosis of asphyxia.

Umbilical Artery Blood Gases

The most important criterion for the diagnosis of fetal asphyxia is severe acidosis (pH ≤ 7.0) in the umbilical artery blood gases. Acidosis can be metabolic or mixed (metabolic and respiratory) and results in a base deficit > 12. Fetuses with respiratory acidosis (pCO_2 ≥ 75 mmHg) and base deficit < 12 do not fulfill the definition of asphyxia even if the pH is ≤ 7.0.

BOX 6-1

Normal cord blood gases

		Percentile	
	Mean ± SD	5th	95th
Umbilical artery			
pH	7.27 ± 0.6	7.12	7.33
pCO_2	56.0 ± 7.6	44.2	71.2
pO_2	15.6 ± 5.7	6.5	26.1
HCO_3	24.7 ± 2.3	20.3	28.0
Base excess	–3.3 ± 2.8	–10.1	–0.3
Umbilical vein			
pH	7.35 ± 0.05	7.25	7.41
pCO_2	42.5 ± 5.9	35.0	50.9
pO_2	27.9 ± 7.7	16.3	41.1
HCO_3	22.8 ± 2.0	18.7	25.6
Base excess	–2.5 ± 2.2	–7.1	–0.2

From Miller JM, Bernard M, Brown HL, et al. Umbilical cord blood gases for term healthy newborns. Am J Perinatol 1990; 7: 157–9.

Box 6-1 shows the mean values and the 5th and 95th percentile limits for umbilical artery and vein blood gases obtained in a population of 147 term, healthy neonates (Miller et al., 1990). According to this box, umbilical arterial blood gases are below the 5th percentile when the pH is ≤ 7.12, the pO_2 is ≤ 6.5 mmHg, the pCO_2 is ≥ 71.2 mm of Hg, and the base deficit >10. As mentioned before, the criteria for the diagnosis of severe asphyxia are more astringent and require a pH < 7.0 and a base deficit > 16. Milder degrees of hypoxia/acidosis correspond to pH values between 7.0 and 7.20.

Umbilical cord blood gases are usually obtained at the time of delivery to determine the severity of fetal asphyxia in depressed newborns requiring aggressive resuscitation. However, in the last few years, evaluation of umbilical cord blood gases has been extended to normal fetuses, because by demonstrating the presence of normal acid-base balance at birth, the obstetrician has evidence that any neurological dysfunction that may develop later in life is not the result of intrapartum hypoxia. Proponents of this approach list additional advantages such as the potential for a better definition of the degree of asphyxia necessary to cause neurological damage, the benefit of having an objective end point to judge the efficacy of interventions directed to prevent asphyxia, and the therapeutic benefits of a better knowledge concerning the respiratory or metabolic mechanism of the acidosis (Johnson et al., 1990; Thorp et al., 1996). Opponents of the routine use of umbilical blood gases at delivery observe that the incidence of cerebral palsy (CP) is 1 in 2000 births while the incidence of intrapartum acidosis is 6–20% depending on the end point selected. Therefore, the probability of finding newborns with an acidotic pH is many times greater than that of finding babies who may develop CP and have a normal pH, and routine determination of umbilical blood gases more frequently will result in incriminating evidence in the patient's chart rather than in useful data for malpractice defense.

As a response to this controversy the American College of Obstetricians and Gynecologists or ACOG (1994) recommended to double-clamp and divide a segment of the umbilical cord following delivery of the baby, to place it on the delivery table, and obtain umbilical artery blood gases if any serious abnormality in the delivery process or problems in the neonatal condition persist beyond the first 5 minutes of life. Venous blood should be obtained if it is not possible to obtain arterial blood. A clamped segment of cord will keep the blood stable for blood gases measurements for at least 15 minutes and a heparinized blood sample in a syringe will be stable for up to 60 minutes. This recommendation makes sense and will avoid useless, expensive, and potentially incriminatory blood gases measurements in healthy neonates.

Apgar Score

The relationship of a low Apgar score with asphyxia is interesting because the diagnosis of asphyxia cannot be made unless the Apgar score is markedly abnormal (0–3 for 5 minutes or more), but an abnormal Apgar score does not necessarily mean that asphyxia is present. Most asphyxiated newborns have an initial Apgar score of 0 or 1. They require positive pressure ventilation, chest compression, and endotracheal intubation. Spontaneous respiration is delayed in some cases for more than 10 minutes and muscle tone and spontaneous movement for even longer periods. However, not all infants with low Apgar scores are asphyxiated and a similar clinical picture may be present in newborns with chromosomal abnormalities, congenital heart disease, and metabolic disorders (Box 6-2).

BOX 6-2

Causes of low Apgar scores

- Prematurity
- Medications given during labor
- Fetal infection
- Fetal congenital abnormalities
- Fetal chromosome abnormalities
- Fetal neuromuscular disorders
- Birth trauma
- Inadequate resuscitation
- Meconium aspiration
- Fetomaternal hemorrhage
- Birth asphyxia

There is a poor correlation between low Apgar scores and fetal asphyxia and many newborns with low Apgar scores have normal or minimally altered umbilical cord gases. The opposite is also true and a significant number of newborns with normal Apgar scores have an umbilical cord blood pH in the acidotic range. This is not surprising because the Apgar score is a system to assess the overall condition of the neonate at birth which is affected by many factors different from hypoxia and acidosis. The Apgar score provides valuable information about the overall health of the newborn but is not an index of the newborn acid-base balance. A low Apgar score identifies depressed newborns in need of immediate attention and perhaps resuscitation but tells nothing about the etiology of the newborn's depression. Freeman and Nelson (1988) defined quite well the clinical significance of low Apgar:

A low one-minute Apgar indicates an infant who may need resuscitation. It neither indicates that substantial hypoxia or ischemia has occurred nor has much prognostic significance. A low Apgar score at 5 minutes indicates the infant who needs continued resuscitative efforts. An Apgar score that continues to be 3 or less at 10 minutes indicates that the infant has remained hypoxic or hypoperfused despite resuscitative efforts. A score of 3 or less at 15 or 20 minutes after delivery, despite resuscitative efforts, indicates that the full-term infant has suffered a severe antecedent injury with the possibility of additional postnatal effects.

The need for neonatal resuscitation of the asphyxiated neonate is obvious. Resuscitation is extensive and frequently requires endotracheal intubation, chest compression, and administration of epinephrine and bicarbonate. Ideally, the resuscitation of an asphyxiated newborn should be carried out by a neonatologist or a neonatal nurse practitioner. Similarly to the Apgar score and the umbilical artery blood gases, the need for resuscitation does not necessarily imply that the cause was intrapartum asphyxia. Meconium aspiration, neonatal depression due to medications, and airway obstruction due to tumors are some of the reasons why a nonasphyxiated newborn may need extensive resuscitation.

CAUSES OF FETAL ASPHYXIA

As shown in Box 6-3, fetal asphyxia has multiple causes that can be divided in three groups: chronic fetal conditions, acute complications during labor and delivery, and neonatal problems. For the obstetrician the distinction between antepartum (chronic fetal conditions) and intrapartum causes of asphyxia is of the largest importance, particularly in medical-legal situations.

BOX 6-3

Causes of fetal asphyxia

Chronic fetal conditions
- Fetal growth restriction
- Placental insufficiency
- Metabolic abnormalities
- Chromosome abnormalities
- Congenital abnormalities
- Inborn errors of metabolism

Acute complications during labor and delivery
- Abruptio placenta
- Uterine rupture
- Umbilical cord prolapse
- Maternal cardiac arrest
- Amniotic fluid embolization
- Shoulder dystocia

Neonatal problems
- Meconium aspiration

Differential Diagnosis Between Antepartum and Intrapartum Asphyxia

The criteria that are used to differentiate between antepartum and intrapartum origin of fetal/neonatal asphyxia can be broadly divided into three categories: antepartum, intrapartum, and neonatal. As we will see they have different sensitivity and specificity.

Antepartum criteria

Antepartum fetal testing. Antepartum fetal assessment with ultrasound, umbilical, cerebral, and uterine Doppler, nonstress test (NST), and biophysical profile (BPP) is usually limited to women at high risk for placental insufficiency. Adequate use of these tools for antepartum evaluation will be useful to detect fetuses affected by abnormal placental gas exchange that may be born asphyxiated. The challenge is the detection of affected fetuses in women at low risk. Careful prenatal care with close attention to fetal growth and maternal perception of fetal movements are essential for the detection of affected fetuses in low-risk patients.

Decreased fetal movement. A common complaint of women with antepartum conditions that may result in neonatal asphyxia is decreased fetal movements. This is

an important symptom that needs careful evaluation including ultrasound assessment of fetal growth, fetal anatomy, and amniotic fluid volume, umbilical and mid-cerebral arteries Doppler, and NST or BPP. The findings of poor fetal growth, decreased amniotic fluid volume, abnormal umbilical/cerebral Doppler, and nonreactive NST are highly suggestive of chronic placental insufficiency causing fetal hypoxia and acidosis which may result in the birth of an asphyxiated infant even if delivery is accomplished by cesarean section. In these cases the BPP has prognostic value and acidosis will be progressively more severe with loss of respiratory movements, loss of body movements, and loss of tone. In other cases the evaluation will reveal causes of decreased fetal movement that do not necessarily result in fetal hypoxia and acidosis. In the majority of cases the evaluation will be negative and the mother can be reassured about the fetal health.

Intrapartum criteria

The origin of fetal/neonatal asphyxia, antepartum or intrapartum, can be suspected by analyzing the course of labor. In general, the course of labor before the birth of an asphyxiated newborn can be categorized into three different clinical presentations.

1. Sentinel event present. In this group the birth of an asphyxiated infant is preceded by a major, acute, severe complication occurring during labor or at the time of delivery. Examples of this clinical presentation are depressed infants born following uterine rupture, amniotic fluid embolization, acute abruption, umbilical cord prolapse, severe shoulder dystocia, and difficult breech delivery.

An important sentinel event is the development of fever during labor. In the majority of cases fever during labor is a sign of chorioamnionitis which is an independent risk factor for CP (Wu et al., 2003). The risk of CP increases if birth asphyxia occurs within the setting of acute chorioamnionitis, conditions that frequently coexist. The mechanism of chorioamnionitis-induced CP is unknown although there is evidence suggesting that some fetuses have the genetic potential to develop a severe inflammatory response (Gomez et al., 1998) in the setting of chorioamniotic infection with the production of large amounts of proinflammatory cytokines that will directly injure the fetal brain (Yoon et al., 1996).

2. Normal followed by abnormal FHR pattern. The second group corresponds to those cases where there is a normal, reactive fetal heart rate (FHR) at the beginning of labor and, in the absence of a sentinel event, the tracing becomes ominous (severe, prolonged bradycardia or absent or markedly decreased variability and recurrent late or variable decelerations) before the birth of the asphyxiated infant.

3. Abnormal FHR pattern from the beginning of labor. The third group is made up of cases where the birth of an asphyxiated newborn is preceded by an FHR tracing that has no accelerations and decreased variability from the time of admission to the hospital. The FHR tracing may remain without significant changes or may become ominous before the birth of the asphyxiated newborn.

The main difference between these three groups is in the health of the fetus at the beginning of labor. Fetuses in the first group are healthy before the sentinel event. Those in the second group are healthy at the beginning of labor but have decreased reserves that are exhausted during the intrapartum period. Fetuses in the third group have been damaged before labor and have limited functional reserves. When the FHR pattern is abnormal from the beginning of labor, it may be argued that intrapartum events had a contributory role to the development of newborn asphyxia. As we will see later, more than the severity of the intrapartum insult the main determinant of short- and long-term outcomes is the health of the fetus before the hypoxic event.

Neonatal criteria

In addition to antepartum and intrapartum criteria, other valuable methods to determine the timing of the event causing birth asphyxia are early neurological imagining with ultrasound, magnetic resonance imaging (MRI) or CT scanning, and electroencephalography. Ultrasound is useful in the evaluation of preterm infants while the MRI is preferred in the assessment of asphyxiated term infants. As we will see later, the MRI is the most informative of the presently available neonatal imaging techniques. Irrespective of the technique, the demonstration of brain edema in the absence of focal lesions in the first 48 hours after birth is strong evidence of an intrapartum event causing the asphyxia.

Neonatal ultrasound is particularly useful in detecting periventricular leukomalacia (PVL) and focal brain injuries. PVL is usually the result of an ischemic/hypoxic insult to the premature brain. The initial change in PVL is the presence of parenchymal echodensities in the white matter dorsal and lateral to the external angles of the lateral ventricles. This is followed 10–14 days later by the development of cystic lesions. This characteristic sequence of changes indicates an antepartum origin for echodensities or cystic lesions detected in the immediate newborn period.

The MRI clearly differentiates gray from white matter, evaluates myelination and can detect subtle congenital abnormalities. In term infants, an early MRI can show evidence of recent (intrapartum) hypoxic/ischemic insult such as brain edema and abnormal signal intensity in the basal ganglia, the subcortical and periventricular white

areas, and the brain cortex. Chronic antepartum insults usually result in areas of focal infarction with atrophy, cystic lesions, asymmetry in ventricular shape or size, or areas of long-standing hemorrhage.

The neonatal electroencephalogram (EEG) is a useful tool in the evaluation and prognosis of the newborn with encephalopathy. A normal interictal EEG in the week following birth is good evidence against the possibility of an intrapartum event and a valuable prognostic sign of a high probability of normal neurological development (Rose et al., 1970). Abnormal interictal EEG patterns include burst suppression, low-voltage, multifocal sharp waves, and electrocerebral inactivity. Burst suppression and extremely low-voltage background patterns are highly predictive of a poor outcome (Holmes and Lombroso, 1993). An abnormal EEG provides no indication of the etiology or the timing of the brain insult. Its value is in revealing the severity of the insult and the neurological prognosis of the newborn with encephalopathy.

ACOG's criteria

According to the American College of Obstetricians and Gynecologists (ACOG, 2005), the criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, e.g., 0–48 hours) but are not specific to asphyxial insults are the following:

1. A sentinel (signal) hypoxic event occurring immediately before or during labor
2. A sudden and sustained fetal bradycardia or the absence of FHR variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal
3. Apgar scores of 0–3 beyond 5 minutes
4. Onset of multisystem involvement within 72 hours of birth
5. Early imaging study showing evidence of acute nonfocal cerebral abnormality

The ACOG criteria include variables related to the diagnosis (criteria 3), the severity (criteria 4), and the timing of asphyxia (criteria 5) and variables describing intrapartum events (criteria 1 and 2). The first two criteria are of special importance for the practicing obstetrician because the type and timing of the response to them will be critically analyzed in medical-legal cases.

The use of multiple organ damage as a criterion to determine intrapartum occurrence has been criticized because there is no evidence or compelling arguments indicating that acute hypoxic insults happening during labor cause multisystem involvement more frequently than events occurring before labor. In contrast, the evidence suggests that multisystem involvement may occur more frequently in chronically than in acutely asphyxiated infants. Korst et al. (1999) reviewed the medical records of 47 neurologically impaired infants, all of them at more than 37 weeks' gestation, who had normal FHR pattern prior to undergoing a sudden prolonged FHR deceleration that lasted until delivery. In 45% of the cases the FHR abnormality followed a catastrophic obstetrical event (uterine rupture, cord prolapse, abruptio). They searched the records for four criteria of intrapartum asphyxia, severe enough to cause brain injury (profound acidemia (pH < 7.00), Apgar score ≤ 3 for 5 minutes or longer, seizures within 24 hours of birth, and multiorgan system dysfunction). Only 10 (21%) of the 47 cases fulfilled the four criteria, 14 (30%) fulfilled three criteria, 14 (30%) fulfilled only two criteria, 8 (17%) fulfilled only one criterion, and 1 case (2%) did not fulfill any of the four criteria. With respect to multiorgan dysfunction, 14 (30%) of the neonates had no organ damaged other than the brain. There was a relationship between the number of organs affected and the type of obstetric sentinel event. Cases of uterine rupture, maternal cardiac arrest, and fetal exsanguination had fewer organs involved than fetuses with shoulder dystocia, abruption, cord prolapse, or unknown reason. This study suggests that when hypoxia is acute and severe such as in cases of uterine rupture, maternal cardiac arrest, and fetal exsanguinations, there is no time for centralization of the fetal circulation and brain injury may occur in the absence of other organ damage. In cases where centralization occurs, the acute shunting of blood away from other organs in an attempt to protect the brain will cause ischemia and hypoxic damage to those organs.

The diagnosis and management of sentinel events causing fetal hypoxia/acidosis are described in other chapters of this book. Next, we will analyze FHR monitoring patterns and the available methods to assess fetal well-being when the FHR pattern is not reassuring.

FHR MONITORING

Continuous electronic FHR monitoring was introduced in the early 1970s and enthusiastically adopted by obstetricians as a significant improvement in intrapartum fetal assessment. Unfortunately, several prospective, randomized studies involving thousands of subjects have failed in demonstrating better perinatal outcomes with the use of FHR. These studies have involved term and preterm infants and the perinatal outcome has been determined by the frequency of low Apgar scores, fetal acidosis, admission to intensive care nursery, need for assisted ventilation, incidence of intrapartum stillbirths, and incidence of neonatal seizures. Also, follow-up studies of term and preterm children involved in some of these trials have failed to show any long-term benefits of FHR monitoring in the prevention of neurological problems. Furthermore, some of these controlled studies have shown an increased rate of cesarean

sections and operative vaginal deliveries secondary to erroneous diagnoses of fetal distress in electronically monitored patients. Despite the controversy regarding its usefulness, FHR monitoring provides the obstetrician with information that allows the reliable determination of the presence of fetal well-being (reassuring FHR pattern), allows, with a high degree of reliability, the determination of the presence of severe fetal problems (ominous FHR patterns), and suggests the possibility that fetal problems may be present (nonreassuring FHR patterns).

A reassuring FHR pattern (Box 6-4) is highly reliable, and there are no reports of severely asphyxiated fetuses in the presence of a normal FHR pattern. Ominous FHR patterns are also highly reliable, and it is uncommon to deliver a healthy neonate when an ominous pattern is present before delivery. However, nonreassuring patterns are not reliable and frequently result in unnecessary cesarean deliveries. The interested reader may consult an excellent review of this subject by Freeman (2002).

A committee of the National Institutes of Health of the United States published research guidelines for interpretation of FHR monitoring (National Institute of Child Health and Human Development Research planning Workshop, 1997). They produced a new set of definitions that will be followed in the course of this chapter. FHR patterns were categorized as baseline, periodic, or episodic. Baseline changes are tachycardia and bradycardia. Periodic changes are those associated with uterine contractions. Episodic changes are not associated with contractions. The periodic patterns were distinguished on the basis of the shape of the waveform (abrupt vs gradual) rather than their relation to the peak of the uterine contractions. No distinction was made between short-term and long-term variability, and the definition of variability was based visually on the amplitude of the complexes with exclusion of the sinusoidal pattern. The committee also recognized that FHR patterns are gestational age dependent and therefore the gestational age should be considered in a full description of a pattern.

Reassuring FHR Pattern

A reassuring FHR pattern has the characteristics described in Box 6-4. When it is present the possibility of severe fetal hypoxia or acidosis is very low. Each of the components of a reassuring FHR tracing correlate with signs of fetal well-being: a normal baseline rate (> 110 and < 160 bpm) indicates the absence of extrinsic influences upon the FHR; the presence of accelerations (visually apparent abrupt increases in baseline FHR ≥ 15 beats/minute (bpm) above baseline lasting ≥ 15 seconds and < 2 minutes from onset to return to baseline) indicates that the fetal pH is > 7.2. Before 32 weeks' gestation, accelerations are defined as having an increase of ≥ 10 bpm above the baseline and a duration of ≥ 10 seconds. A normal variability, as defined below, indicates integrity of the fetal central nervous system and the absence of decelerations indicates that there are no hypoxic insults or cord compression affecting the fetus.

BOX 6-4

Characteristics of a reassuring fetal heart rate pattern

1. Stable baseline rate between 110 and 160 bpm
2. Normal beat-to-beat variability
3. No decelerations
4. Accelerations (> 15 bpm for > 15 seconds) with fetal movements and with contractions

Ominous FHR Patterns

Ominous FHR patterns are usually seen when there is a profound alteration of the fetal central nervous system because of developmental anomalies, chromosome abnormalities, or because of a severe derangement of the O_2 and CO_2 exchange between mother and fetus. An alteration in the fetal gas exchange producing an ominous FHR pattern may be the result of a severe acute obstetrical complication or a sentinel event, such as uterine rupture, umbilical cord compression, severe abruptio placenta, umbilical cord prolapse, acute fetomaternal bleeding, amniotic fluid embolization, and maternal asystole. The alteration in fetal gas exchange may also be secondary to obstetrical interventions such as uterine hyperstimulation following administration of uterotonic drugs or maternal hypotension secondary to regional anesthesia. In other cases the alteration in fetal gas exchange is chronic and becomes aggravated during labor such as in cases of severe fetal growth retardation, severe placental insufficiency, and in fetal infections causing a fetal inflammatory response syndrome. In these cases the effect of labor in the uteroplacental circulation precipitates the appearance of the ominous pattern. How much uterine activity is necessary to produce hypoxemia and how severe the effects of the hypoxemia will be in these fragile fetuses depend to a large extent on the nature and severity of their antepartum condition.

The most widely recognized ominous FHR patterns are as follows:

1. Sustained fetal bradycardia with absent variability
2. Late decelerations with absent or markedly decreased FHR variability
3. Variable decelerations with absent or markedly decreased FHR variability

Late and variable decelerations

Late decelerations (Figure 6-3) are periodic changes characterized by a *gradual* decrease (onset of deceleration to nadir ≥ 30 seconds) and return to baseline of the FHR

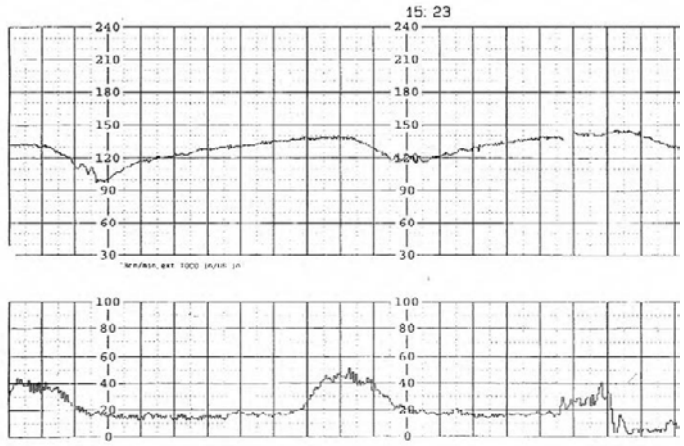

Figure. 6-3. Late decelerations. Decreased variability and late decelerations after each uterine contraction. This is an ominous pattern.

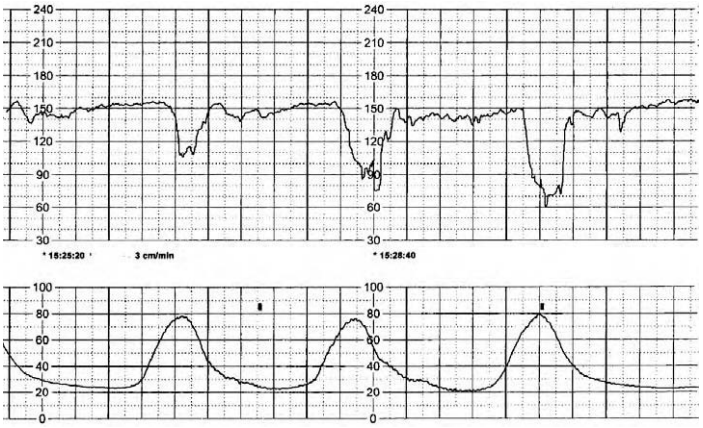

Figure. 6-4. Variable decelerations. Three moderate variable decelerations with preserved variability. Variable decelerations are characterized by the shape of the deceleration and may occur before, during, or after a contraction.

associated with uterine contractions. The deceleration is delayed in timing *and* the nadir of the deceleration occurs after the peak of the contraction.

Variable decelerations (Figure 6-4) are periodic or episodic FHR changes characterized by an *abrupt* decrease (onset of deceleration to nadir < 30 seconds) below baseline. The decrease in FHR is ≥ 15 bpm, lasting ≥ 15 seconds and < 2 minutes from onset to return to baseline. When variable decelerations are associated with contractions, they are frequently confused with late decelerations. However, the characteristic shape of the waveforms and their frequent variation in onset, depth, and duration allow a correct identification in the majority of cases.

Fetal bradycardia

FHR bradycardia (FHR < 110 bpm) with absent variability is an ominous pattern that may or may not be preceded by late decelerations (Figure 6-5). Ominous fetal

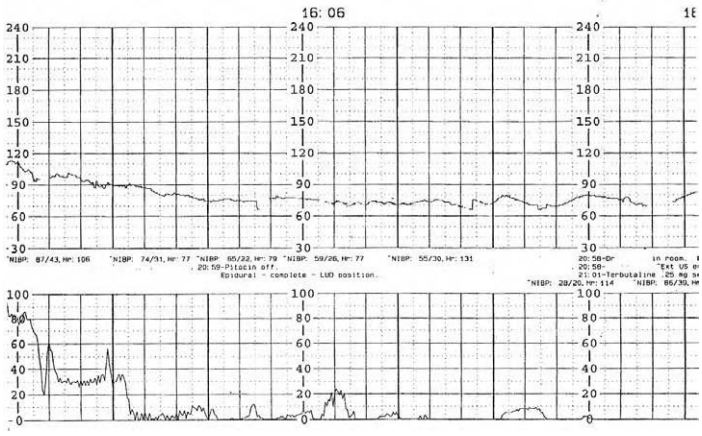

Figure. 6-5. Prolonged fetal heart rate bradycardia with decreased variability. This is an ominous pattern.

bradycardia needs to be distinguished from baseline bradycardia—a pattern that corresponds to an FHR between 100 and 120 bpm without coexistent periodic changes and with adequate variability. Baseline bradycardia is a benign pattern that does not demand intervention.

Decreased variability

Baseline FHR variability consists of fluctuations of the baseline FHR that are irregular in amplitude and occur with a frequency of 2/minute or greater. They are quantified as follows:

1. Absent variability: amplitude range undetectable
2. Minimal variability: amplitude range > undetectable ≤ 5 bpm
3. Moderate variability: amplitude range 6–25 bpm
4. Marked variability: amplitude range > 25 bpm

FHR variability depends on the interaction between the adrenergic and the cholinergic systems and requires anatomic and functional integrity of the fetal central nervous system. Variability is affected by fetal hypoxemia and acidosis. It is also affected by fetal sleep and by the action of medications that interact with the fetal neurovegetative system.

Nonreassuring FHR Patterns

Nonreassuring FHR patterns are a problem for the obstetricians because of their high false positive rate. While the correlation of reassuring and ominous FHR monitoring patterns with the health of the fetus is usually excellent, nonreassuring tracings are poor indicators of fetal hypoxia and only one out of every five fetuses with nonreassuring patterns has a low pH.

In the presence of a nonreassuring FHR pattern the obstetrician needs to find additional evidence to rule out or confirm the presence of fetal hypoxia/acidosis. In many cases the explanation for the pattern is obvious (uterine

hyperstimulation, effect of drugs on the fetus, maternal hypotension, etc.) but in other cases there is no apparent explanation and it becomes necessary to use additional tests of fetal well-being such as fetal scalp stimulation or vibroacoustic stimulation (VAS). The most common "nonreassuring" FHR patterns are as follows:

1. Absent or decreased variability without periodic changes
2. Late decelerations with normal variability and accelerations
3. Variable decelerations with slow return to baseline
4. Fetal tachycardia without decelerations
5. Variable decelerations in the second stage of labor.

Absent or decreased variability without periodic changes

FHR variability is one of the most important pieces of information that the obstetricians can obtain from the examination of a monitoring tracing. FHR variability is an index of the integrity of the fetal central nervous system and its tolerance to hypoxic insults. The best way to evaluate variability is with a fetal scalp electrode.

Decreased FHR variability without periodic or episodic FHR changes is usually caused by episodes of fetal sleep or is the result of medications such as magnesium sulfate, atropine, propranolol, diazepam, meperidine, stadol, scopolamine, phenobarbital, and morphine, drugs often used in patients in labor. The FHR variability is also dependent on the degree of maturation of the fetal central nervous system and is decreased in preterm infants. Fetal tachycardia decreases the beat-to-beat intervals and FHR variability without necessarily meaning that hypoxia is present. A FHR tracing with absent or minimal variability from the time of admission to labor and delivery is suggestive of antepartum neurological damage to the fetus. All these variables must be taken into consideration when evaluating an FHR pattern with decreased variability.

Late decelerations with normal variability and accelerations

Late decelerations have been traditionally considered an indicator of abnormal placental functional reserve. They indicate that the oxygen content of the placental blood at the time of a uterine contraction is insufficient to fulfill the fetal needs. The decreased oxygen content of the placental blood may be due to placental insufficiency but commonly is the result of maternal problems or pharmacologic interventions. For example, late decelerations occur in up to 25.8% of all patients receiving epidural anesthesia during labor and may be corrected by repositioning the patient and giving intravenous fluids to compensate for the effect of peripheral blood pooling. Late decelerations are also present in the majority of patients who develop spontaneous or oxytocin-induced hypertonic labor. In these cases the decelerations disappear with measures that decrease uterine contractility. Late decelerations often follow maternal administration of hypotensive agents such as diazoxide, hydralazine, nifedipine, or labetalol but they disappear after stabilization of the maternal blood pressure.

Late decelerations need to be persistent (occurring with 50% or more of the contractions) and accompanied by decreased or absent variability before they can be accepted as an indicator of fetal hypoxia/acidosis. In most cases late decelerations with preserved variability and with accelerations are not associated with fetal hypoxia.

Variable decelerations with slow return to baseline

Variable decelerations are the most common periodic changes seen during labor. They receive their name because of the inconsistency of their relation to the uterine contractions and their variable configuration. There is evidence from animal and human studies that variable decelerations result from compression of the umbilical cord with baroreceptor and chemoreceptor stimulation, provoking transient vagal bradycardia. However, in more than 50% of the cases it is not possible to document entanglement of the cord around the fetal neck or the fetal parts. It is probable that stimuli different from cord compression may also produce the vagal response that causes variable decelerations.

Variable decelerations may be mild, moderate, or severe (Box 6-5). The possibility of fetal hypoxia increases with the severity and frequency of decelerations and is greater when variability is decreased and the return to baseline is slow. In compromised fetuses it is not unusual to see an acceleration or "overshoot" following severe variable decelerations. When mild or moderate variable decelerations occur in an otherwise reactive FHR tracing, the fetus is not hypoxic and intervention is not necessary. In many cases they disappear with further progress in labor. In some cases they become progressively more severe and the variability of the FHR tracing becomes poor or disappears, indicating the need for intervention.

BOX 6-5

Classification of variable decelerations

Mild
- Less than 30 seconds' duration regardless of level
- More than 80 bpm regardless of duration

Moderate
- Less than 80 bpm regardless of duration

Severe
- Less than 70 bpm for more than 60 seconds

Variable decelerations may be atypical with slow return to the baseline, suggesting exhaustion of the fetal compensation and the need for intervention with amnioinfusion or cesarean.

Variable decelerations during the second stage of labor

Severe variable decelerations during the second stage of labor are usually the result of a vagal reflex elicited by compression of the fetal head or the umbilical cord. Frequently they are associated with maternal pushing efforts and if they persist for long periods of time the fetus may be born asphyxiated. However, in the majority of cases the newborn is normal or responds to minimal stimulation at birth. To be certain about the fetal situation, it is necessary to stop maternal pushing, decrease the intensity and frequency of contractions by giving terbutaline (250 µg IV and 250 µg SC simultaneously) to the mother, and perform scalp stimulation or fetal scalp blood sampling. Preservation of variability in the interval between decelerations or eliciting accelerations with scalp stimulation are good prognostic signs. Poor variability of the FHR between decelerations is an indication for cesarean delivery.

Intermittent Auscultation

The FHR can be monitored by intermittent auscultation with an aural stethoscope or a hand-held Doppler device (American College of Obstetricians and Gynecologists, 1995). Auscultation with a fetoscope was for many years the only available method to evaluate fetal health during labor. The auscultation should be performed during a contraction and for 30 seconds following the contraction. For high-risk patients it is recommended to evaluate and record the FHR frequency at least every 15 minutes during the active phase of labor. During the second stage of labor in high-risk patients the FHR should be evaluated and recorded every 5 minutes. For low-risk patients ACOG recommends to evaluate and record FHR at least every 30 minutes during the active phase and at least every 15 minutes during the second stage of labor. ACOG recognizes that there are no data to demonstrate optimal time intervals for intermittent auscultation of low-risk patients.

There are few studies on the use of intermittent auscultation for intrapartum fetal monitoring and the sensitivity, specificity, and predictive values of the method for the detection of fetal asphyxia are unknown. Most of the information on intermittent auscultation comes from comparative research studies with electronic monitoring using a one-to-one nurse to patient ratio and specific intervals for auscultation, conditions that are rarely met in practice. The data from the Collaborative Perinatal Project obtained before the advent of electronic monitoring show that intermittent auscultation was unable to anticipate fetal jeopardy. A prior study concluded that intermittent auscultation was equivalent to nonsurveillance.

According to ACOG an FHR obtained by intermittent auscultation is considered to be nonreassuring if:

1. The average heart rate between contractions is less than 100 bpm.
2. The heart rate is less than 100 bpm 30 seconds after a contraction.
3. There is an unexplained average heart rate of more than 160 bpm between contractions, especially in at-risk patients in whom the tachycardia persists through three or more contractions (10–15 minutes) despite corrective measures.

According to ACOG, when a nonreassuring FHR frequency is detected by auscultation, continuous electronic monitoring, fetal scalp sampling, or VAS may be helpful in ruling out or confirming the presence of hypoxia. If the abnormal findings persist despite conservative measurements and other tests are not available or cannot be used, expedite delivery may be considered.

Despite ACOG endorsement intermittent auscultation of FHR rate is rarely used in USA and continuous electronic monitoring remains firmly as the current standard of care. There are multiple reasons for the resistance of obstetricians and hospitals to use intermittent auscultation for intrapartum fetal surveillance. Some of these reasons are the need for a 1:1 nurse to patient ratio, the lack of studies evaluating the accuracy of this methodology, the lack of adequate definition of the frequency and duration of auscultation in low-risk patients, the intuitive conviction that intermittent auscultation is inaccurate and unreliable, the lack of ability of intermittent auscultation to discriminate benign from ominous FHR changes, and the feeling that a return to intermittent auscultation negates the knowledge acquired during the last 20 years about different types and degrees of FHR alterations during labor.

Assessment of Fetal Well-Being when a Nonreassuring FHR Pattern is Present

FHR response to scalp stimulation

It has been known for years that acceleration of the FHR in response to stimuli such as sound, movement, and manual stimulation is an excellent indicator of fetal well-being. For this reason Clark and Miller (1982) made a retrospective review of their experience with fetal scalp sampling and found that the presence of an FHR acceleration of at least

15 bpm lasting at least 15 seconds at the time of scalp sampling was associated in 95.9% of the cases with a fetal scalp pH of 7.28 or larger. None of the fetuses with pH < 7.2 responded to stimulation. In a subsequent study the same investigators (Clark and Miller, 1984) found that a FHR response with acceleration after firm digital pressure and pinching of the fetal scalp with an Allis clamp was uniformly associated with a scalp pH > 7.19. The incidence of scalp pH < 7.19 was 38% among those fetuses that did not respond to scalp stimulation.

Scalp stimulation is an important tool to further assess fetal well-being in patients with nonreassuring FHR monitoring patterns. A positive response indicates that the fetus pH is not in the acidotic range. However, a negative response not necessarily indicates the presence of fetal hypoxia and more than 50% of nonresponsive fetuses will have normal pH at birth. However, due to its simplicity, the use of scalp stimulation has caused the disappearance of fetal scalp pH sampling to assess fetal well-being from Labor and Delivery Units in USA.

FHR response to VAS

Fetal VAS has been used for several years as an adjunct to antepartum FHR monitoring and as a test to predict intrapartum asphyxia. Smith et al. (1986) found in fetuses with nonreassuring FHR patterns that a response to VAS with FHR acceleration of at least 15 bpm lasting a minimum of 15 seconds was uniformly associated with a scalp pH > 7.25. On the other hand, the incidence of pH < 7.25 was 50% among those fetuses that failed to respond to stimulation. Polzin et al. (1988) also found that the fetal response to VAS reliably predicted pH > 7.2 in fetuses with nonreassuring FHR monitoring patterns.

VAS stimulation has been also found to be useful in the prediction of fetal well-being when it is used at the beginning of labor. Ingemarsson et al. (1988) found a 75% incidence of abnormal FHR monitoring tracings during labor when the FHR tracing at the initiation of labor was nonreactive and VAS was negative. Sarno et al. (1990) studied 201 patients, 60% of them with complications of pregnancy and found that those fetuses with a nonreactive response to VAS at the beginning of labor had a significantly high incidence of abnormal FHR patterns, meconium staining, and Apgar scores < 7 at both 1 and 5 minutes.

Reactivity to VAS in fetuses with nonreassuring FHR patterns indicates that the fetal pH is not in the acidotic range. However, a negative response to VAS does not necessarily indicate that the fetus is hypoxic and approximately 50% of the fetuses will have normal blood gases at birth.

Fetal scalp blood gases

Measurement of the fetal scalp blood gases is a method to determine the acid–base balance of the fetus during labor that has almost disappeared from Labor and Delivery suites around the United States. The test is difficult to perform and requires accurate calibration and maintenance of the necessary equipment. It provides only an instantaneous reflection of a rapidly changing environment and in many cases because of the sample size the evaluation is limited to the fetal pH without distinguishing between respiratory and metabolic types of acidosis. Also, the development of indirect methods to evaluate the fetal acid–base balance such as scalp stimulation and VAS and the easy access to cesarean delivery have made scalp sampling rarely used.

Fetal pulse oximetry

Fetal pulse oximetry had the theoretical potential to be the most significant advance in intrapartum fetal assessment since the introduction of continuous electronic fetal monitoring. It was expected that with the use of this tool the obstetricians would acquire the ability to directly assess fetal oxygenation in contrast to the indirect assessment provided by electronic FHR monitoring (Carbonne et al., 1997). Unfortunately, randomized clinical trials demonstrated that the use of fetal pulse oximetry did not improve the outcome of women in labor and the manufacturer of the device discontinued its production (Garite et al., 2000).

FETAL ASPHYXIA AND CP

The potential cause–effect relationship between perinatal asphyxia and CP has been a heavy burden for the practicing obstetricians since 1861 when all of the cases of spastic diplegia were attributed to difficult labors, preterm birth, and neonatal asphyxia (Little, 1861). Although more recent evidence (Nelson and Ellenberg, 1985, 1986) suggests that intrapartum events are responsible for no more than 8–10% of all the cases of CP, obstetricians continue to be sued in most cases of serious neurological dysfunction during childhood. Unfortunately, because of the long interval between birth and diagnosis of CP, the lack of specificity of the tests used to establish the time of injury, and the high cost of the care of neurologically impaired subjects, obstetricians frequently are found guilty of malpractice and punished with multimillion dollar penalties. The consequences of this situation are multiple and include very high malpractice insurance premiums, increasing number of professionals leaving obstetrics, decreased number of applications for obstetrical residency training, practice of high cost defensive obstetrics, and generalized dissatisfaction with the practice of obstetrics among medical professionals.

BOX 6-6

Causes of cerebral palsy

- Developmental abnormalities
- Chromosomal abnormalities
- Infection
- Prematurity
- Trauma
- Birth asphyxia

There are multiple causes of CP (Box 6-6) and birth asphyxia seems to be responsible for approximately 8–10% of the cases. Most severely asphyxiated fetuses either die or survive intact. In fact, despite an incidence of acidosis (pH < 7.20) of 12–20% at birth the incidence of CP is approximately 2 per 1000 and intrapartum fetal death at term in the absence of risk factors occurred in less than 1 per 25,000 patients in the Collaborative Perinatal Study (Lilien, 1970).

The evidence that perinatal asphyxia causes brain damage is based mainly on animal experiments. In animals, asphyxia must be severe, very close to that causing death, to produce cerebral lesions. In the humans, fetal death or survival with an intact brain seems to be the most common outcome following episodes of severe intrapartum asphyxia. Also, there is compelling evidence indicating that fetuses with conditions affecting the central nervous system may develop hemodynamic alterations during labor secondary to their brain disease. In other words, asphyxia may be the result rather than the cause of their brain damage.

The American College of Obstetricians and Gynecologists (2003) has defined a series of essential criteria to define an acute intrapartum hypoxic event as sufficient to cause CP. These criteria are as follows:

1. Evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH < 7.0 and base deficit ≥ 12 mmol/L)
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation
3. CP of the spastic quadriplegic or dyskinetic type
4. Exclusion of other identifiable etiologies such as trauma, coagulation abnormalities, infectious conditions, or genetic disorders.

Abnormal electronic FHR monitoring patterns are not included among the criteria to characterize fetal asphyxia severe enough to cause brain damage because several studies have demonstrated that they have extremely poor predictive value (Nelson et al., 1996). This seems to be paradoxical because severe fetal asphyxia usually results in abnormal FHR monitoring patterns. One reason why ominous FHR patterns are not predictive of neurological outcome is that they result of alterations of the fetal central nervous system or dysfunction of the fetal heart that may occur because of multiple reasons different from perinatal asphyxia. Another reason is that the large majority of newborns with birth asphyxia recover without neurological sequelae.

Another variable not included in the ACOG criteria for fetal asphyxia severe enough to cause neurological damage is the Apgar score. Similarly to FHR monitoring, a low Apgar score has a poor correlation with CP and it is impossible to predict neurological outcome from a low Apgar score value. The data of the Collaborative Perinatal Project (Nelson and Ellenberg, 1981) show that of 120 children with CP only 26% had a 1-minute Apgar and 15% a 5-minute Apgar score of 0–3. Among all newborns with Apgar scores 0–3 at 1 and 5 minutes, more than 93% did not manifest CP. On the other hand, a normal Apgar score is an excellent predictor of neonatal well-being and it has been shown that virtually no infant with Apgar score > 5 at 10 minutes of life has an abnormal neurological outcome (Levene et al., 1986).

Several studies have shown that the predictive value for brain damage of isolated umbilical artery pH is poor. One of these studies (Dijxhoorn et al., 1985) compared the umbilical cord pH of 805 infants with normal, suspected, and abnormal neurological diagnosis and found no difference in the distribution of umbilical blood pH values. Another study (Ruth and Raivio, 1988) investigated the relationship between acidosis at birth and brain injury by measuring umbilical artery pH in 982 consecutive births. They found an incidence of neonatal acidosis (pH < 7.16) of 12%. The sensitivity of low pH to detect ulterior brain damage was only 21% and the positive predictive value only 8%. A similar poor predictive value was found for low Apgar scores at 5 minutes and a high lactate concentration in umbilical cord. Fee et al. (1990) examined the relationship between severe acidosis (pH ≤ 7.05) at birth and subsequent neurological dysfunction in 142 neonates and found that severe acidosis was a poor predictor of future neurological function. A summary of the world literature on this subject was made by Kirkendall and Phelan (2001). They found nine articles describing 314 infants born with severe acidosis and only 27 (8.6%) were subsequently found to be brain-damaged. In contrast, they found that the incidence of brain damage in asphyxiated newborns without severe acidosis (pH ≥ 7.0) was 61 of 94, or 64.8%.

Different to low umbilical artery pH, neurological damage secondary to intrapartum asphyxia cannot occur in the absence of neonatal encephalopathy. However, not all newborns with neonatal encephalopathy develop CP and the outcome of this condition is variable, ranging from normal to severe CP. Neonatal encephalopathy is a syndrome of abnormal neurological function with or without seizures occurring during the first 48 hours of

life, which is characterized by difficulty initiating and maintaining respiration, abnormal tone, poor feeding, and altered level of consciousness. Neonatal encephalopathy has replaced HIE which was a term used to indicate a specific cause without consideration to the etiologic plurality of the syndrome. The incidence of neonatal encephalopathy is between 1.9 and 3.8 per 1000 live births. Neonatal encephalopathy is classified as stage I (no seizures, hyperalertness), stage II (reduced tone, seizures, decreased level of arousal), and stage III (severely depressed EEG background pattern, flaccidity, delayed seizures) according to its severity. Newborns with stage I usually recover without sequelae while those with stage III usually have abnormal neurological outcome. The outcome of newborns with stage II encephalopathy is variable and difficult to predict. There are multiple risk factors (Box 6-7) and multiple causes of neonatal encephalopathy (Box 6-8) and there is no sign(s) that suggests the cause or the timing of the brain insult.

BOX 6-7

Risk factors for neonatal encephalopathy

Maternal/Placental
- Chorioamnionitis
- Thrombophilia
- Trauma
- Thyroid disease
- Polyhydramnios
- Substance abuse

Fetal
- Genetic syndromes
- Congenital malformations
- Fetal infections
- Multifetal pregnancies
- Fetal hydrops
- IUGR

BOX 6-8

Partial list of causes of neonatal encephalopathy
- Birth asphyxia
- Chromosomal abnormalities
- Neonatal hypoglycemia
  Hyperinsulinism, hereditary metabolic defects
- Primary anatomic abnormalities
  Porencephalic cyst, hydranencephaly
- Lower motor neuron disorders
  Arthrogryposis, Werdnig–Hoffman disease
- CNS degenerative diseases
  Tay-Sachs disease, Canavan disease
- Organic acid abnormalities
  Galactosemia, maple syrup urine disease
- Neonatal hyperammonemia
  Urea cycle defects

There are multiple causes of neonatal encephalopathy but most of them are rare and the most frequent is perinatal asphyxia. Conditions other than asphyxia occur more frequently in cases where the birth of an asphyxiated infant is a surprise and follows a normal labor without significant FHR abnormalities. Rare etiologies are also more common when the FHR shows decreased variability without periodic changes from the beginning of labor. In any situation where fetal asphyxia and neonatal encephalopathy are unexpected or there are antenatal events (decreased fetal movements, nonreactive NST) or intrapartum suggestions (lack of reactivity, decreased variability, no decelerations) that the hypoxic insult occurred before labor, the obstetrician should request that the neonatologists perform an early MRI of the newborn brain.

The inclusion of spastic quadriplegia and dyskinetic CP in the ACOG essential criteria to attribute CP to an intrapartum hypoxic event is based on a study by Nelson and Grether (1998). This was a retrospective case-control study of 46 children with unexplained CP and 378 normal control subjects. They found that a "tight" nuchal cord, a potentially asphyxiating condition, was present in all 8 children with quadriplegic CP and in 15 control subjects. Indicators of fetal stress, markers of neonatal illness, and characteristics of labor and delivery were not different in newborns with potentially asphyxiating conditions than in control subjects. This study has all the weakness of a retrospective record review of a small number of cases and the main finding, association between "tight" nuchal cord and quadriplegic CP, is not robust because it involves an obstetrical variable with a large degree of subjectivity that frequently is not associated with neurological problems as shown by the 15 infants in the control group that also had "tight" nuchal cords. In our opinion, the third essential ACOG criterion lacks adequate scientific support and should not be used.

Neonatal MRI and CP

MRI is an excellent method for the evaluation of asphyxiated newborns with or without neonatal encephalopathy. The MRI can precisely differentiate gray matter from white matter and unmyelinated from myelinated white matter. It can provide detailed structural and functional information about the newborn brain. The unique value of MRI is its ability to demonstrate lesions that are not revealed by other imaging techniques such as abnormal signal intensity in the basal ganglia, periventricular and subcortical white matter, and the cerebral cortex. Furthermore, the characteristics of the lesions detected with MRI correlate well with the long-term neurological outcome of asphyxiated newborns with neonatal encephalopathy (Rutherford et al., 1996).

Newborns with neonatal encephalopathy secondary to intrapartum asphyxia exhibit brain swelling on MRIs performed in the first days of life that usually disappears after 1 week. The absence of cerebral swelling in a newborn with neonatal encephalopathy basically rules out the existence of severe intrapartum asphyxia and switches etiologic considerations to antepartum causes. When the MRI is performed between 1 and 4 weeks after birth, infants with no changes or minimal white matter changes in the periventricular white matter and with no loss of gray–white matter differentiation have an excellent prognosis. When the MRI shows focal abnormalities in the white matter but the basal ganglia, thalami, and posterior limb of the internal capsule are normal, the prognosis is good and the newborn will be neurologically normal or have only minor motor abnormalities at school age. Newborns showing extensive changes in the white matter and cortex, abnormal signal from the internal capsule, and transient or unilateral basal ganglia abnormalities have a poor prognosis and will develop microcephaly and CP. Most will have diplegia or mild quadriplegia but will learn to walk with support. Newborns with focal abnormalities in the basal ganglia and thalami, abnormal signal from the internal capsule, and with or without cortical high-lightening will develop athetoid or dystonic CP but will have normal cognitive development. When the newborn with neonatal encephalopathy shows widespread abnormalities in all regions of the basal ganglia and thalami, absent myelin in the internal capsule, and lesions in the white matter and cortex the prognosis is extremely poor and spastic or dystonic tetraplegia, microcephaly, severe global delay, and abnormalities of the visual system should be anticipated (Barnett et al., 2002).

In addition to conventional MRI, early functional MRI with diffusion-weighted imaging (DWI) can demonstrate changes diagnostic of hypoxic-ischemic damage at a time when other imaging modalities are negative or show nonspecific changes (Cowan et al., 1994). DWI measures the self-diffusion of water from a region of high concentration to a region of lower concentration, a property that is altered shortly after a hypoxic insult. Magnetic resonance spectroscopy (MRS) is another technique that allows in vivo assessment of brain metabolism. MRS makes it possible to detect elevated concentrations of lactic acid, creatine and phosphocreatine, glutamate, glutamine, and myoinositol, metabolites which are produced in excess after an acute hypoxic brain insult, opening the possibility of studying the brain biochemistry and the pathophysiology of perinatal brain injury (Huppi and Amato, 2001).

One recent MRI study indicates that more than 90% of term infants without specific syndromes or congenital defects that develop neonatal encephalopathy or neonatal seizures or both have evidence of perinatal insult that in the large majority of them occurred during the intrapartum period (Cowan et al., 2003). These investigators studied 351 full term infants with neonatal encephalopathy, early seizures, or both and used MRI to distinguish lesions acquired antenatally, intrapartum, and early postpartum. They considered that the insult was antenatal or resulted from a developmental abnormality if the MRI revealed irregular ventricular dilatation, widening of the interhemispheric fissure, enlarged extracerebral space, established cystic lesions, focal infarction with atrophy, long-standing hemorrhage, marked asymmetries in ventricular size, hemispheric size, cerebellum, brain stem, or operculum, and developmental anomalies such as cortical dysplasia, midline abnormalities, or abnormal cerebellar development. They considered as signs of acute intrapartum asphyxia the presence of brain swelling, cortical highlighting, focal or global loss of gray–white matter differentiation, abnormal signal intensity in basal ganglia and thalami, loss of normal signal intensity in the posterior limb of the internal capsule, acute and subacute parenchymal, intraventricular, or extracerebral hemorrhage, and acutely evolving focal infarction in a parasagittal or watershed distribution. They found that 80% of infants with neonatal encephalopathy had evidence of an acute hypoxic-ischemic event while antepartum conditions were present in less than 1% of them. They also evaluated 90 infants that had seizures within 72 hours of birth but did not meet criteria for neonatal encephalopathy and found acute ischemic or hemorrhagic lesions in 69% and evidence of antepartum conditions in 3%. This is an important study because it contradicts earlier information indicating that only 8–15% of term infants with neonatal encephalopathy and much less with neonatal seizures have evidence of intrapartum asphyxia (Nelson and Leviton, 1991; Mercuri et al., 1995). If this study is confirmed by prospective investigations the findings may have an important effect in obstetrical practice.

MANAGEMENT OF FETAL ASPHYXIA

Prompt delivery by cesarean section is the best management for fetal asphyxia suggested by ominous FHR monitoring patterns. However, in the majority of cases, the obstetrician is faced with nonreassuring FHR patterns that frequently are transient and correctable without need for emergency cesarean section. The first steps in these cases are to discontinue oxytocin, positional changes, administration of oxygen, intravascular volume expansion with crystalloid solutions, and administration of a tocolytic agent. Simultaneously it is important to find out if there are fetal or maternal risk factors for intrapartum asphyxia and neonatal encephalopathy. If

they are present, preparations to deliver by cesarean should start while efforts for fetal resuscitation continue. Another important initial step is fetal scalp stimulation or VAS. A reactive FHR response to either maneuver indicates that the fetus is not acidemic and labor may be allowed to continue.

An important and frequently overlooked cause of nonreassuring FHR patterns is spontaneous or oxytocin-induced uterine hyperstimulation. In many of these cases the external monitoring fails in recognizing the uterine hyperstimulation because the patient is uncomfortable with the contractions and moves constantly displacing the external tocodynamometer and making the evaluation of the uterine activity through abdominal palpation difficult. The immediate treatment for this condition is to discontinue the oxytocin administration and simultaneously administer 250 µg of terbutaline intravenously and 250 µg subcutaneously. All 500 µg of terbutaline may be given subcutaneously if an intravenous line is not available. If the abnormal pattern continues, the possibility of hypoxemia and acidemia is high and the pregnancy must be delivered by cesarean section. An improvement in the FHR pattern strongly suggests that the fetus has recovered and that continuation of labor is possible. Esteban-Altirriba et al. (1980) demonstrated that fetal pH increases after tocolytic therapy in 84.8% of nonreassuring patterns secondary to excessive uterine activity, in 72% of cases due to umbilical cord compression, and in 69.6% of abnormal patterns due to other causes. When a nonreassuring FHR pattern is secondary to placental insufficiency, a successful response is observed in only 31.4% of the cases. A favorable response happens in 76.9% of the cases when the fetal pH is between 7.20 and 7.24, and in approximately 50% of fetuses with pH less than 7.20. If a nonreassuring FHR pattern does not improve following terbutaline administration, the next step should be delivery by cesarean section. Figure 6-6 summarizes the steps in the management of nonreassuring FHR patterns during labor.

Variable decelerations occur more frequently in patients with ruptured membranes, post-term pregnancies, IUGR (intrauterine growth restricted) babies, and in other situations with decreased amniotic fluid volume. When they occur, the patient must be immediately examined to rule out a cord prolapse or a funic presentation—umbilical cord present in the pelvis before the body of the infant—either of which is an indication for cesarean section. If the pelvic examination is negative, positional changes and tocolytic therapy must be used to correct the deceleration. If the variable deceleration pattern persists or recurs, pulse oximetry and amnioinfusion are indicated. Amnioinfusion is performed by giving a bolus of 200–300 ml of warm saline solution in approximately 30 minutes through an intrauterine pressure catheter. If the

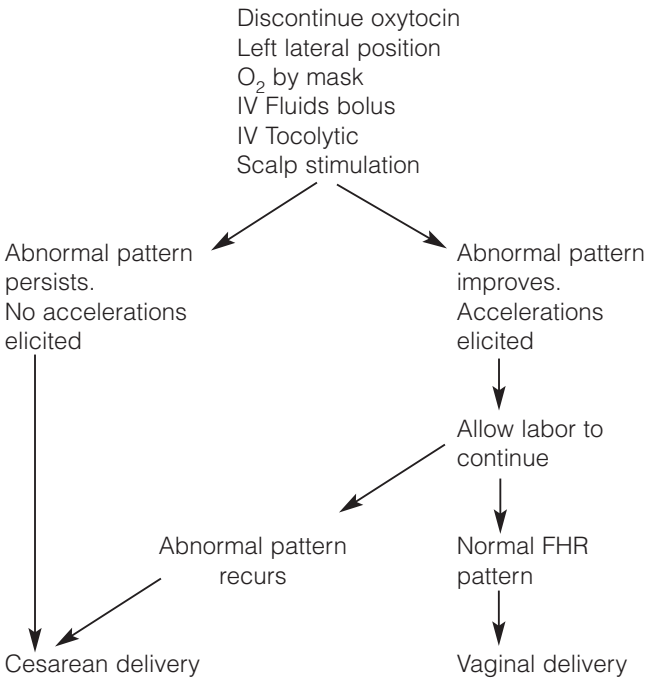

Figure. 6-6. Management of nonreassuring FHR patterns during labor.

saline solution escapes quickly from the uterine cavity the administration of normal saline should be maintained after the initial bolus at approximately 100 ml/hour. Continuous amnioinfusion should not be used when the uterine outlet is well occluded by the presenting part and there is no external drainage of the saline solution following the initial bolus.

The main problems with amnioinfusion are continuous administration when the fluid is not draining in the vagina and subchorionic insertion of the catheter. In the first instance the uterus becomes overdistended with the continuous amnioinfusion, the resting uterine pressure increases, the contractions become more frequent but are not strong, and the course of cervical dilatation may be abnormal. When the insertion of the catheter is subchorionic, there is

BOX 6-9

What to do at delivery of an asphyxiated infant

- Request assistance by the neonatologists if they are not present at the time of delivery.
- Obtain umbilical artery pH, pO_2, pCO_2, and base excess.
- Document in the chart the presence or absence of ACOG criteria for neonatal encephalopathy including but not limited to the description of cord blood gases, sentinel events during labor, characteristics of the FHR pattern, Apgar scores, prenatal evaluation of risk factors, presence of infection, etc.
- Send the placenta for pathology examination.
- Communicate with the neonatologist and insist in the need for early and late MRI examinations.
- Communicate with the pathologist about risk factors.

blood return through the catheter and frequently the uterus develops a pattern of hyperstimulation similar to that seen in abruption placenta with a high resting pressure and frequent contractions that in many occasions are followed by rapid delivery.

There are several important things to do following the delivery of an asphyxiated infant that are summarized in Box 6-9.

INDIAN EXPERIENCE WITH BIRTH ASPHYXIA

Birth asphyxia is an important cause of perinatal morbidity and mortality. The normal newborn baby succeeds in establishing respiration within 20–30 seconds of birth. Birth asphyxia is not uncommon. The 1-minute Apgar score indicates the need for resuscitation, and the 5-minute Apgar score is a good determinant of subsequent outcome (Bhakoo, 1986). Birth asphyxia has an inverse relationship between a low Apgar score at birth and later association of neurological sequelae (Guha, 1995). However, at the time of birth of the baby which fails to initiate respiration in spite of clearing the mouth of secretions, a quick assessment of its color and heart rate help to determine whether resuscitation measures are called for. If the heart rate is 100 or above, general measures like suction of the mouth, drying the baby and keeping it warm, stroking of the feet, and nasal O_2 with catheter should generally suffice. But if the baby is gasping and the heart rate is slow, or there is no response to initial measures, clearing of the secretions from the mouth, nose, and laryngoscopic aspiration of the throat should be followed with endotracheal intubation and positive pressure ventilation to revive the baby. If the above facility is not available, positive pressure ventilation with Ambu bag and mask should be attempted. In case oxygen is not available, room air may be used (Ramji et al., 1993). Sometimes mouth-to-mouth breathing with chest compression, though less effective, may remain the only method of resuscitation in a dire emergency (Safer et al., 1958). If the mother has been given inj. pethidine/morphine for pain relief shortly before birth, neonatal depression can be due to drug effect which can be countermanded by administering inj. nalorphine 1.0 mg into the umbilical vein. The decision to administer sodium bicarbonate to the neonate to correct acidosis is best left to the judgment of the neonatologist. Some of the asphyxiated neonates who take more than 5–10 minutes to establish regular respiration and show persistent neurological abnormality in early neonatal life may demonstrate developmental retardation in later life (Bhakoo, 1986; Singh et al., 1992).

Meconium aspiration is uncommon in infants below 37 weeks of gestation except in listeriosis. But the risks increase in post-term, IUGR, or breech deliveries. It is generally associated with moderate to severe intrapartum asphyxia; often multiple organ pathology is present. It is important to clear the upper airway under direct vision (laryngoscopy). If the meconium is thick, tracheal lavage via an endotracheal tube is recommended (Vidyasagar et al., 1975).

In an FOGSI study (Mehta and Jayant, 1981), asphyxia and birth trauma accounted for 42.8% of perinatal deaths. The incidence of birth asphyxia is higher in preterm babies and following birth trauma.

In perinatal mortality surveys from India, prematurity has been the leading cause of early neonatal deaths followed by birth asphyxia as the second most common cause. The incidence of birth asphyxia reported varied from 9.0 to 22.0% (Gaddi and Seetharam, 2001; Jotwani et al., 2001; Kamat and Jindal, 2001; Kameswaran et al., 1993).

IMPORTANT POINTS

1. There is no universally accepted, specific definition of fetal asphyxia. Most investigators agree that it means severe impairment of the fetal gas exchange resulting in hypoxia (pO_2 less than 6.5 torr), acidosis (pH less than 7.00), and metabolic acidosis (base deficit ≥ 12).
2. The majority of interferences with the fetal gas exchange affect the ability to eliminate CO_2, causing respiratory acidosis. This condition responds promptly to neonatal resuscitation.
3. Decreased transfer of oxygen to the fetus resulting in anaerobic metabolism and formation of lactic acid is the mechanism of production of metabolic acidosis.
4. Meconium staining of the amniotic fluid is an unreliable and inaccurate indicator of fetal asphyxia.
5. The Apgar score is an index to assess the condition of the newborn that may be affected by multiple factors different from hypoxia and acidosis. Only a small percentage of newborns with low 1- and 5-minute Apgar score have a pH below 7.0.
6. Intrapartum asphyxia usually does not result in neurological damage of the newborn. Fetal death or survival with an intact brain is the most common outcome following fetal asphyxia.
7. There are multiple causes of CP. Most cases are due to genetic, metabolic, and developmental conditions.
8. The ACOG criteria to suspect perinatal asphyxia as a cause of CP require that the following conditions are present: (a) Severe neonatal acidemia with pH less than 7.0 and base excess less than –16; (b) early onset of moderate or severe neonatal encephalopathy in infants born at 34 or more weeks of gestation;

(c) CP of the spastic quadriplegic or dyskinetic type; (d) exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders.

9. There are few studies on the use of intermittent auscultation for intrapartum fetal monitoring. The sensitivity, specificity, and predictive values of this technique are unknown. It requires a 1:1 nurse to patient ratio.
10. A reassuring continuous electronic FHR monitoring pattern is reliable evidence of fetal well-being. There are no reports of severely asphyxiated babies born in the presence of a reassuring FHR pattern.
11. Ominous FHR patterns are usually seen when there is a profound alteration of the fetal central nervous system secondary to developmental anomalies, chromosome abnormalities, and fetal asphyxia.
12. One problem with electronic FHR monitoring is the nonreassuring patterns because in most of these cases the fetus is healthy but there is no reliable means to rule out the possibility of fetal compromise.
13. The presence of a FHR acceleration of at least 15 bpm lasting at least 15 seconds following pinching of the fetal scalp with an Allis clamp or following VAS is uniformly associated with a scalp pH greater than 7.19.
14. The routine determination of umbilical blood gases is unnecessary and should be discouraged. Rather than being useful for malpractice defense they may become potentially incriminating evidence. Umbilical blood gases should be obtained only if any serious abnormality in the delivery process or problems in the neonatal period persist beyond the first 5 minutes of life.
15. Variable decelerations are the most commonly observed FHR abnormality. Amnioinfusion may eliminate or decrease the severity of variable decelerations.

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Section II

OBSTETRICAL COMPLICATIONS

7

Preterm Parturition Syndrome

CHAPTER OUTLINE

Preterm birth is a condition that occurs in 6.0–15.0% of all deliveries and is the most frequent cause of fetal and neonatal death and morbidity. Preterm birth is more common in African-American than in Caucasian women. Preterm birth is defined as birth before 37 weeks of gestation. The preterm birth rate in USA increases every year and increased from 9.4% of all live births in 1981 to 12.7% in 2005. Late preterm births (between 34 weeks and 0 days and 36 weeks and 6 days) account for about 74% of all preterm births while the very preterm (less than 32 weeks) rate has remained relatively constant during the last two decades.

The incidence of preterm births ranges between 10 and 15%. The antecedent causes in the mother leading to preterm delivery coupled with low birth weights expected in preterm births contribute to an enhanced perinatal mortality rate (PNMR).

The incidence of PNMR in India varies from 40 to 150 per 1000 births in contrast to 10–20 in the developed countries. There has been a steady decline of PNMR in India over the years, but much remains to be achieved. The importance of preterm labor lies in the fact that 75% of all perinatal deaths occur in preterm infants, and when lethal anomalies are excluded, 85% of all neonatal deaths occur in preterm infants. An analysis of preterm deliveries reveals that 70% of these occur in induced labor or in pregnancies associated with high-risk factors like hypertensive disorders, antepartum hemorrhage, multiple gestation, IUGR, fetal anomalies, and premature rupture of membranes (Daftary and Desai, 2006).

Table 7-1 gives the PNMR quoted by Indian workers from different parts of India. It shows the high overall PNMR in the country. It continues to be higher in rural communities and in urban slums.

There are multiple causes for the alarming rate of increase of late preterm births. In the West, amongst the various contributory factors are the identification of more high-risk pregnancies, the practice of defensive medicine, a neonatal survival rate near 100% after 34 weeks' gestation, an increased rate of elective inductions and repeat

Table 7-1. Perinatal mortality in preterm births

Author	Year	Place/ Locality	Urban/ Rural	PNMR
Agarwal	1995	Varanasi	Urban	56/1000
Bhavsar et al.	1981	Pune	Urban	74/1000
Malik and Mir	1992	Srinagar	Urban	50.2/1000
Shinde	2001	Ambejogai	Rural	91.8/1000
Jotwani	2001	Wardha	Rural	64.7/1000

cesarean before 39 weeks, an erroneous general public perception about the safety of late preterm delivery, and changes in clinical management related to "risk tolerance." Unfortunately, late preterm delivery is not safe and there is abundant literature demonstrating increased temperature instability, hypoglycemia, respiratory distress, clinical jaundice, feeding difficulties, and sepsis when the outcome of these infants is compared with term infants.

In India, socioeconomic factors like young maternal age, low maternal weight, poor nutritional status, illiteracy, uncontrolled fertility, poor sanitation and hygiene causing endemic diseases leading to general ill health, hard manual work, lack of prenatal care, broken homes, unmarried status, substance abuse, and emotional stress continue to adversely affect the incidence of preterm births.

The four major causes of preterm birth are preterm labor, premature rupture of the membranes (PROM), incompetent cervix, and indicated preterm delivery. These conditions share with normal term labor a common pathway of parturition which is the mechanism that causes the expulsion of the products of conception to the outside world. The understanding of preterm birth as a syndrome with multiple etiologies and diverse mechanisms resulting in premature activation of the common pathway of parturition (Figure 7-1) and the discovery of clinical markers to detect the premature activation of this pathway have been fundamental advances that have changed our vision and our approach to this problem.

In this chapter we will describe first the components of the common pathway of parturition. Then we will discuss the causes of preterm birth, the mechanisms to activate the common pathway of parturition, and some of the most important neonatal consequences of preterm birth. In other chapters of this book we will describe the diagnosis and management of women with preterm labor, PROM, incompetent cervix, and the most frequent conditions causing indicated preterm birth.

COMMON PATHWAY OF PARTURITION

The common pathway of parturition has three components: cervical ripening, activation of the myometrium, and activation of the fetal membranes. In normal term birth these components are activated simultaneously. In preterm birth it is not unusual to have predominant activation of one or two of the components, resulting in variations in symptoms and signs. Premature ripening of the cervix is the predominant feature in women with incompetent cervix, premature activation of the membranes is the key event in women with preterm rupture of membranes, and premature activation of the myometrium is the cardinal feature in women with preterm labor and intact membranes.

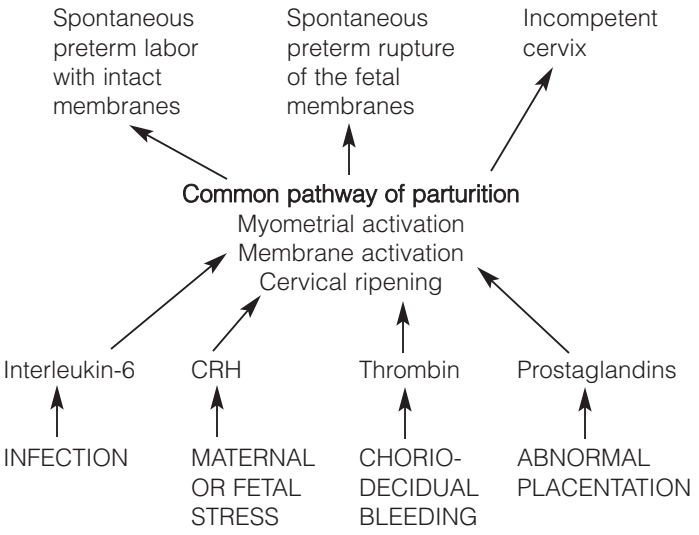

Figure 7-1. Schematic representation of the present understanding of preterm birth as a syndrome with multiple causes and intermediate substances.

Cervical Ripening

The function of the cervix during pregnancy is to retain the products of conception. This ability depends on the firmness and strength of the cervical connective tissue. At the end of a pregnancy, term or preterm, the cervix undergoes dramatic changes known as cervical ripening. Cervical ripening consists of the transformation of the cervix from a structure that is long, hard, and rigid to a tissue that is soft and easily distendable.

For many years cervical ripening and cervical dilatation were considered to be the result of uterine contractions. Today it is known that cervical dilatation and cervical ripening are different processes. Cervical dilatation, the marker of active labor, is the result of uterine contractions pulling the cervix against resistance posed by the presenting part. Cervical ripening is the result of a complex series of biochemical reactions completely different from those involved in the production of uterine contractility (Leppert, 1995). Under normal circumstances cervical ripening is apparent before the onset of regular uterine contractions and is a necessary prerequisite for cervical dilatation during the active phase of labor.

The cervix is made up of smooth muscle fibers and fibrous connective tissue. The connective tissue is the predominant element and is formed by fibroblasts and an extracellular matrix or ground substance. The muscle fibers represent less than 10% of the organ. The extracellular matrix is made up of substances produced by the fibroblast, mainly collagen, glycosaminoglycans, and glycoproteins. Before pregnancy all the elements comprising the cervix, particularly the collagen fibers, are tightly aggregated giving to the organ its peculiar hard consistency. At the end of the pregnancy, before and during the early stages of labor, collagenase activity in the extracellular matrix increases and there is increased fibroblastic production of hyaluronic acid, a hydrophilic molecule. As a consequence of these changes the collagen content decreases and the water content of the cervix increases. There is infiltration of the extracellular matrix by inflammatory cells particularly neutrophils and macrophages with production of cytokines, metalloproteinases, and prostaglandins. The cervix becomes soft and can be stretched by the pressure of the fetal presenting part and the pulling effect of the uterine contractions.

The trigger for the initiation of cervical ripening is unknown although there is substantial evidence indicating a role for sex steroid hormones and prostaglandins. The role of sex steroid hormones is evidenced by the administration of progesterone antagonists, such as RU487, a powerful inductor of cervical ripening in humans and in other animal species. Also, there is laboratory evidence demonstrating the ability of estradiol to stimulate collagen degradation. Prostaglandins are powerful pharmacologic inductors of cervical ripening and may play a central role in the physiology of the process. This property of prostaglandins is extensively utilized in clinical obstetrics where they are commonly used for cervical ripening and induction of labor. Prostaglandins exert their effects on the cervix by modulating fibroblast activity and inducing the production of hyaluronic acid with mobilization of water into the extracellular matrix and by promoting changes in the glycoprotein composition of the cervix. Prostaglandins also have the ability to mobilize leukocytes and macrophages into the extracellular matrix that will be responsible for the production of enzymes that will cause changes in the cervical ground substance.

Some of the changes associated with cervical ripening can be detected by digital examination of the cervix. However, as it will be discussed in other chapters of this book, endovaginal or perineal ultrasound allow the recognition of changes in endocervical canal length and in the diameter and shape of the internal cervical os before they are apparent to the fingers of the examiner. Numerous studies have demonstrated the accuracy of cervical ultrasound in the diagnosis of cervical ripening and the prediction of preterm birth. The advent and popularization of cervical examination by means of endovaginal ultrasound had a significant impact in the definition, prediction, and therapy of women at risk of or in preterm labor.

Activation of the Fetal Membranes

In term and preterm births, there are a series of biochemical reactions that cause the separation of the chorioamnion from the decidua in the lower uterine segment and culminate with rupture of the membranes. In term birth this process usually occurs after cervical ripening and simultaneously with the activation of the myometrium. In women with prolonged preterm rupture of the membranes, activation of the membranes occurs before the activation of the other two components of the common pathway.

Most of the tensile strength of the fetal membranes depends on the concentration and cross-linkage of collagen and the presence of elastin, laminin, and fetal fibronectin in the amnion. Fibronectin is the cement for the fusion of the chorioamniotic membranes with the decidua, a process that is completed after 22 weeks of gestation. One of the most important features during membrane activation is the loss of tensile strength of the amnion due to alterations in collagen concentration and function. Collagen is produced in large amounts in the fibroblast layer of the amnion early in pregnancy but its synthesis decreases progressively after 20 weeks. The degradation of collagen is the result of the sequential and concerted activity of several matrix metalloproteinases. The increased activity of matrix metalloproteinases occurs simultaneously with a decrease in the activity of specific tissue inhibitors of those metalloproteinases. The trigger of membrane activation is not known. There are several substances that may be responsible for this process but cytokines and prostaglandins are thought to be the best candidates.

The biochemical marker of activation of the fetal membranes is the leakage of fetal fibronectin from the uterine membranes into the cervicovaginal secretions. Fibronectin is a glycoprotein normally present in cervical and vaginal secretions before 22 and after 37 weeks. At any other time its presence is predictive of preterm birth in symptomatic and asymptomatic high-risk women. However, the predictive value of fibronectin in low-risk women is poor and does not justify testing for its presence as a screening test for prematurity. As it will be discussed later, the positive and negative predictive values for preterm birth of cervicovaginal fibronectin are similar to those of cervical assessment by endovaginal ultrasound. When both tests give similar results the predictive values increase (Gomez et al., 2005). Determination of

fetal fibronectin in the cervicovaginal secretions is a test that has changed the categorization of risk in women at risk of preterm birth and with increased uterine activity.

Activation of the Myometrium

During normal pregnancy the uterus is under the effect of a series of inhibitors of uterine contractions, among them progesterone, relaxin, nitric oxide, and prostacyclin. At the end of the pregnancy the quiescent effect of these substances begins to disappear and the uterus becomes responsive to estrogen and increases the synthesis of gap junctions, oxytocin and prostaglandin receptors, and calcium channels, becoming prepared to respond to the effect of uterotonic substances such as oxytocin and prostaglandins (Arias, 2000; Arias et al., 1999). These molecular events translate clinically into a gradual increase in frequency of uterine contractions during the last weeks of gestation.

The production of uterine contractions requires an increase in myometrial intracellular calcium concentration. This occurs by influx of calcium from the outside of the myocyte through calcium channels or by release of calcium deposited in the endoplasmic reticulum. Calcium will bind to calmodulin and the calcium–calmodulin complex will bind to the enzyme myosin light chain kinase which will phosphorylate the short chains of myosin, causing synthesis of ATP and muscle contraction. The activity of myosin light chain kinase is central to the process of muscle contraction, and most pharmacologic agents used to stimulate or inhibit uterine contractions operate through metabolic pathways that lead to this enzyme.

The changes in myometrial activity that occur during term and preterm labor are clinically more apparent than the changes in the cervix or the activation of the membranes. For this reason, analysis of myometrial function and the role of the myometrium in preterm birth have dominated the clinical and basic research in this area. Unfortunately, the accuracy and predictive values of uterine contraction monitoring in the prediction of preterm birth are disappointing (Iams et al., 2003).

CONDITIONS CAUSING PREMATURE ACTIVATION OF THE COMMON PATHWAY OF PARTURITION

The common pathway of parturition can be activated by multiple agents. The most clearly identified is chorioamniotic infection. Other causes are maternal or fetal stress, placental insufficiency, and bleeding in the chorioodecidual interface. These agents operate through the production of intermediary substances that activate one or more of the components of the common pathway of parturition. The pathological activation of the common pathway of parturition may be similar to that occurring during normal term labor or may be a preferential stimulation of only one or two of the components of the pathway. For example, maternal and fetal stress activate the components of the final pathway of parturition in a similar way to what occurs in normal term labor while infection and bleeding usually cause predominant activation of one or two of the components.

Maternal and Fetal Stress

Maternal stress is a well-recognized cause of activation of the mechanism of normal parturition. The stress response in human beings is regulated by the hypothalamic secretion of corticotropin-releasing hormone or CRH (Hobel et al., 1999). CRH is a 41-amino acid polypeptide that stimulates the release of adrenocorticotropic hormone (ACTH) by the pituitary gland. During pregnancy the placenta is a major producer of CRH and in contrast to the hypothalamus, placental production of CRH is stimulated rather than inhibited by glucocorticoids. Environmental stress stimulates the production of CRH by the maternal hypothalamus and the increased concentration of CRH causes increased synthesis of ACTH by the pituitary gland that in turn stimulates the maternal adrenal gland to produce cortisol which in turn stimulates the placental production of CRH. The placental CRH will cause increased production of fetal ACTH with production of cortisol and DHEA (dehydroepiandrosterone) by the fetal adrenal. The fetal cortisol will stimulate the production of placental CRH with the formation of a vicious circle, resulting in more CRH, cortisol, and DHEA synthesis (Figure 7-2). The fetal DHEA will eventually be transformed into estriol—a molecule that has multiple properties including the ability to increase the number of myometrial gap junctions, increase the density

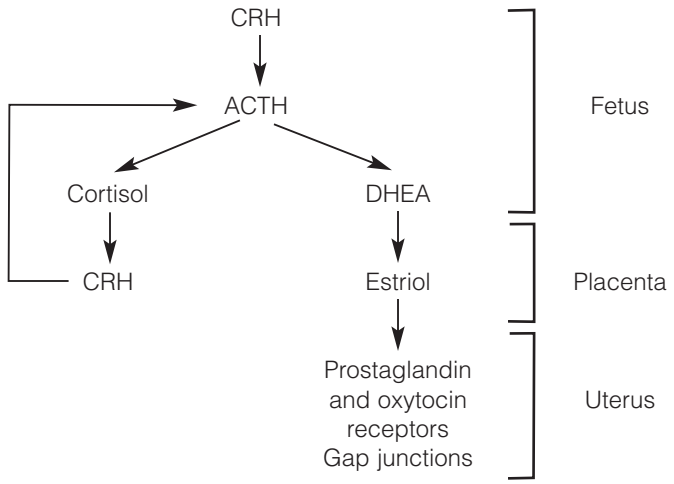

Figure 7-2. Corticotropin-releasing hormone (CRH) effects on parturition.

of prostaglandin and oxytocin receptors, increase oxytocin release by the hypothalamus, and increase prostaglandin production from the decidua. Prostaglandins will cause cervical ripening and oxytocin will stimulate the myometrium, provoking the onset of contractions.

In many cases a sick fetus is the initiator of labor, term or preterm (Challis and Smith, 2001). In these cases the mechanism of labor starts with the fetal production of CRH as a response to stress. Fetal stress is possibly the cause of preterm birth in pregnancies with a fetus affected by a congenital, metabolic, or infectious disease.

Infection

Infection is the most clearly recognized and more widely studied cause of preterm birth. Infection is responsible for between 20 and 40% of all cases of preterm birth, and this variation depends on the criteria used for the diagnosis of infection. The most rigorous criteria are positive cultures or demonstration of bacterial "fingerprints" by polymerase chain reaction (PCR) in the amniotic fluid. The less stringent criterion is the presence of leukocytic infiltration in the placenta. The evidence demonstrating that intrauterine infection is a cause of preterm birth is overwhelming and involves positive cultures indicating bacterial colonization and invasion of the chorioamnion, the amniotic fluid, and the fetus; histologic demonstration of infection in the placenta, membranes, and umbilical cord; and hematologic and biochemical findings consistent with infection.

The most accepted mechanism of infection causing preterm birth is ascending infection. According to this theory a break occurs in the normal physiologic barrier that separates the products of conception from the bacteria of the vaginal flora. The vaginal bacteria ascend and colonize the decidua and the chorion, eventually proliferating and invading the amniotic fluid and the fetus. The fundamental support for this theory comes from the fact that the microorganisms isolated from amniotic fluid cultures are similar to those normally found in the vagina. A most important question is the nature of the alteration in the host woman that allows the development of ascending chorioamniotic infection. Under normal circumstances the membranes are separated from the vaginal flora by the cervix and the endocervical mucus. It is possible that unrecognized cervical changes facilitate the occurrence of ascending infections. Changes in the antibacterial properties of the cervical mucous (Hein et al., 2001) may also play an important role in facilitating ascending infection. On the other hand, colonization of the lower genital tract by *Chlamydia, Gonococcus*, group B streptococcus, *Trichomonas*, and bacteroid species has been shown to increase the risk of PROM, but evidence that treatment of colonized patients prevents PROM is lacking. Also, clinical trials have demonstrated that factors which theoretically could increase the possibility of ascending infection, such as sexual intercourse, pelvic digital examinations during pregnancy, and history of prior cervical dilatation for abortion or D&C, have no significant association with this outcome.

More recent evidence suggests that the endometrial cavity is not sterile and bacteria are present inside the uterine cavity before conception. During pregnancy some women will develop a severe inflammatory reaction to the bacteria they harbor in their uterus that would manifest clinically as preterm labor. The ability to mount a severe inflammatory reaction and develop preterm labor is genetically determined and it has been shown that women with bacterial vaginosis and polymorphisms in the promoter region of the tumor necrosis factor (TNF) gene are at higher risk of developing preterm labor than women with bacterial vaginosis and intact TNF gene (Macones et al., 2004). It is apparent that the host response is as important as the properties of the infecting organism in the production of preterm labor of infectious/inflammatory origin.

Infection or inflammation of the products of conception may manifest clinically as incompetent cervix, preterm labor, or PROM. The reason why infection may have different clinical expressions most probably depends on the ability of the bacteria to produce or not to produce metalloproteinases that degrade the amnion and cause rupture of the membranes or it is due to peculiarities in the host–bacteria relationship. Infection may be overt or subclinical. When amniotic infection is present the diagnostic tests and the treatment are the same irrespective of the clinical presentation.

Acute chorioamnionitis

Acute chorioamnionitis occurs in 0.5–1.0% of all pregnancies. There are variations in the incidence of acute chorioamniotic infection depending on the socioeconomic status of the population. The condition occurs more frequently in the poor and uneducated. The diagnosis of acute chorioamnionitis is clinical. It requires the presence of fever (≥100 F or 37.8°C) and at least two of the following conditions: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor of the amniotic fluid, or maternal leukocytosis (Gibbs et al., 1982). Women with signs and symptoms of overt acute chorioamnionitis have reached a final stage in the progression of their uterine infection. In these cases, labor is a mechanism of fetal and maternal protection and should not be interrupted. The opportunities to prolong pregnancy and postpone delivery in women with overt chorioamnionitis may be in the prevention of infection, but once the clinical signs and

symptoms are present the only curative intervention is delivery.

The bacteria most frequently found in the amniotic fluid and the placenta of women with chorioamnionitis are *Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, Fusobacterium spp., Bacteroides bivius*, group B streptococcus, peptostreptococci, Escherichia coli, and enterococci (Gibbs et al., 1988). In the majority of cases the infection is polymicrobial and the cultures identify more than one type of bacteria. The mycoplasmas (*U. urealyticum* and *M. hominis*) are the bacteria most frequently isolated but their role in the production of infection is unclear. *Chlamydia trachomatis* is not an etiologic agent of acute chorioamnionitis. Most of the organisms found in the amniotic fluid are members of the normal vaginal flora. Some of them are more virulent than others and group B streptococcus, *E. coli*, and Enterobacteriaceae which are present in only 20% of cases of chorioamnionitis are responsible for 67% of the cases of maternal and fetal bacteremia and clinical sepsis. Rarely chorioamnionitis is secondary to hematogenous dissemination, a typical case being the infection due to *Listeria monocytogenes*. Characteristically, in listeria infection the placenta has multiple microabscesses.

Chorioamniotic infection by anaerobic bacteria usually does not cause systemic maternal signs or symptoms of sepsis and the neonates, although foul smelling, rarely develop significant septic complications. Women with anaerobic chorioamnionitis have little or no postpartum morbidity as long as delivery is vaginal. However, if they require cesarean, postpartum endometritis is the rule.

Acute chorioamniotic infection may be recognized in practically 100% of the cases by histologic examination of the placenta. The opposite is not true and histologic evidence of infection is frequently found in women without signs or symptoms of infection. Safarti et al. (1968) found histologic evidence of infection in 27% of placentas and membranes obtained after preterm delivery as compared to 4.7% when the placentas and membranes were obtained from normal patients delivering at term. We found (Arias et al., 1993) histologic chorioamnionitis in approximately 40% of women who had preterm delivery as a result of preterm labor. However, only a few of them had overt acute chorioamnionitis. Hillier et al. (1988) isolated microorganisms from the area between the chorion and the amnion in 61% of women who delivered before 37 weeks and in only 21% of those delivering at term. In a similar study Zhang et al. (1985) were able to culture pathogenic organisms in 44% of placentas with varied degrees of histologic chorioamnionitis. Romero et al. (1992) studied the correlation between histologic chorioamnionitis and amniotic fluid cultures and found a prevalence of positive cultures of 38%. Acute inflammation of the chorionic plate and the umbilical cord were the most sensitive indicators of the presence of bacteria in the amniotic fluid.

Acute chorioamnionitis is associated with significant maternal morbidity and occasional mortality. The most frequent maternal morbidities are postpartum endometritis, puerperal septic thrombophlebitis, adult respiratory distress syndrome, and septicemia. Other problems associated with acute chorioamnionitis are the development of uterine contractions and fetal heart rate monitoring abnormalities that result in a high incidence of cesarean delivery and in intrapartum and postpartum bleeding.

Postpartum endometritis is a relatively frequent event in women with chorioamnionitis. However, this risk is less than the risk of neonatal infection. Only 5.1% of all women with chorioamnionitis that have vaginal deliveries develop postpartum endometritis, while 10–20% of their babies show clinical infection (Gunn, 1970). Maternal endometritis is five times more frequent when the mother with acute chorioamnionitis is delivered by cesarean section. Maternal infection occasionally may be severe and causes maternal mortality. Women with postpartum endometritis typically have postpartum fever and palpation of the abdomen reveals a tender uterus. The best approach to decrease the severity of this problem is to initiate aggressive administration of antibiotics during the antepartum period, as soon as the diagnosis is made. Because of the polymicrobial nature of the infection it is necessary to use triple antibiotic therapy or broad-spectrum agents. Antibiotic administration should continue until the woman has been afebrile for 24–48 hours.

Puerperal septic thrombophlebitis should be suspected in women who develop postpartum endomyometritis and despite overall improvement in the general condition continue to have chills and fever. The infection may be localized in the venous complex in the base of the broad ligaments or may involve one or both of the ovarian venous plexus. In some cases it is possible to palpate a tender mass in either upper side of the uterus. The diagnosis is confirmed by CT (computed tomography) scan or MRI (magnetic resonance imaging). Clinical improvement usually occurs soon after initiation of anticoagulation therapy.

Adult respiratory distress occurs frequently before delivery in women with chorioamnionitis. There is evidence suggesting that proinflammatory cytokines produced locally by the pulmonary epithelial cells or by pulmonary macrophages may be responsible for the production of the acute adult respiratory syndrome that occurs during infection. A decreased production of inhibitors of anti-inflammatory cytokines may be a contributory factor as well as an excessive amount of intravenous fluids. The association between pulmonary congestion and infection in the pregnant woman is so close that intrauterine infection should be suspected and ruled out in those with ruptured membranes or with spontaneous preterm labor who

develop adult respiratory distress syndrome. These patients usually respond to a combination of intravenous fluids restriction, furosemide, and delivery.

Acute chorioamnionitis has an inhibitory effect on uterine contractility (Mark et al., 2000). Once the infection is clinically apparent, the frequency, regularity, and intensity of uterine contractions are altered as well as the sensitivity of the uterus to oxytocin. As a result, the incidence of cesarean section is high (40%) as well as the incidence of bleeding during vaginal delivery (30.5%) or during cesarean section (60.7%). Labor abnormalities secondary to intrauterine infection are more common in nulliparous than in multiparous women. Furthermore, severe variable decelerations and decreased beat-to-beat variability are fetal heart rate abnormalities common in women with chorioamnionitis (Salafia et al., 1998).

The immediate and long-term neonatal complications of acute chorioamnionitis are frequent and severe. Low 5-minute Apgar score, respiratory distress syndrome (RDS), intraventricular bleeding/hemorrhage (IVH), periventricular leukomalacia (PVL), seizures in the first 24 hours of life, sepsis, and death are common occurrences in premature neonates delivered to mothers with chorioamnionitis (Alexander et al., 1998). Chronic lung disease (CLD) and cerebral palsy (CP) are some of the long-term consequences. The risk of these complications is inversely related to the gestational age at birth.

Subclinical chorioamnionitis

Subclinical chorioamnionitis is an infection of the products of conception without clinical signs or symptoms of disease. Subclinical chorioamnionitis occurs frequently in women in preterm labor, with ruptured membranes, or with incompetent cervix. Uterine contractions may be the only sign of a subclinical intrauterine infection. Frequently women with subclinical chorioamnionitis present with advanced cervical dilatation or with uterine contractions resistant to conventional treatment with tocolytic agents. In other cases the contractions subside with treatment, but after a few days fever develops and acute chorioamnionitis becomes obvious.

The diagnosis of subclinical chorioamnionitis is by amniotic fluid analysis. There are several amniotic fluid tests that can be used for this purpose, among them are the Gram stain and white cell count, determination of the concentrations of interleukin (IL)-6, glucose, lactate dehydrogenase (LDH), and aerobic and anaerobic cultures. The Gram stain is a simple and rapid test for the diagnosis of amniotic fluid infection (Romero et al., 1988). It can be performed in both centrifuged and noncentrifuged specimens. We prefer to centrifuge the fluid at 3000 rpm for 5 minutes, decant the supernatant, and use for the Gram stain one or two drops of the fluid rich in cellular elements that remains at the bottom of the tube. The presence of any bacteria is indicative of infection (positive predictive value of 100%). However, a negative Gram stain does not rule out the possibility of an infection localized in the decidua, of not shedding bacteria into the amniotic fluid, or of infection by organisms that are not detected by the Gram stain. Cultures for aerobic and anaerobic bacteria provide definite evidence of the presence of amniotic fluid infection. The most frequent isolates in amniotic fluid specimens are *U. urealyticum, Fusobacterium* spp., and *G. vaginalis* (Romero et al., 1989). The most frequent isolates from placentas of infants delivered prematurely are *U. urealyticum*, found in 47% of the cases and *G. vaginalis*, found in 26% of the cases (Hillier et al., 1988).

The presence of leukocytes in the amniotic fluid is a sign of fetal inflammatory response. When the leukocyte count is more than 20 cells per high-power field, the diagnosis of subclinical chorioamnionitis is almost certain. The leukocyte count in the amniotic fluid should be performed manually by a well-trained technician. The automated counting includes all the nucleated cells present in the fluid, including epithelial cells, giving false positive results. The presence of leukocytes in the amniotic fluid in the absence of bacteria recognized by the Gram stain is a situation suggestive of mycoplasma infection. In these cases the acridine orange stain may allow visualization of the mycoplasma in the amniotic fluid. In other cases the Gram stain and the cultures will be negative because the infection is localized in the decidua and the bacteria have not invaded the amniotic cavity.

The concentration of glucose in the amniotic fluid has been a relatively popular method for the fast, easy diagnosis of chorioamniotic infection. Unfortunately, the test is not perfect and different investigators have adopted different thresholds (≤ 5 mg/dl to ≤ 17 mg/dl) to indicate the presence or absence of infection. As expected, a high threshold increases the sensitivity of the test but lowers its positive predictive value. LDH has been measured in blood and in different body fluids as a marker of acute inflammation. One study (Garry et al., 1996) found that elevated amniotic fluid LDH is as sensitive and specific as the leukocyte count, Gram stain, and glucose in the prediction of a positive amniotic fluid culture.

The best marker of amniotic fluid infection is the concentration of IL-6 in the amniotic fluid. Romero (1993a and b) demonstrated that concentrations of IL-6 greater that 7.9 ng/ml in women with ruptured membranes and greater than 11.3 ng/ml in women with intact membranes are better predictors of positive amniotic fluid cultures than the Gram stain, leukocyte count, or glucose concentration. Unfortunately, determinations of IL-6 are not available for clinical use, and it is necessary to rely on other markers that can be measured rapidly for

this diagnosis. The sensitivity, specificity, and positive and negative predictive values of the Gram stain, leukocyte count, glucose, LDH, and IL-6 in the diagnosis of microbial invasion of the amniotic cavity in women with preterm labor and intact membranes and in women with preterm premature rupture of the fetal membranes will be found in the respective chapters about these conditions.

Since amniotic fluid analysis requires the performance of amniocentesis, there has been a great deal of interest in the development of methods to diagnose subclinical infection without using invasive procedures. One useful test is the determination of C-reactive protein (CRP) concentration in the maternal plasma. CRP is an acute-phase reacting protein, synthesized in the liver when an inflammatory process is present in any location in the body. This is a sensitive test to identify women who may have subclinical amniotic infection (Potkul et al., 1985). In the case of amniotic infection the most probable triggers for CRP synthesis are the cytokines produced by the macrophages and leukocytes present at the site of infection. This mechanism is supported by the correlation that exists between elevated CRP (>1.5 mg/dl) and elevated IL-6 levels (Burrus et al., 1995). This means that in the usual course of intrauterine infection the increase in amniotic fluid cytokines will precede the elevation in serum CRP. However, the time interval between the increase in amniotic fluid cytokines and the increase in maternal serum CRP most probably is not critical, and it has been suggested that women in preterm labor with normal CRP levels do not require amniocentesis for the purpose of ruling out intra-amniotic infection (Mazor et al., 1993).

CRP values equal to or above 0.8 mg/dl have high sensitivity and positive predictive value for the diagnosis of chorioamniotic infection (Dodds and Iams, 1987). CRP concentrations above this limit should be followed by repeated testing in 6, 12, or 24 hours depending on the clinical situation. An upward trend almost certainly indicates that chorioamnionitis is present. Similarly, values above 3 or 4 mg/dl almost certainly indicate infection. High levels of CRP (8 mg/ml and above) in women *without* symptoms of overt amnionitis usually represent a viral infection or an infection outside the uterus.

Extrauterine infections

Approximately 5–10% of patients in preterm labor have an infection outside of the uterus, most commonly in the urinary tract. Romero et al. (1988) presented evidence suggesting that extrauterine infections may cause preterm labor by a mechanism involving the production of interleukins and TNF by the maternal macrophages, which in turn trigger the production of prostaglandins by the amnion.

Approximately 25% of patients admitted to the hospital because of preterm labor have a urine sediment suggestive of UTI, although culture-proven infection is documented in only half of them. Also, the presence of group B streptococcus in the urine is associated with preterm labor and treatment to prevent recolonization reduced the incidence of the problem (Thomsen et al., 1987).

The association between asymptomatic bacteriuria and preterm birth is controversial. Kaas et al. (1970) suggested that asymptomatic patients with two or more urine cultures having more than 100,000 colonies of pathogenic bacteria per milliliter of urine have two to three times more risk of preterm labor than do controls with negative cultures. Some investigations have supported these conclusions whereas others have not. The overall weight of the evidence, however, seems to favor the existence of an association between asymptomatic bacteriuria and preterm labor (Romero et al., 1989).

Another extrauterine infection associated with preterm birth is gingivitis (Jeffcoat et al., 2001). The incidence of inflammatory gum disease is higher in women who deliver preterm than in those who deliver at term. The bacteria that proliferate in women with periodontal disease are similar to those found in placental cultures of women with preterm labor. It is possible that these bacteria may colonize the uterus by the hematogenous route, causing preterm labor.

Fetal inflammatory response syndrome

Leviton (1993) originally proposed that the inflammatory response of the host was the cause of the brain abnormalities associated with intrauterine infection. Growing evidence has accumulated during the last 10 years in support of this hypothesis. For microbiological and lung maturity studies, particularly important is a 3-year follow-up study of 123 preterm newborns who had amniocentesis (Yoon et al. 2000b). It was found that newborns that developed CP were born to women with high concentrations of IL-6 and IL-8, high white blood cell counts in the amniotic fluid, and with neutrophil infiltration into the umbilical vessels or the Wharton's jelly. This study strongly suggests that it is the fetal and not the maternal inflammatory response which is the factor that predisposes to CP.

The clinical symptoms and signs of the fetal inflammatory response syndrome are similar to those caused by severe fetal hypoxia. Fetal tachycardia, minimal or absent variability, severe variable or late decelerations, episodes of fetal bradycardia, and meconium in the amniotic fluid are indicators of nonreassuring fetal situations that may be caused by hypoxia or by inflammation. The presence of fever or any other evidence of overt or subclinical chorioamnionitis suggests fetal inflammatory response, and

their absence intrapartum hypoxia. The situation becomes more complex when infection and hypoxia coexist, and it is difficult or impossible to assess the relative contribution of each of these factors to the clinical picture.

At the time of birth the similarities between fetal inflammatory response and intrapartum hypoxia continue. The infants have poor tone and low Apgar scores which require intensive resuscitation. The umbilical cord gases are usually in the acidotic range. Seizures develop in the first few days of life as well as periventricular white matter abnormalities detected by ultrasound, CT scan, or MRI. In the majority of cases the clinical picture and the brain insult are attributed by the neonatologists and the pediatric neurologists to intrapartum hypoxia or "hypoxic-ischemic encephalopathy." The possibility that an inflammatory response to intra-amniotic infection is the cause of the neonatal problems is usually rejected because the amniotic fluid and neonatal cultures are negative.

The fetal inflammatory response syndrome is characterized biochemically by the production of proinflammatory cytokines, particularly IL-1β, IL-6, and TNF-α (Gomez et al., 1998; Yoon et al., 1996, 1997) and infants at risk of CP can be identified by measuring the concentration of IL-1, IL-6, and IL-8 in the amniotic fluid (Yoon et al., 1997, 2000b). Also, a fetal plasma IL-6 concentration greater than 11 pg/ml is the threshold above which fetuses with inflammatory response syndrome are identified (Gomez et al., 1998). These cytokines increase the permeability of the blood-brain barrier and have a direct cytotoxic effect on oligodendrocytes that are the cells responsible for the production of myelin. Brain development in the preterm infant is dependent on the availability of myelin and CP will result from the interference of cytokines with myelin production.

The histologic mark of the fetal inflammatory response is the presence of funisitis, defined as neutrophilic infiltration into the umbilical vessel wall or the Wharton's jelly (Yoon et al., 2000c). This lesion is associated with elevated fetal plasma IL-6 concentrations (Naccasha et al., 2001). The leukocytes infiltrating the umbilical cord are fetal in origin in contradistinction to those infiltrating the chorion and amnion that are a part of the maternal inflammatory response to infection. The correlation between funisitis and elevated umbilical cord plasma IL-6 concentration varies with the type of vessel involved in the inflammatory process. The most severe form of inflammation involving the arteries, the vein, and the Wharton's jelly is associated with the highest levels of IL-6. The concentration of IL-6 decreases when the inflammation is localized in the arteries and is even lower when the umbilical vein is the only structure affected (Kim et al., 2001).

A significant problem in the diagnosis and characterization of the fetal inflammatory response syndrome is the failure of conventional microbiologic techniques to identify the bacteria causing the infection. In up to 50% of cases of elevated amniotic fluid cytokines and negative cultures the infection is not detected by conventional microbiological techniques but could be evidenced by PCR assays (Hitti et al., 1997; Markenson et al., 1997; Yoon et al., 2000a). Similarly, a significant number of newborns with placentas showing funisitis have negative microbiological cultures suggesting that in those cases the fetal infection has escaped detection by conventional techniques. Yoon et al. (2000a) demonstrated that conventional cultures missed 40% of the amniotic fluid infections with *U. urealyticum*. An important clinical finding in that study was that women with positive bacterial fingerprints by PCR and negative cultures in the amniotic fluid had similar poor outcomes as found in women with positive amniotic fluid cultures.

Abnormal Placentation

Several evidences indicate that abnormal placentation may be one of the etiologic agents causing preterm birth. In as many as 40% of women who deliver preterm following preterm labor or PROM, histologic examination of the placenta shows that the spiral arteries have not completely experienced the physiologic changes necessary for the development of a normal pregnancy (Arias et al., 1993). In these cases, the placenta is small and has extensive infarction, fibrosis, and calcification. Histologic examination shows in addition to the inadequate development of the spiral arteries, spiral artery thrombosis, accelerated maturation, and placental infarcts. The compromise of the uteroplacental circulation is reflected in decreased fetal growth, and there is evidence indicating that among newborns delivered before term there are a high proportion of low-weight infants (Lackman et al., 2001). Most of these infants have advanced lung maturity and require little or no ventilatory support. Doppler studies of the uterine arteries have shown that the incidence of preterm labor is significantly higher in women with abnormal Doppler early in gestation (Strigini et al., 1995). All these evidences suggest that abnormal placental implantation causing decreased uteroplacental blood flow is a cause of preterm birth. In these cases the mechanism that triggers the activation of the final pathway or parturition is not known. The most commonly held hypothesis is that uteroplacental blood flow restriction causes fetal stress that, in turn, elicits the production of CRH and activation of the final pathway of parturition.

Preterm birth is also common in pregnancies with abnormalities in the morphology, implantation, or function of the placenta. Anatomic abnormalities such as battledore placenta, circumvallate placenta, and marginal insertion of the umbilical cord are frequently associated with preterm birth. These are uncommon problems and

the incidence of one of them, battledore placenta, is approximately 1 out of 1000 deliveries. The mechanism of preterm birth secondary to placental anatomic abnormalities is unknown.

Bleeding in the Choriodecidual Interface

Vaginal bleeding is frequently the first sign of a sequence of events leading to preterm birth. One type of bleeding characteristically associated with preterm birth occurs in abruptio placenta. In severe abruptio the onset of bleeding is followed by intense uterine activity that is usually resistant to tocolytic agents. Women with lesser degrees of abruptio usually present with vaginal bleeding, frequently erroneously classified as "bloody show," and frequent uterine contractions. In some cases ultrasonographic evaluation of the placenta shows alterations consistent with abruptio and the D-dimer test is strongly positive, indicating the presence of a retroplacental or intraplacental clot. Characteristically the uterine activity of these women is resistant to tocolytic agents and requires large amount of medication to achieve uterine quiescence. Recent investigations suggest that in the case of bleeding in the choriodecidual interface the agent that causes activation of the myometrium is thrombin (Phillippe et al., 2001).

Preterm birth is also common in women with placenta previa. It is possible that in women with previa the uterine contractions that normally occur during gestation cause separation of the placenta from its implantation site in the cervix and lower uterine segment, causing bleeding in the choriodecidual interface, thrombin release, and activation of the final pathway of parturition. Another possibility is that the uterine contractions are caused by stress activation of the fetal hypothalamic-pituitary-adrenal axis secondary to fetal growth restriction that is a common finding in women with abnormal placentation. In the majority of patients with placenta previa, contractions occur simultaneously or shortly after a bleeding episode and, similarly to what happens in women with abruptio, they are resistant to tocolysis. Mukherjee et al. (2003) from Kolkata (India) reported a high incidence of preterm labor following antepartum hemorrhage. The incidence following placenta previa was 23% as against 30% in cases of abruptio placenta.

Uterine Abnormalities

Congenital anatomic abnormalities of the uterus and cervix are present in 1–3% of all cases of preterm birth. They are the result of a failure in the fusion, canalization, or absorption of the Mullerian ducts during embryonic development. The most clinically significant of these conditions are the septate and the bicornate uterus. In these patients the incidence of spontaneous abortion is 27% and the incidence of preterm birth, if the pregnancy continues beyond 20 weeks, varies between 16 and 20%. The possibility that a congenital malformation of the uterus is present should be considered in all women with history of recurrent spontaneous midtrimester abortions or recurrent preterm birth and in women with recurrent malpresentations, such as breech and transverse lie. It is important that these conditions are diagnosed, because once they are identified it is possible to adopt corrective measures to avoid further preterm births and pregnancy losses. About 50% of these cases will benefit from surgical correction. The mechanism of preterm labor in patients with anatomical abnormalities of the uterus is unknown.

Kondaveeti et al., (2003) investigating patients of repeated pregnancy loss reported uterine septum in 7.0% cases and bicornuate uterus in 3.5%. After surgical correction of the defect 20 out of 35 patients became pregnant and 18 of them progressed to viability.

Uterine Overdistention

Excessive stretching of the uterus such as that happening in multiple gestations or in women with polyhydramnios is capable of initiating premature labor or premature rupture of the fetal membranes. Multiple gestations represent between 12 and 25% of all preterm deliveries. The majority of preterm deliveries in multiple pregnancies are due to infection manifested as incompetent cervix, preterm labor, or preterm rupture of the membranes but in some cases the cause is uterine overdistention. The mechanism that triggers the common pathway of parturition in the case of uterine overdistention is not known but most probably is through early activation of CRH and the physiologic pathway of parturition. Another possible mechanism is that mechanical force may lead to activation of protein kinase C and mitogen-activated protein kinases and increased expression of G proteins and other substances that induce myometrial contractility.

Abnormalities of the Cervix

Approximately 5% of preterm births are the result of anatomic or physiologic abnormalities of the uterine cervix. Classical examples of anatomic abnormalities of the cervix causing preterm birth are those found in women exposed to diethylstilbestrol during intrauterine life and women who had extensive conizations or LEEP (loop electrosurgical excision procedures) (Nohr et al., 2007) because of cancer of the cervix. However, these are relatively rare occurrences, and the large majority of preterm deliveries usually diagnosed as incompetent cervix are cases of early activation of the common pathway of parturition secondary to chorioamniotic infection. This topic is extensively analyzed in Chapter 10 of this book.

Shirodkar (1955) from India described his new method of operative treatment for habitual abortions in the second trimester of pregnancy which received worldwide acclaim. The original principle of tightening of the internal cervical os has been simplified and several modifications have been successfully introduced and practiced. Sardesai and Mittal from Solapur (2001) reported 66% success rate with their modified technique for cervical incompetence where earlier surgical attempts had failed.

Preterm Birth of Unknown Origin

It is not possible to establish precisely the cause of preterm birth in approximately 20–30% of the cases. The search for the trigger of parturition in these cases is an area of active investigation.

INDICATED PRETERM BIRTH

One-third of preterm births are due to the intervention of the obstetrician in situations where delivery is indicated because of maternal or fetal complications. The conditions most commonly causing maternal and fetal jeopardy requiring preterm birth are preeclampsia and severe fetal growth restriction secondary to uteroplacental insufficiency. Other obstetrical problems frequently demanding interruption of the pregnancy are placenta previa and abruptio placenta. Rh isoimmunization, maternal diabetes, maternal cardiac disease, chronic hypertension, chronic renal disease, and sickle cell anemia are also occasional contributors to indicated preterm birth. These conditions are reviewed in different chapters of this book. A summary of the relative frequency of clinical conditions resulting in preterm birth is shown in Table 7-2.

Table 7-2. Clinical syndromes resulting in preterm birth

Syndrome	Relative frequency (%)
Preterm premature rupture of membranes	35
Preterm labor with intact membranes	30
Incompetent cervix:	
Secondary to early preterm labor	12
Secondary to cervical conditions	3
Indicated preterm birth:	
Hypertensive disorders	12
Fetal growth restriction	5
Antepartum bleeding	3

MATERNAL AND FETAL CONSEQUENCES OF PRETERM BIRTH

Maternal mortality and morbidity as a consequence of preterm birth are rare. The most common maternal complication is postpartum endometritis. However, most women who develop endometritis respond rapidly to the administration of antibiotics. In contrast to the good maternal prognosis following preterm birth the effect of this condition on the fetus may be devastating, depending on the gestational age at the time of birth. Neonatal survival for preterm infants is directly related to their gestational ages and birth weights. Tables 7-3 and 7-4 show the neonatal survival and severe morbidity by birth weight and gestational age in tertiary care facilities in USA. It is clear from Table 7-4 that survival figures are acceptable after 26 weeks and are excellent after 28 weeks. However, survival is not the only consideration. Severe morbidity, such as IVH, RDS, BPD (bronchopulmonary dysplasia), NEC (necrotizing enterocolitis), is common before 28 weeks and extends into the 30–32 weeks' range.

Prematurity may be classified according to gestational age into three groups: severe prematurity, when birth occurs before 30 weeks; intermediate prematurity, when birth occurs between 30 and 34 weeks; and late or mild

Table 7-3. Neonatal survival and morbidity at different birth weights

Birth weight (g)	Survival	RDS	Sepsis	IVH III–IV	NEC
500–749	65.4	100	34.6	23.4	23.1
750–999	87.3	92.9	14.3	9.8	3.6
1000–1499	98.6	86.3	15.1	3.6	9.6
1500–1999	99.0	36.6	3.0	0.8	4.0
2000–2499	97.6	27.8	1.6	0	0
2500–2999	99.2	28.0	3.0	0	0
≥ 3000	99.6	11.4	3.1	0	0

RDS = respiratory distress syndrome; IVH = intraventricular bleeding; NEC = necrotizing enterocolitis.

Table 7-4. Neonatal survival and morbidity at different gestational ages

Gestational age (weeks)	Survival	RDS	Sepsis	IVH III–IV	NEC
≤ 23	37.5	100	25.0	37.5	25.0
24	72.7	100	36.4	27.3	18.2
25–26	89.9	100	22.2	11.1	22.2
27–28	91.1	97.8	24.4	15.6	2.2
29–30	100	87.2	10.3	5.1	5.1
31–32	98.4	58.1	1.6	3.2	0
33–34	100	30.9	0.8	0.8	0
35–36	99.2	29.5	3.0	0	0
37–38	97.8	18.8	4.3	0	0
39–40	99.2	3.8	3.1	0	0
>40	100	0	5.9	0	0

RDS = respiratory distress syndrome; IVH = intraventricular bleeding; NEC = necrotizing enterocolitis.

prematurity, between 34 and 37 weeks. All the obstetrical resources should be used to avoid severe and intermediate prematurity and these births should occur in tertiary centers with adequate neonatal intensive care facilities. Mild prematurity can be managed in hospitals with level II nurseries.

To adequately cover the large number of problems that may occur in preterm infants as a consequence of being delivered too early is beyond the scope of this book. However, we need to look closely to RDS and IVH because these two conditions are the most important causes of neonatal mortality and morbidity in the preterm infant. We will also comment on obstetrical aspects of CP, devastating long-term sequelae of preterm birth.

Neonatal RDS

Neonatal RDS is a condition characterized by grunting, intercostal retraction, nasal flaring, cyanosis in room air, and the requirement of oxygen to maintain adequate arterial oxygen pressure. There are multiple causes of neonatal RDS. They include (a) transient tachypnea of the newborn, caused by wet lungs or by transient intrapartum asphyxia; (b) congenital pneumonia resulting from intra-amniotic infection; (c) pulmonary hypertension; and (d) congenital defects such as diaphragmatic hernia or pulmonary hypoplasia secondary to Potter's syndrome. However, the most frequent cause of neonatal RDS is hyaline membrane disease (HMD). Chest x-ray examination is essential in differentiating HMD from other causes of RDS.

HMD occurs because of inadequate production of pulmonary surfactant by the alveolar cells type II of the newborn. The surfactant is a heterogeneous mixture of lipids and proteins in which the predominant component is the phospholipid dipalmitoyl phosphatidylcholine (DPPC). The surfactant spreads in the lung tissue–air interface, preventing alveolar collapse during expiration and allowing the alveoli to open easily at the next inspiration. When surfactant is not present in adequate amounts, the alveoli collapse during expiration and each inspiration will require considerable effort. This situation rapidly leads to fatigue, decreased respiratory effort, hypoxia, cyanosis, acidosis, and eventually death.

DPPC is the main component of the pulmonary surfactant. DPPC accumulates in osmophilic structures called lamellar bodies that consist of multiple closely packed phospholipid bilayers. The lamellar bodies are released from the alveolar cells into the alveolar fluid and secreted into the amniotic fluid. This makes possible to assess the biochemical maturation of the fetal lungs by determining the concentration of lamellar bodies or by analysis of the phospholipid composition of the amniotic fluid.

Tests for assessment of fetal pulmonary maturity

The first reliable test to determine the biochemical maturation of the fetal lungs was the measurement of the lecithin to sphingomyelin ratio (L/S ratio) in the amniotic fluid (Gluck et al., 1971). This test involves extraction of the amniotic fluid with chloroform/methanol, precipitation of surface active phospholipids with cold acetone, and determination of the L/S ratio by thin-layer chromatography. The finding of a mature L/S ratio, 2.3 or greater, predicts with 95% accuracy the absence of HMD. The 5% of cases in which the prediction is incorrect correspond to infants of diabetic mothers or to infants born after significant intrapartum asphyxia. The L/S ratio is not a good predictor of lack of pulmonary maturity and when the L/S ratio is less than 2.3, only 54% of the newborns will develop HMD. This high proportion of false predictions of pulmonary immaturity is a serious defect of the L/S ratio, because pregnancies in which early delivery is desirable may be prolonged unnecessarily. The L/S ratio is not useful if the amniotic fluid is contaminated with blood or meconium or is collected from a vaginal pool.

The false positive answers obtained with the L/S ratio can be decreased by the simultaneous determination of phosphatidyl glycerol (PG) in the amniotic fluid sample. PG appears in the amniotic fluid usually after 36 weeks and is a marker of the final biochemical maturation of the fetal lungs. If PG is present in a sample with a mature L/S ratio, the infant will not develop HMD even if the pregnancy is complicated by maternal diabetes or by intrapartum asphyxia. How PG works is not precisely known, although it has been suggested that it may stabilize the surfactant complex. The measurement of PG in the amniotic fluid has been facilitated by the availability of immunological slide testing, which is rapid, precise, and inexpensive. However, the immunological test is not as sensitive for detecting small amounts of PG as the chromatographic technique.

A quantitative determination of DPPC may be used instead of the L/S ratio to assess fetal pulmonary maturity. DPPC is not present in blood, meconium, or in vaginal secretions, allowing its use in contaminated amniotic fluid samples. DPPC can be separated from other phospholipids because its unsaturated fatty acid can be selectively oxidized, changing its chromatographic migration and facilitating its identification. A DPPC concentration greater than 500 μg/dl is predictive of fetal lung maturity (FLM). A comparison between DPPC and L/S ratio (Torday et al., 1979) showed significant advantages for the DPPC method, which had a 97% positive predictive value (90% for the L/S ratio) and an 83% negative predictive value (55.5% for the L/S ratio). When the fluid is stained with blood, meconium, or vaginal products,

DPPC may be the best way to evaluate pulmonary maturity. Despite its advantages DPPC determination is not commonly used.

The Abott "TDx - FLM" test is an application of fluorescence polarization. The test is based on the competitive binding between albumin and surfactant for a ligand named PC16. This substance exhibits increased fluorescence polarization when it is bound to albumin and fluorescence decreases when it is bound to surfactant. Since the albumin concentration in the amniotic fluid remains relatively constant during the third trimester of pregnancy, decreases in fluorescence polarization of the fluid reflect increased concentration of surfactant. This test is rapid, quantitative, and requires a small amount of fluid. An FLM concentration of greater than 70 mg/g has a 95% predictive value for fetal pulmonary maturity. The accuracy of the FLM test compares favorably with the L/S ratio and the PG tests (Hagen et al., 1993).

Measurement of the concentration of lamellar bodies in the amniotic fluid is an excellent test to assess fetal pulmonary maturity. The amniotic fluid specimen is centrifuged at 500 rpm for 3 minutes to remove cellular debris and the lamellar bodies quantified using a hematologic Coulter counter calibrated for the size parameters used for platelet counts. The lamellar body concentration increases with gestational age and correlates well with the L/S ratio and with fetal pulmonary maturity. The test is quick and readily available and can be used as initial screening for FLM. A lamellar body count of less than 8000 is 100% specific for fetal pulmonary immaturity. A count of 32,000 or greater is 98% specific and has a 99% positive predictive value for fetal pulmonary maturity. Values between 8000 and 32,000 require additional testing of the fluid with the L/S ratio (Mol et al., 1999). Other investigators use 30,000 as the cutoff limit.

Acceleration of fetal pulmonary maturity with steroids

It is possible to accelerate the maturation of the fetal lungs with steroids in patients at high risk for preterm delivery. The seminal study on this area was by Howie and Liggins (1977) in New Zealand. They had 411 patients in a betamethasone-treated and 410 in a control group. The incidence of RDS was 8.8% in the treated versus 28.7% in the control group, indicating a significant difference. The perinatal mortality was significantly lower in the corticosteroid-treated group. Similar studies in other parts of the world have confirmed the original observation of Howie and Liggins and have demonstrated a second beneficial effect of steroids in reducing the incidence and severity of IVH and PVL (Maher et al., 1994).

Another study (Elimian et al., 1999) suggests that the effectiveness of antenatal steroids varies with the obstetrical population studied. Their effect is optimal when given to women with preterm labor and intact membranes. In women with preterm PROM, the effect on the prevention of RDS is less clear but the protective neurological effect is still present. In women who require early delivery because of fetal growth restriction or severe preeclampsia (indicated preterm birth), minimal or no beneficial effects of steroid administration were found. Other investigators have found that steroids are safe and efficient in the prevention of RDS in women with preeclampsia.

Several questions are frequently asked about glucocorticoids and FLM. One is the minimal time necessary for the drug to have a protective effect on the fetus. According to Howie's and Liggins' study (1977), 24 hours seems to be the minimal time necessary to obtain a significant effect. Another question is the duration of the drug effect. In the study by Howie and Liggins (1977) when infants were delivered between 7 and 21 days after treatment, there was a higher incidence of RDS in betamethasone-treated infants (21.2%) than in the control group (7.1%). These data suggest that the glucocorticoid effect is transient and this was the rationale behind the practice of administering repeated doses of steroids to high-risk women whose delivery was delayed more than 7 days after the initial treatment. However, recent studies have demonstrated that repeated courses of steroids do not alter the outcome of the newborn and are associated with adrenal suppression, decreased fetal growth, and increased perinatal death rate (Banks et al., 1999; French et al., 1999). Even studies showing improved postnatal lung function after repeated prenatal steroid administration suggest that this effect is achieved at the cost of impaired fetal growth and altered neurological development (Jobe et al., 1998). The current practice is administration of glucocorticoids only once, i.e., when it is estimated that delivery is going to occur.

Another frequently asked question concerns the gestational age at which glucocorticoid treatment is effective. According to the data of Howie and Liggins (1977) the effect of therapy is best in infants between 30 and 32 weeks, but there is also a significant reduction in the incidence of RDS in babies between 28 and 30 weeks and in those between 32 and 34 weeks. Thus, for women in preterm labor, glucocorticoids should be administered in any situation in which FLM is desirable from viability to 34 weeks of gestation. At less than 26 weeks, the effect of steroids in the fetal lung is almost negligible but they may have a protective effect for IVH. After 34 weeks, the risk of IVH is small and steroids have little influence on the respiratory outcome of the newborn.

Surfactant replacement therapy

The outcome of babies with HMD has changed dramatically with the development of surfactant replacement therapy.

Fujiwara et al. (1980) reported a dramatic improvement in gas exchange in infants with severe HMD treated with a modified bovine surfactant. This observation stimulated the development of clinical trials, and today surfactant treatment is a well-established therapeutic modality for infants with HMD. Surfactant is a complex mixture of phospholipids and proteins. The most important phospholipids are DPPC and PG. The most important proteins are surfactant-associated-proteins A, B, and C.

Both natural and artificial surfactants have been used for the treatment of neonatal HMD. Natural surfactant can be obtained from human amniotic fluid, cow, calf, and pork lungs. The process of preparation of animal surfactants causes the loss of apoprotein A. The best known of the natural surfactants is "Survanta" that is obtained from bovine lungs. The artificial surfactants contain no associated proteins. They are made of mixtures of DPPC and PG with or without emulsifiers. The best known are "Exosurf" and "ALEC."

Surfactant can be used as soon as a preterm baby is delivered and before the development of symptoms and signs of HMD. It also can be used after symptoms have developed. It is administered via endotracheal tube. It is given in one or multiple doses according to different protocols. The response to surfactant administration is immediate and consists of decreases in the oxygen concentration and pressure necessary to ventilate the infant. The effect may be transient and repeated doses may be necessary. There is no increase in neurodevelopmental problems in preterm survivors following surfactant treatment. The use of surfactant has been an important factor in the present survival rate of preterm infants. As shown in Table 7-4, survival rates of 70% for newborns of 24 weeks are possible today.

Intraventricular Hemorrhage

IVH is one of the most serious complications of preterm birth and is one of the three best characterized causes of cerebral damage in the preterm infant, the other two being chorioamnionitis and cerebral ischemia. The most common site of bleeding in the preterm infant is the subependymal germinal matrix (germinal matrix hemorrhage, or GMH). The blood vessels in this particular region of the fetal brain are fragile because of deficient deposition of basal lamina and delayed junction between the endothelial cells and lack an adequate supporting glial structure. Preterm infants have inadequate vascular autoregulation and cerebral blood flow has similar fluctuations as those in the systemic blood pressure. The fragile blood vessels of the germinal matrix rupture easily with changes in systemic blood pressure which commonly occur in the premature infant. To further aggravate the situation, there is an abundance of plasminogen activator in the germinal tissue, causing locally excessive fibrinolysis, and this may be the reason why the bleeding frequently continues until the blood fills the ventricular system. However, not all subependymal hemorrhages progress into the ventricular system, and 40% are confined to their place of origin.

The long-term consequences of GMH/IVH are directly related to the severity of the bleeding. The severity of IVH can be estimated by ultrasound scanning and CT scan of the baby's head and is classified as grade I–IV, depending on the characteristics of the bleeding. Grade I is bleeding confined to the germinal matrix. In grade II the bleeding extends to the lateral ventricles. Grade III is IVH with ventricular enlargement and grade IV is bleeding extending into the cerebral parenchyma. Mild and even moderate degrees of bleeding (grades I and II) are usually associated with good prognosis and with recovery without neurological sequelae. In contrast, severe bleeding (grades III and IV) may be fatal, and survivors frequently develop hydrocephaly and long-term disabilities. The most common problem following severe IVH is the development of hydrocephalus that occurs in approximately 35% of the cases and usually is the result of obstructive arachnoiditis in the ventricular system. When intraparenchymal bleeding and periventricular hemorrhagic necrosis occur, the result may be formation of periventricular cysts (PVL) and the ulterior development of motor deficits similar to those seen in CP caused by hypoxia or chorioamnionitis. Some investigators believe that when IVH is caused by prematurity the bleeding is located in the germinal matrix and the ventricles, while parenchymal bleeding indicates the presence of an ischemic-hypoxic insult in addition to prematurity. Irrespective of the mechanism, the combination of IVH and PVL will result in complex and severe neurological lesions with a wide spectrum of clinical expressions.

IVH usually occurs during the first 5 days of life but more frequently happens in the 1st and 2nd days (75% of the cases). In one study 20% of the cases occurred during the 1st hour of life (Shaver et al., 1992). It can be asymptomatic or it may result in respiratory depression, neurological depression, hypotension, falling hematocrit, and bulging anterior fontanelle. The diagnosis is made by ultrasound that is performed routinely in preterm infants since approximately 50% of the cases are clinically silent.

Several studies have tried to identify preventable obstetrical events placing the fetus at high risk for IVH. The most common associations are extreme prematurity, birth weight less than 1500 g, and neonatal complications. Labor, intrapartum hypoxia, and blood pressure fluctuations are other important factors associated with IVH in the preterm infant. Hypoxia causes damage to the vascular endothelium of the fragile veins of the preterm

infant and this, along with the venous congestion caused by hypoxia, may result in rupture of blood vessels. A contributory factor may be elevated plasma osmolarity secondary to the overenthusiastic use of sodium bicarbonate in the course of the infant's resuscitation.

Several studies suggest an association between labor and IVH in preterm infants. In one prospective study, 40 neonates less than 35 weeks' gestation had ultrasound examination of their heads as soon as possible after birth and 17 (42.5%) had IVH in the 1st day of life. Infants with GMH and IVH had significantly longer labors, significantly longer second stages of labor, and significantly slow rates of cervical dilatation. If the duration of labor was less than 12 hours, the incidence of GMH/IVH was 33% and it was 100% if labor was longer than 12 hours (Meidell et al., 1985). In another prospective study of 79 infants with birth weight less than 1750 g that had cranial ultrasound within 1 hour after birth (Anderson et al., 1988), it was found that the incidence of GMH/IVH was 39.6% after vaginal birth, 50% when cesarean was done in the active phase of labor, and 7.7% when the cesarean was performed before the active phase of labor. They also found that 83.3% of infants born by cesarean in the active phase of labor progressed from grade I to grade III or IV while none of those delivered before the active phase of labor had progression of their condition. Leviton et al. (1991) in a study of 449 newborns with birth weight less than 1500 g found that babies delivered vaginally were more likely to have GMH than babies delivered by cesarean and that GMH in babies delivered by cesarean occurred only in women with chorioamnionitis. In a prospective study of 229 infants with birth weight between 600 and 1250 g it was found that 43 had GMH/IVH within 12 hours of life. The risk factors identified were the mode of delivery (the incidence of GMH/IVH was 32.5% in infants delivered by cesarean versus 56.4% in infants having vaginal birth), use of tocolytic agents, and cephalic presentation. Progression of bleeding occurred in 27.9% of infants delivered vaginally versus 3.2% in those delivered by cesarean, suggesting that labor may be an important factor in the progression of bleeding. In another study (Anderson et al., 1992) progression of bleeding occurred in 66.7% of the cases if cesarean was done in the active phase of labor, in 9.9% if cesarean was done during the latent phase of labor, and in 6.7% if the cesarean was done in women who were not in labor. Another prospective study (Ment et al., 1992) of 505 preterm infants between 600 and 1250 g birth weight, assessed within 12 hours of birth found an incidence of IVH of 29% in infants delivered by cesarean versus 55% when delivery was vaginal. Finally, a large study of 1607 infants with birth weight 500–1500 g found that vaginal delivery was associated with increased risk of IVH and the risk was greater in infants exposed to labor and when labor duration was greater than 12 hours (Hansen and Leviton, 1999). When adjustments were made for the presence of placental vasculitis, the association of IVH with vaginal delivery was lost but the association with labor persisted after adjustment for placental infection. In conclusion, the evidence indicating that labor is the main intrapartum event associated with GMH/IVH is compelling.

Intrapartum Hypoxia and Acidosis

There are important differences in the pathophysiology and the clinical manifestations of hypoxia-ischemia between preterm and term infants. In term infants the neurological lesion caused by ischemia-hypoxia affects predominantly the subcortical white matter and the basal ganglia of the brain. In severe cases the basal ganglia and the thalamus acquire a marbled appearance recognized as "status marmoratum." These lesions manifest clinically as spastic quadriplegia or as dyskinetic syndromes with abnormal athetotic or choreic movements. Hypoxia-ischemia in the premature are characterized by necrosis of the periventricular white matter and given the name of periventricular leukomalacia, or PVL. The preterm infant is more severely affected by hypoxia and acidosis that the fetus at term. The reasons for this phenomenon are varied and include relatively poor buffering capacity, presence of border zones or watershed regions in the periventricular white matter, poor autoregulation of cerebral blood flow, and increased vulnerability of the vascular system and the developing oligodendrocytes to oxygen deficits. As a consequence of these and other factors, ischemia and hypoxia will be severe in the periventricular white matter and the resulting ischemic necrosis will cause the development of cystic cavities. Astrocyte proliferation and infiltration by microglia eventually will cause decrease in the size of the cysts. This lesion is characterized by gliosis or periventricular cysts in the watershed area between the ventriculopetal and ventriculofugal components of the arterial circulation of the brain. This lesion is characteristic of a hypoxic-ischemic insult but not necessarily of IVH because in IVH the bleeding originates in the germinal matrix rather than in the watershed area of the brain. However, IVH may be associated with PVL when the IVH causes hypotension leading to hypoperfusion and ischemia of the periventricular white matter and also when prematurity and intrapartum hypoxia coexist. Differences in the origin and severity of the bleeding will cause differences in the clinical expression of the cerebral damage, and ischemia-hypoxia and amniotic infection usually result in severe forms of CP while the majority of uncomplicated cases of IVH have a better prognosis.

The periventricular white matter necrosis associated with PVL affects the corticospinal tracts controlling movement of the extremities, causing preferentially a form of CP known as spastic diplegia. The most common manifestation of spastic diplegia during infancy is increased tone of the lower extremities. After 1 year of age the motor function abnormalities of the lower extremities become apparent. At age 3, there is marked adduction of the thighs, abnormal flexion of the knees, and internal rotation of the hips and deformities of the feet are there. In mild cases the symptoms are limited to the lower extremities but in severe cases there is limitation of the upper extremities movements and poor hand function. Mental retardation and visual, hearing, and other perceptual abnormalities are common.

In addition to the differences in histopathologic findings and long-term clinical manifestations, term and preterm infants differ significantly with respect to the symptoms that they exhibit during the immediate neonatal period. Intrapartum hypoxia severe enough to cause severe neurological damage in the term infant is universally preceded by a complex of symptoms and signs recognized as neonatal encephalopathy. On the other hand, an intrapartum hypoxic-ischemic insult in the preterm infant has unspecific signs that are difficult to identify in infants that frequently are critically ill as a result of prematurity.

Cerebral Palsy

CP is a chronic, nonprogressive condition, with onset early in life, characterized by abnormal movements and posture. CP is a deeply incapacitating condition requiring long-life multidisciplinary support. The effects of CP on the quality of life of the individual affected and the members of his/her family are devastating. The occurrence of CP is directly related to the gestational age at birth. When delivery occurs at 23–24 weeks, approximately 54% of the survivors will have severe neurological and/or developmental disabilities. At 24 weeks the prevalence of severe disability is approximately 45% but it decreases dramatically after 32 weeks and is minimal at term.

The use of advanced methods of neuroimaging, particularly MRI, have had a significant impact in the understanding of the characteristics of the ischemic-hypoxic insult to the developing brain. One of the most important findings is that loss of signal on T1-weighted spin-echo MRI in the posterior limb of the internal capsule is a reliable sign of severe hypoxic-ischemic injury. The reason behind this finding is that this is the first area to myelinate in the immature brain. The MRI permits the early detection of other signs of acute perinatal insult such as brain swelling, focal or global loss of gray–white matter differentiation, and abnormal signal intensity in the basal ganglia, thalami, and posterior limb of the internal capsule. On the other hand, ventricular dilatation, porencephalic cysts, focal infarction, asymmetries, and developmental abnormalities are findings suggestive of antenatal insult or developmental abnormalities.

For many years CP has been attributed to the occurrence of intrapartum hypoxia (Box 7-1). Epidemiologic studies suggest that the incidence of CP secondary to perinatal events is 8–15% in the studies of Mercuri et al. (1995, 1999) and 28% in studies performed in Sweden (Hagberg et al., 2001). Recent MRI studies found evidence of acute insult in the immediate perinatal period in 80% of term newborns with neonatal encephalopathy (Cowan et al., 2003). These figures are not in contradiction because the populations under study are different and the contribution of intrapartum events to the total number of infants with CP identified in population studies is relatively low while the incidence of acute hypoxic perinatal insult in newborns with neonatal encephalopathy is quite high.

There is a consensus among academic and professional obstetrical associations in the Western World (McLennan, 1999) about the essential criteria that should be met before intrapartum events may be considered to be the cause of CP (Box 7-2). The requirement of metabolic acidosis demonstrable by umbilical cord blood gases or early

BOX 7-1

Some causes of cerebral palsy other than intrapartum hypoxia

- Maternal infection (chorioamnionitis)
- Fetal infection (CMV, rubella, varicella)
- Fetal inflammatory response syndrome
- Metabolic diseases (aminoacidurias, fatty acids, mitochondrial diseases, congenital hypothyroidism)
- Congenital syndromes (Smith–Memli–Opitz, Cornelia de Lange, Beckwith–Wiedemann)
- Chromosomal abnormalities (T21, T18, T13)
- Brain malformations (holoprosencephaly, absent corpus callosum, Dandy–Walker, porencephalic cysts)
- Maternal or fetal thrombophilia (factor V Leiden, prothrombin promoter mutation, protein S, protein C)
- Twin–twin transfusion syndrome
- Postnatal causes (trauma, neonatal pulmonary failure, low perfusion status)

BOX 7-2

Essential criteria to define an intrapartum event as possible cause of cerebral palsy

1. Evidence of metabolic acidosis in intrapartum umbilical arterial blood or very early neonatal blood samples (pH < 7.0 and BD (base deficit) ≥ 12.0 mmol/L)
2. Early onset of moderate or severe neonatal encephalopathy in infants ≥ 34 weeks' gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type
4. Exclusion of other identifiable etiologies such as trauma, coagulation, or genetic disorders

(less than one hour) neonatal blood gases and the presence of neonatal encephalopathy are the two criteria that are most important to the obstetrician because it is highly improbable that CP is the result of intrapartum events if these criteria are not present. Both these criteria should be present and neither of them in isolation is an absolute indicator of intrapartum events. Umbilical or neonatal blood gases indicating metabolic acidosis occur in 1–2% of all deliveries, but the large majority of these babies do not develop neonatal encephalopathy or CP. If no blood gases are obtained at the time of delivery or within 1 hour in the neonatal period, it is impossible to say with certainty that intrapartum hypoxia was the cause or contributed to the development of CP and this linkage should rest on the demonstration of a series of criteria that together suggest intrapartum timing, although individually they are nonspecific (Box 7-3). Neonatal encephalopathy is a required criterion to attribute CP to intrapartum events but by itself and in the absence of umbilical cord or neonatal blood gases, evidence of acidosis is not absolute proof of intrapartum hypoxia or asphyxia, because there are multiple causes for this syndrome (Box 7-4). The most common cause of neonatal encephalopathy in the absence of hypoxia-ischemia is the fetal inflammatory response syndrome that should be the prime suspect when CP occurs in the context of chorioamnionitis or maternal fever during labor.

One of the most important and frequent causes of neonatal encephalopathy and CP is intrauterine infection.

BOX 7-3

Criteria that together suggest an intrapartum event that may be responsible for cerebral palsy but by themselves are not specific

1. A sentinel hypoxic event occurring immediately before or during labor
2. A sudden, rapid, and sustained deterioration of the fetal heart rate pattern usually following the sentinel event where the pattern was previously normal
3. Apgar scores of 0–6 for longer than 5 minutes
4. Early evidence of multisystem involvement
5. Early imaging evidence of acute nonfocal cerebral abnormality

BOX 7-4

Nonhypoxic causes of neonatal encephalopathy

- Fetal inflammatory response syndrome
- Fetal hypoglycemia
- Fetal infection
- Fetal congenital disease
- Maternal infection
- Fetal metabolic disorders
- Toxic effects of drugs
- Congenital myopathies

The evidence supporting this causal association is robust and a meta-analysis of 229 publications has shown that clinical and histologic chorioamnionitis are significant risk factors for CP and cystic PVL (Wu and Colford, 2000). Also, it is well known that newborns with proven sepsis or born to infected mothers are at increased risk for the development of CP (Murphy et al., 1995; Perlman et al., 1996; Verma et al., 1997). Furthermore, the development of fever during labor, a sign usually associated with infection or with epidural anesthesia, has a strong correlation with the development of neonatal seizures (3.3% versus 0.2% for afebrile) that commonly are a forbearer of CP (Lieberman et al., 2000). Another study (Impey et al., 2001) of 4915 low-risk women followed prospectively during labor found that encephalopathy developed in 7 of 16 newborns (43.8%) whose mother's labor was complicated by intrapartum fever. The odds ratio for fever and CP was 4.72. This is higher than the odds ratio for CP of babies with metabolic acidemia (2.2) or for admission to the NICU (neonatal intensive care unit) (1.78). For microbiologic and lung maturity studies, more evidence in favor of an association between intra-amniotic infection and CP has been provided by studies of preterm singleton newborns who had cordocentesis or amniocentesis. Infants with periventricular cystic lesions or persistent increased periventricular echogenicity with definite periventricular tissue loss diagnosed by neurosonography have higher concentrations of IL-6 in umbilical cord plasma, higher frequency of acute histologic amnionitis, and increased levels of IL-1β and IL-6, and TNF-α in the amniotic fluid than normal infants (Yoon et al., 1996, 1997). TNF and IL-6 are capable of altering the blood–brain barrier and inducing oligodendrocyte damage. Immunohistochemical studies have demonstrated overexpression of these compounds in the microglia of PVL lesions (Deguchi et al., 1996; Yoon et al., 1997). The relationship between perinatal infection and CP is apparent in both term (Grether and Nelson, 1997) and preterm infants (Perlman et al., 1996) and applies also to extrauterine infections (Mays et al., 1995). Chorioamnionitis may be responsible for about 12% of the cases of spastic CP in term infants and about 28% of the cases in preterm babies (Schendel et al., 2002).

The current understanding of the mechanism of production of CP in women with chorioamnionitis is that in some fetuses bacterial infection stimulates the production of a fetal inflammatory response syndrome, characterized by increased synthesis of proinflammatory cytokines that affect the permeability of the blood–brain barrier and have direct cytotoxic effects on the oligodendroglia (Wu and Colford, 2000; Yoon et al., 2000b). It seems that the exaggerated fetal inflammatory response rather than the specific bacterial insult on the brain is the mechanism of brain damage. Therefore, the key to the prevention of CP in the context of chorioamnionitis

may be the pharmacologic blockade of the fetal inflammatory response or stimulation of the production of anti-inflammatory cytokines.

Most fetuses exposed to intra-amniotic infection develop inflammatory responses that do not lead to CP. The question to be solved in the next few years is the identification of factor(s) that predisposes some fetuses to have an exaggerated inflammatory response, leading to CP. The most attractive hypothesis is that the intensity and the quality of the inflammatory response and therefore the possibility of CP are genetically determined. Certain genotypes have alterations in the promoter regions of proinflammatory cytokines. Stimulation of the synthesis of cytokines in these individuals will result in higher than normal production, increasing their vulnerability to CP when exposed to intrauterine infections.

The clinical expression of the brain damage caused by ischemia-hypoxia depends on several factors that include but are not limited to the acuity or severity of the hypoxic episode, the localization of the histologic lesions in the brain, and the gestational age of the fetus when the hypoxic insult occurred. Acute, severe, prolonged intrapartum hypoxia in a previously normal, term fetus usually results in ischemic lesions of the thalamus and basal ganglia (caudal nucleus, putamen, globus pallidus), giving a marble aspect to these structures during macroscopic examination that is recognized as "status marmoratum." The consequences of this extensive neurological damage are profound mental retardation, severe spastic paresis, and involuntary choreic or athetotic movements (spastic dyskinesia) of all limbs. Chronic hypoxia in term fetuses affects predominantly the subcortical white matter or parasagittal area, resulting clinically in spastic quadriplegia. Acute hypoxia in the preterm infants affects the periventricular white matter (PVL), resulting in spastic diplegia. Although there is overlapping among the clinical forms of CP resulting from chronic or acute prenatal hypoxia, most investigators believe that forms of CP different to spastic diplegia, spastic quadriplegia, and spastic dyskinesia most probably are not the result of a hypoxic insult. Figure 7-3 is a diagram that attempts to summarize the characteristics of acute intrapartum and chronic antepartum hypoxic brain injuries.

A form of CP that is not caused by hypoxic intrapartum events is spastic hemiplegia. This lesion occurs frequently in infants with ischemia secondary to thromboembolism in the area of distribution of the anterior cerebral artery. Thrombosis is usually the result of a congenital or acquired predisposition to the formation of clots or thrombophilia. The most common of the congenital abnormalities of the fetal hemostatic system are the factor V Leiden mutation, prothrombin promoter mutation, 4G/4G plasminogen activator inhibitor-1 mutation, protein C deficiency, protein S deficiency,

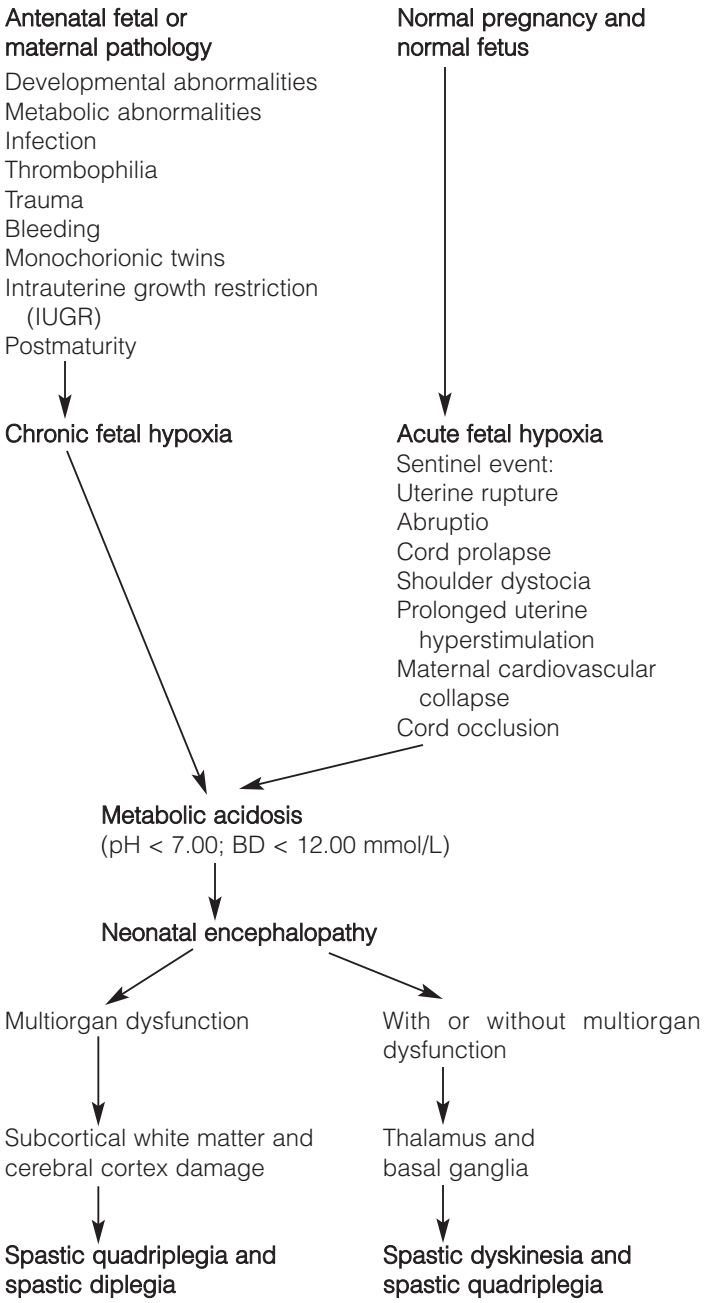

Figure 7-3. Sequence of events following chronic antepartum and acute intrapartum hypoxia and acidosis.

antithrombin III deficiency, and elevated factor VIII. The most common form of acquired thrombophilia is maternal anticardiolipin antibodies that may cross the placenta and affect the fetus. In many cases of congenital thrombophilia, a careful examination of the placenta demonstrates umbilical stem vessel thrombosis with resulting ischemic changes in the chorionic villi (Redline and Pappin, 1995). Most newborns with cerebral infarction do not exhibit a clinical picture of neonatal encephalopathy, and the most common presentation is the sudden onset of seizures. The diagnosis of cerebral infarction is made by MRI.

In many medical-legal cases of CP, no umbilical or neonatal blood gases are obtained at the time of delivery. In these cases the alleged occurrence of intrapartum hypoxia rests on other indicators such as findings in the electronic fetal heart rate monitoring, Apgar score, presence of meconium in the amniotic fluid, and development of neonatal encephalopathy and seizures in the neonatal period. In this situation is important to remember the following:

1. There is no FHR monitoring pattern *diagnostic* of fetal hypoxia and acidosis. The only FHR monitoring pattern that is frequently but not always associated with potentially damaging fetal hypoxia and acidosis is absent heart rate variability with persistent (associated with more than 50% of the uterine contractions in a 20-minute period) late or variable decelerations or with fetal bradycardia. Other abnormal patterns are nonreassuring but have poor correlation with fetal hypoxia and acidosis.
2. A low Apgar score at 5 and 10 minutes is an index of neonatal depression, but it does not indicate the cause of the depression. There are many reasons why some infants have increased duration of a low Apgar score (Box 7-5), including inadequate neonatal resuscitation.
3. Meconium in the amniotic fluid is an insensitive index of the condition of the fetus or the newborn and there are no reliable methods, including placental pathology, to distinguish with absolute certainty if meconium is old or fresh, or to date the time when meconium was passed in the fluid.
4. Neonatal encephalopathy is a syndrome with multiple causes (Box 7-4) and intrapartum hypoxia is just one of them.
5. Neonatal seizures outside the context of neonatal encephalopathy are usually the result of a fetal/neonatal insult different from hypoxia.

Chronic Lung Disease

Another long-term sequela of acute intrauterine infection is CLD or BPD. There is histologic and biochemical evidence suggesting that similarly to CP the fetal inflammatory response has a predominant role in the pathogenesis of the CLD of the premature neonates. The lungs of premature neonates exposed to chorioamnionitis show severe infiltration by inflammatory cells and have increased expression of IL-8 messenger RNA (Schmidt et al., 2001). Also, neonates who develop BPD have a significantly higher concentration of umbilical cord plasma IL-6 than those who do not develop this condition (Yoon et al., 1999).

BOX 7-5

Causes of increased duration of a low Apgar score other than intrapartum hypoxia

- Inadequate neonatal resuscitation
- Congenital abnormalities (diaphragmatic hernia, congenital cystic adenomatoid malformation, pulmonary hypoplasia secondary to prolonged oligohydramnios)
- Chromosomal abnormalities
- Fetal metabolic diseases
- Fetal neuromuscular diseases

INDIAN EXPERIENCE OF PRETERM PARTURITION SYNDROME

The incidence of preterm labor ranges from 5 to 10%. The importance of preterm labor lies in the fact that 75% of all perinatal deaths occur in preterm births, and when lethal congenital fetal anomalies are excluded, 85% of all perinatal deaths occur in preterm neonates. Further it has been observed that approximately 70% of preterm births occur in induced labors or in pregnancies associated with high-risk factors (hypertensive disorders complicating pregnancy, antepartum hemorrhage, multiple pregnancy, IUGR, premature rupture of the membranes, congenital fetal anomalies, uncontrolled medical disorders, etc.). In an interesting clinical analysis (Chhabra, 2001) of risk factors in preterm labor, the authors reported the following findings (see Table 7-5) .

Contributory Factors

Socioeconomic factors like young maternal age (<20 years), unmarried status, poor nutritional status, occupation involving hard manual labor, emotional stress and broken home are the contributory factors of preterm labor. The incidence of preterm births increases with the number of fetuses. In women with multiple gestation, about 50% of preterm births are preterm and contribute to 10% of all preterm births (Kore et al., 2000). Congenital (Mullerian) anomalies of the uterus and uterine fibroids are associated with a high incidence of preterm births. Cervical incompetence can lead to repeated preterm births; however it is amenable to correction. Genital tract infections and urinary

Table 7-5. Risk factors for preterm labor

Historical	Current pregnancy
Previous preterm labor	Multiple gestation
Cervical incompetence and cervical conization	Antepartum hemorrhage
Multiple induced second trimester abortions	Cigarette smoking (tobacco addiction)
Uterine anomalies	Urinary tract infections and anemia
Diethylstilboestrol offspring	Premature cervical dilatation–effacement

Adapted from Chhabra S. Study of factors causing and arresting preterm labor. J Obstet Gynaecol India 2001; 51(4): 99–103.

Table 7-6. Comparison of clinical profiles of 100 women with preterm labor and controls

Parameter	Patients with preterm labor	Normal controls
No. of cases	100	100
Teenagers	10.0%	4.0%
Previous PTL	27.0%	3.0%
Overweight	6.0%	3.5%
Mean height	149 cm	153 cm
Cervical swab positive	18.0%	7.0%
Urine culture positive	14.0%	6.0%

tract infections predispose to preterm delivery. Uncontrolled medical disorders such as hypertension, severe anemia, diabetes, congestive cardiac failure, and the like contribute to preterm births. Obstetric problems like placenta previa, antepartum bleeding, hydramnios, and congenital fetal malformations are associated with a higher incidence of preterm births.

Chhabra (2001) from Wardha compared the clinical profiles of women with preterm labor (PTL) with controls as shown in Table 7-6.

Medical Disorders

Medical disorders are often associated with a high incidence of preterm delivery. Bhatt (2002) from Baroda reported a higher incidence of low birth weight babies (preterm and IUGR) in women with severe anemia. These newborns have poor iron reserves and suffer from anemia in infancy; they are prone to infections, are slow learners, and have poorer cognitive skills. Awasthi et al. (2001) from Indore reported an incidence of preterm labor in 13.2% of anemic mothers as compared to 4% in nonanemic controls, and Leela Raman (1986 ICMR Report) stated that pregnancy anemia was implicated in 37% of low birth weight infants. Chia et al. (1998) reported that the incidence of PTL increases in women with cardiac problems, however Suneja et al. (2002) from New Delhi reported that in women with Eisenmenger's complex, the incidence of preterm births exceeded 50%.

Genitourinary tract infections predispose to PTL and PROM. Desai et al. (2001) from Belgaum reported that the incidence of PTL and PROM was higher in women with genitourinary tract infections. They emphasized the role of estimating C-reactive protein in the diagnosis of subclinical infections and claimed it's superiority over cervical swab cultures, placental culture, and placental histology. Jayaram and Sudha (2001) from Guntur reported that following coitus there was a 56% risk of acquiring genital tract infection and 11.5% risk of PROM. Khodke et al. (2000) from Yeotmal reported genital tract infections in 48.5% and that 89% of these were asymptomatic. Shenoy et al. (2000) reported the prevalence of *C. trachomatis* in 15% pregnant women, the incidence of preterm labor in affected women was 42.8% and perinatal mortality rate was 37.5%.

Multiple pregnancy is associated with a higher risk of preterm delivery. Pandole et al. (2003) from Mumbai, Pathania et al. (2001) from Shimla and Chhabra (2001) from Wardha reported an incidence exceeding 60%.

Cervical os incompetence is a known cause of repeated PTL. Careful clinical examinations and serial sonography help in detecting many of these patients. A timely cerclage operation helps to salvage many such cases. Godbole et al. (2002) from Wardha stated that endovaginal sonography revealing a cervical length of < 30 mm is associated with a 25% incidence of PTL as compared to 6% when the cervical length was 39 mm or more. Funneling of the cervix was also indicative of an enhanced risk of PTL. Tondare et al. (2002) from Mumbai reported a successful pregnancy outcome in a patient with repeated pregnancy losses due to high amputation of the cervix for genital prolapse. An abdominally high placed suture for cervical os tightening led to the successful outcome.

Antepartum hemorrhage accounts for several preterm births. Mukherjee et al. (2003) from Kolkata reported 30% incidence of PTL.

IMPORTANT POINTS

1. The four clinical conditions responsible for the majority of preterm births are preterm labor with intact membranes, preterm premature rupture of the fetal membranes, incompetent cervix, and indicated preterm birth. Each one of the three first syndromes accounts for approximately 30% of all preterm births and incompetent cervix for about 10%.
2. The obstetric conditions resulting in preterm birth are similar in that all of them activate or stimulate the common pathway of parturition.
3. The common pathway of parturition has three components: cervical ripening, membrane activation, and myometrial activation.
4. The marker of membrane activation is the presence of fetal fibronectin in the cervicovaginal secretions. Uterine contractions are the marker of myometrial activation. The marker of cervical ripening is effacement of the cervix.
5. The syndrome of preterm labor with intact membranes syndrome may result from intrauterine infection, extrauterine infection, fetal or maternal stress, abnormal placentation, bleeding in the choriodecidual interface, and uterine overdistention.
6. The syndrome of preterm PROM may result from intrauterine infection, abnormal placentation, defective collagen synthesis, cervical incompetence, or repetitive stretching.

7. The syndrome of cervical incompetence may be caused by genetic alterations in collagen synthesis, trauma to the cervix, congenital anatomic abnormalities of the cervix, or cervical conization.
8. The most common and important maternal morbidities associated with preterm birth are acute chorioamnionitis and postpartum endometritis. The most frequent immediate neonatal morbidities associated with preterm birth are RDS, sepsis, IVH, and NEC. The most severe late morbidities are CP and BPD.
9. The obstetrical conditions more closely associated with the occurrence of CP in the preterm infant are chorioamnionitis, IVH, fetal/neonatal thrombophilia, and intrapartum hypoxic ischemic insults.
10. Most cases of CP (90%) are not caused by intrapartum hypoxia.
11. In order for intrapartum events to be considered responsible for the ulterior appearance of CP in infants > 34 weeks, it is necessary to meet the following essential criteria:
    (a) Metabolic acidosis (pH < 7.0; BD < 12.0 mmol/L) demonstrated by umbilical cord or neonatal blood gases obtained within 1 hour of birth
    (b) Early onset of moderate to severe neonatal encephalopathy
    (c) CP of the spastic quadriplegic or spastic dyskinetic types
    (d) Exclusion of other identifiable causes of CP
12. When umbilical or neonatal blood gases are not obtained, the following findings are suggestive of an association between intrapartum events and CP:
    (a) Occurrence of a severe hypoxic event (sentinel event) occurring immediately before or during labor
    (b) A sudden, rapid, and sustained deterioration of the fetal heart pattern usually following the sentinel event where the pattern was previously normal
    (c) Apgar scores of 0–6 for longer than 5 minutes
    (d) Early evidence of multisystemic involvement
    (e) Early evidence of acute, nonfocal cerebral abnormality
13. Focal ischemic events in a major brain artery or vein are usually the result of fetal thrombophilia and not of intrapartum hypoxia.
14. There are multiple pre-existent antepartum conditions that may result in neonatal encephalopathy and ulterior development of CP. Some of the more frequent ones are as follows:
    (a) Fetal inflammatory response syndrome
    (b) Severe placental insufficiency with fetal growth restriction
    (c) Fetal and maternal thrombophilia
    (d) Monochorionic twins
    (e) Postmaturity syndrome
    (f) Fetal metabolic abnormalities (amino acids, fatty acids, carbohydrates, etc.)
    (g) Severe, persistent or recurrent neonatal hypoglycemia
    (h) Anatomic abnormalities of the brain.

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8

Preterm Labor

CHAPTER OUTLINE

Preterm labor is a syndrome causing approximately 30% of all preterm births. Preterm labor is defined as the occurrence of regular uterine contractions (four or more in 20 minutes or eight or more in 1 hour) and cervical changes (effacement equal to or greater than 80% and dilatation equal to or greater than 1 cm) in women with intact fetal membranes and gestational age less than 37 weeks. However, a gestational age less than 36 weeks is a more commonly accepted threshold of prematurity, and rarely obstetricians make efforts to delay delivery in women in preterm labor once they reach 36 weeks.

As described in Chapter 7, preterm labor is one of the syndromes characterized by the premature activation of the final pathway of parturition. Preterm labor has multiple causes and the most clearly identified are chorioamniotic infection, abnormal placentation, fetal and maternal stress, and bleeding in the decidual–chorionic interface. Most of these causes can not be modified or abolished by medical intervention and consequently the result of prevention and treatment efforts is disappointing. However, the practitioner should not adopt a nihilistic attitude and efforts should always be made to uncover the underlying reason behind the clinical picture. Even if it is not possible to stop preterm labor, knowledge of the cause of the problem is useful to guide our approach toward important interventions such as tocolysis, antibiotics, and the use of steroids.

DIAGNOSIS

Uterine Contractions

The main symptom of preterm labor is uterine contractions. They should occur regularly, four or more in 20 minutes or eight or more in 1 hour, and each should last more than 40 seconds. The perception of the frequency, intensity, and duration of contractions by different health care providers is frequently inaccurate and the best objective way to determine the frequency and duration of the contractions is by external monitoring with a tocodynamometer.

Digital Pelvic Examination

The main sign of labor, term or preterm, is the presence of cervical changes. Therefore, when a woman comes to the hospital or the obstetrician's office complaining of regular uterine contractions, the first thing to do is a digital examination of the cervix. During this examination the obstetrician should assess the position, length, consistency, and dilatation of the cervix, as well as the development of the lower uterine segment. The two more important variables to assess clinically are the length (effacement) and the dilatation of the cervix. Adequate assessment of the cervical effacement is very important and, unfortunately, there is no clear agreement or guidelines about how to effect this measurement. In USA most obstetricians and midwifes express effacement as a percentage and there is universal agreement that the cervix is 100% effaced when it is paper-thin. The problem is with the estimation of intermediate degrees of effacement, because there is no agreement about what is the length of the uneffaced cervix. It is known by ultrasonography that the length of the cervix at term is between 3 and 4 cm. However, the estimation of cervical length for pregnancy at term among practicing obstetricians in a large medical center had a range from 1 to 4 cm with a mean estimate of 2.47 cm (Holcomb and Smeltzer, 1991). Therefore 50% effacement means a cervical length of 0.5 cm for some and 2.0 cm for others. Furthermore, there is no agreement or guidelines about how to measure the cervical length. Some place one finger inside of the cervix and estimate the length from the external to the internal os. This measurement is imprecise because sometimes it is difficult to recognize the internal os and is impossible to obtain if the cervix is closed. Others estimate cervical length from the distance between the posterior fornix and the external cervical os, a measurement that is also imprecise because in many cases it does not include the supravaginal portio of the cervix. Despite these limitations a consistent measurement of the cervical length (effacement) facilitates communication between clinicians. In patients with closed or minimally opened cervix, we measure effacement as the length between the posterior fornix and the external cervical os. If the cervix is longer than 1 cm, the length is expressed in centimeters. If it is shorter than 1 cm, length is expressed as effacement (0.75 cm = 25% effacement, 0.50 cm = 50% effacement, 0.25 cm = 75% effacement, paper-thin = 100% effacement). If the cervix is dilated enough to admit one finger, the length of the cervix is assessed by estimating the distance from the tip of the examining finger placed in the internal os to the part of the finger that is at the level of the external os. When examined between 20 and 34 weeks of gestation, the large majority of nulliparous patients have cervices pointing posteriorly, closed, at least 2 cm long, and harder in consistency than any other vaginal or uterine tissues. In multiparous women, the cervix may have varying degrees of dilatation, which may be greater in the external than in the internal cervical os.

An important part of the digital examination of the women in preterm labor is the assessment of the lower uterine segment. All pregnant women regardless of their parity or gestational age stretch or develop their lower uterine segment before parturition. When the lower uterine segment is not developed, it is possible to introduce easily the fingers into the vaginal fornices. In contrast, when the lower uterine segment is developed, the examiner finds that the upper third of the vagina is filled with the thinned lower uterine segment. In many patients, development of the lower uterine segment occurs simultaneously with engagement of the presenting part. The finding of a soft, short cervix and a developed lower uterine segment indicates that the cervix is preparing for labor, and investigation about the factors causing the cervical changes is mandatory.

When the digital examination reveals that the cervix is more than 80% effaced and dilated 1 cm or more, the diagnosis of preterm labor is clear. However, the degree of cervical dilatation varies, and it is possible to distinguish two groups of women in preterm labor: those with cervices dilated 3 or more cm are in *advanced preterm labor* and those with a cervical dilatation greater than 1 but less than 3 cm are in *early preterm labor*. Most women with advanced preterm labor are destined to have a preterm birth. This is not the case for women in early preterm labor and, as we will see later, further refinement in the determination of the risk of preterm delivery in this particular group of patients can be achieved with the use of the fetal fibronectin (FFN) test.

The initial digital examination will reveal a large number of women coming to the hospital or to the doctor's office with frequent uterine contractions that do not show cervical changes consistent with the definition of preterm labor. In these cases the next step is to measure the cervical length with ultrasound. If the ultrasound examination shows a cervical length less than 2.5 cm, the woman is in *threatened preterm labor* and at high risk for preterm delivery. If the cervical length is 2.5 cm or more, the subject is in *spurious or false labor* and the risk of preterm delivery is similar to that in the overall obstetrical population.

In summary, in women who present with frequent, regular uterine contractions the initial digital examination will permit to determine if the woman is in advanced preterm labor (cervix effaced 80% or more and cervix dilated 3 cm or more) or in early preterm labor (cervix effaced 80% or more and dilated 1 or more but less than 3 cm). If the cervix is dilated less than 1 cm or is not effaced, endovaginal ultrasound will permit to identify a

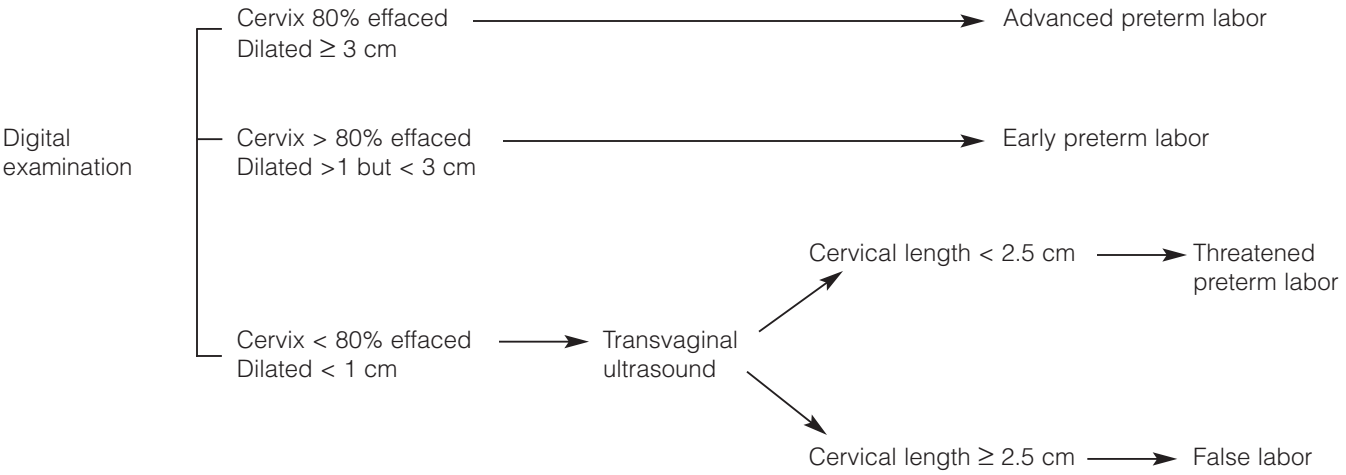

Figure 8-1. Diagnosis of preterm labor.

third group of women in threatened preterm labor (cervical length less than 2.5 cm). We will see later that the management of preterm labor depends on the diagnosis and classification of preterm labor as advanced, early, or threatened at the time of the initial evaluation. The sequence of steps in the diagnosis of preterm labor is illustrated in Figure 8-1.

ADVANCED PRETERM LABOR

If the cervix is effaced 80% or more and the cervical dilatation is 3 cm or more, the woman is in advanced preterm labor. Under these circumstances assessment of the cervical length by ultrasound and determination of FFN in the cervicovaginal secretions are unnecessary. The risk of preterm delivery is high and management will not be changed by performing these tests.

The possibilities of obtaining a significant prolongation of pregnancy for patients admitted to the hospital in advanced preterm labor are limited. Also, for a majority of these patients prolongation of pregnancy offers no fetal advantages because, in these cases, preterm labor is a protective mechanism for fetuses threatened by problems such as infection or placental insufficiency. Because of these reasons, the first step in the management of advanced preterm labor is to determine which patients need to be delivered and which patients may benefit from delaying delivery in order to accrue the benefits of steroid administration.

Identification of Women Who Need to be Delivered

The first step in the management of women in advanced preterm labor is to determine if there are maternal or fetal conditions indicating that labor should not be interrupted (Figure 8-2). The most frequent of these conditions are as follows.

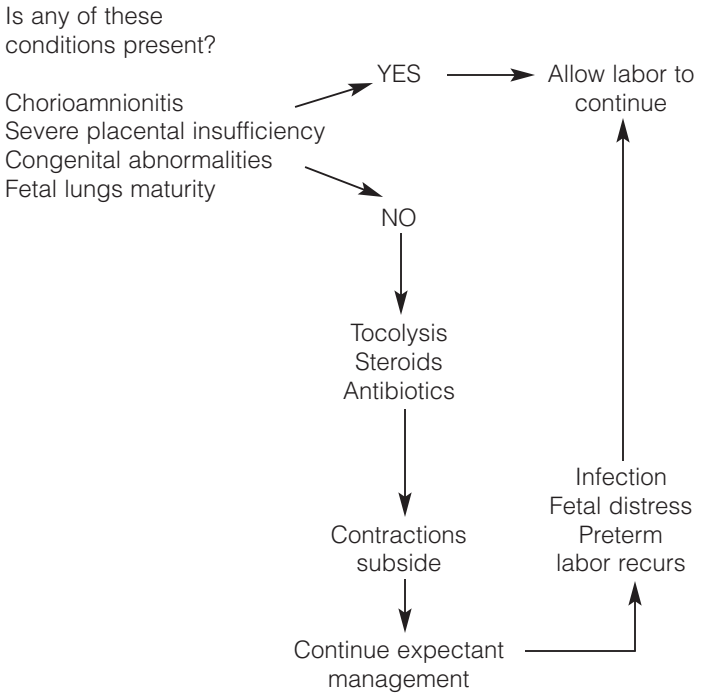

Figure 8-2. Decision tree for women in advanced preterm labor.

Acute chorioamnionitis

Acute or overt chorioamnionitis occurs in 10% or fewer patients with established preterm labor. However, it is important to rule out the presence of this condition. The clinical marker of acute amniotic infection is the presence of fever. Other symptoms and signs are uterine tenderness, fetal and maternal tachycardia, foul-smelling vaginal discharge, leukocytosis, marked elevation of the C-reactive protein (CRP), and resistance to tocolytic agents (Box 8-1). In the large majority of cases the diagnosis of acute chorioamnionitis is obvious and confirmation of the amniotic infection by amniocentesis is unnecessary. For more information about chorioamnionitis the reader is referred to Chapter 7.

BOX 8-1

Diagnosis of acute chorioamnionitis

Fever (maternal temperature ≥ 100.4 F or ≥ 37.8°C)

and two or more of:

- Maternal tachycardia (≥100 bpm)
- Fetal tachycardia (≥160 bpm)
- Uterine tenderness
- Foul odor of the amniotic fluid
- Maternal leukocytosis (≥15,000/mm^3)
- C-reactive protein ≥ 2.7 mg/dl

BOX 8-2

Antibiotic treatment of acute chorioamnionitis

Single agent

- Cefotetan 2 g IV q12 h
- Cefoxitin 2 g IV q6–8 h
- Ceftizoxime 1–2 g IV q8–12 h
- Ampicillin/sulbactam 3 g IV q8 h
- Piperacillin/tazobactam 3.375 g IV q8 h
- Ticarcillin/clavulanate 3.1 g IV q6 h

Double agents

- Clindamycin 900 mg IV q8 h plus gentamycin 5 mg/kg q24 h
- Clindamycin 900 mg IV q8 h plus ceftriaxone 2 g IV q24 h or cefotaxime 2 g IV q8 h

Triple agents

- Clindamycin 900 mg IV q8 h plus ampicillin 2 g IV q6 h plus gentamycin 5 mg/kg q24 h.

The diagnosis of acute chorioamnionitis in women in preterm labor is an indication for discontinuation of tocolysis, initiation of antibiotic treatment, and delivery. Delivery is the most important measure in the treatment of chorioamnionitis because the infection will not resolve until the fetus is delivered. The objective of antibiotic treatment is to prevent dissemination of the infection in mother and fetus until delivery is achieved. To attempt to cure a chorioamniotic infection with antibiotics is foolish and only leads to severe maternal and fetal/neonatal morbidity. There is evidence in the literature indicating that mother and fetus do better when antibiotic treatment is initiated before rather than after delivery. Women with chorioamnionitis should be treated with broad spectrum IV antibiotics and steps should be taken for delivery, as soon as the diagnosis is made. Steroid treatment is contraindicated in the presence of overt infection. There is no consensus about the best antibiotic or antibiotics formulation for women with acute chorioamnionitis and any of the treatments shown in Box 8-2 will be adequate.

As mentioned in Chapter 7, acute chorioamnionitis is a serious obstetrical complication which has a significant association with cerebral palsy and bronchopulmonary dysplasia—problems that occur significantly more frequently in fetuses that develop a fetal inflammatory response syndrome. For that reason, delivery should be achieved rapidly and many practitioners follow this diagnosis with delivery by cesarean section. However, vaginal delivery may be a choice if the patient is in advanced stages of labor, and delivery is anticipated in less than 1 or 2 hours. In many cases, patients with chorioamnionitis have abnormal uterine activity, protracted cervical dilatation and descent, and require delivery by cesarean section. Maternal improvement is common following delivery, and in many cases the temperature becomes normal and the woman shows impressive symptomatic recovery a few hours after delivery. In these cases antibiotic administration may be discontinued shortly after delivery. In other cases the postpartum course is complicated by endometritis, requiring continuation of antibiotic treatment until the patient remains afebrile for 24 hours.

Subclinical chorioamnionitis

Subclinical chorioamnionitis occurs frequently in women in preterm labor without evidence of overt infection. Some of these patients present with cervical dilatation of 3 cm or more and their contractions respond poorly to tocolytic agents, but some of them do not show clinical characteristics that allow differentiation from women in preterm labor and without infection.

As mentioned in Chapter 7, determination of plasma CRP concentration is a sensitive test to identify women in preterm labor who may have subclinical amniotic infection (Mazor et al., 1993; Potkul et al., 1985). There are numerous articles in the literature about the use of CRP in the assessment of patients in preterm labor and with preterm premature rupture of membranes and they differ in the CRP concentration that is considered to indicate infection. The work of Dodds and Iams (1987) suggests that any CRP concentration equal to or above 0.9 mg/dl has high sensitivity and positive predictive value for preterm delivery. Values above this limit may be followed with repeated testing in 12 or 24 hours depending on the clinical situation. An upward trend almost certainly indicates that chorioamnionitis is present and delivery may be necessary. In women without evidence of extrauterine infection, values of 3 or 4 mg/dl are almost certainly indicative of chorioamnionitis. Occasionally, women present with abdominal tenderness, uterine irritability, minimal or no cervical changes, and CRP concentration of 8.0 mg/dl. Most of them have an exaggerated inflammatory response to a viral infection, and amniocentesis will not show indications of acute infection.

When the concentration of CRP obtained at the time of admission is normal (< 0.8 mg/dl) most probably the patient does not have subclinical amnionitis and expectant management is the best course of management. When

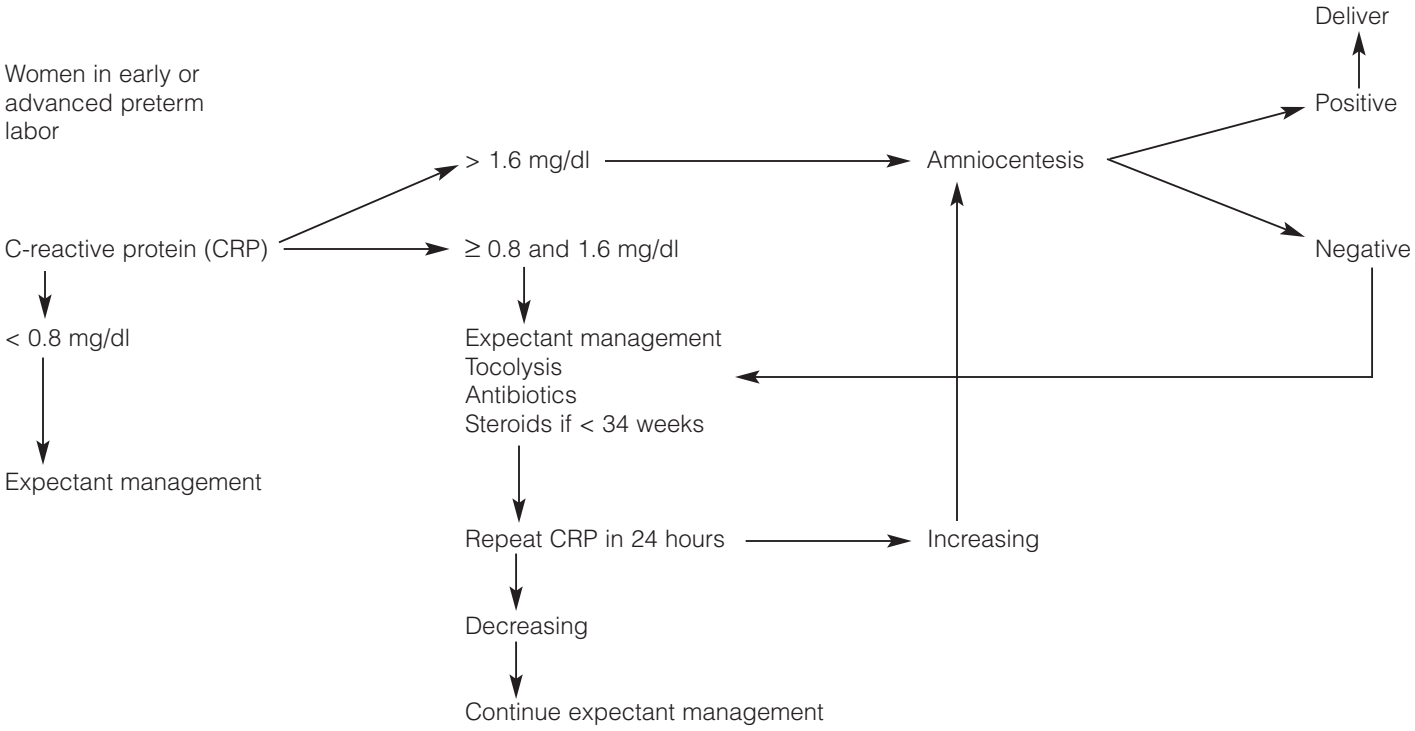

Figure 8-3. Decision tree for diagnosis and management of subclinical amnionitis.

the CRP concentration is between 0.8 and 1.6 mg/dl the CRP must be repeated in 12–24 hours. If the trend is toward lower concentrations, amniocentesis is not performed but if a rising trend is detected, amniotic fluid analysis is recommended. A decision tree for the diagnosis and management of women with subclinical amnionitis based on CRP values is shown in Figure 8-3. Also, the interested reader will find more information about acute and subclinical chorioamnionitis in Chapter 7.

The diagnosis of subclinical chorioamnionitis is made only by amniotic fluid analysis. The maternal serum CRP is useful only to indicate the need for amniocentesis. If the CRP obtained at admission is below the upper limit of normal (0.9 mg/dl), the patient is considered not to be infected and the CRP is not repeated unless a new indication for the test appears later. Amniocentesis is recommended for women without signs of overt intrauterine infection and CRP values equal to or greater than 1.8 mg/dl. Several tests can be performed in the amniotic fluid sample, including Gram stain and cell count, determination of the concentrations of interleukin-6 (IL-6), CRP, glucose, and LDH (Lactate dehydrogenase), and aerobic and anaerobic cultures (Table 8-1). The Gram stain is a simple and rapid test for the diagnosis of amniotic fluid infection (Romero et al., 1988). The presence of bacteria is indicative of infection (positive predictive value of 100%). However, a negative Gram stain does not rule out the possibility of an infection localized in the decidua and not shedding bacteria into the amniotic fluid.

Severe placental insufficiency

If the ultrasound examination performed at the time of admission to the hospital of a woman in preterm labor reveals an estimated fetal weight below the 10th percentile and the expected date of delivery (EDD) is reliable (Box 8-3), the most likely etiology for the preterm labor is placental insufficiency. This etiology will become certain if the amniotic fluid volume is decreased, and assessment of the umbilical and mid-cerebral arteries with Doppler

Table 8-1. Accuracy of amniotic fluid tests for the diagnosis of subclinical amnionitis in preterm labor

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gram stain (+ for bacteria)	75–80	97–99	85–92	96–97
Leukocyte count (≥50 cells/mm^3)	80–91	84–95	78–95	85–91
Lactate dehydrogenase (>225 U/L)	75	90	50	96
Glucose (≥16 mg/dl)	71–87	51–93	47–87	74–97
Leukocyte esterase (positive)	80–91	84–95	78–95	85–91

PPV = positive predictive value; NPV = negative predictive value.
From Carroll et al., 1996; Garry et al., 1996; Gauthier et al., 1992; Hoskins et al., 1987; Romero et al., 1993.

BOX 8-3

Criteria to assess reliability of the expected date of delivery (EDD)

Best

- Reliable menstrual history plus confirmation by ultrasound examination before 14 weeks' gestation

Acceptable

- Uncertain menstrual history plus confirmation by ultrasound examination before 14 weeks
- Reliable menstrual history plus confirmation by ultrasound after 14 and before 20 weeks
- Uncertain menstrual history plus confirmation by two ultrasound examinations 4 or more weeks apart between 20 and 32 weeks

ultrasound reveals increased placenta impedance or brain-sparing effect. In these cases labor is clearly a mechanism of fetal defense against a hostile intrauterine environment and should not be interrupted. If the umbilical artery Doppler does not show reversed diastolic flow and the fetal heart rate monitoring is not ominous, it will be acceptable to delay delivery for 24–48 hours to administer steroids, although the evidence of steroid benefit for fetuses in this condition is weak (Elimian et al., 1999).

Fetal congenital abnormalities

All women in preterm labor should have an ultrasound examination at the time of admission to the hospital. The presence of a major congenital abnormality is an indication to allow preterm labor to continue. Similarly, labor should not be interrupted if it is known that the fetus has a major chromosomal abnormality.

Fetuses with adequate pulmonary maturity

In some occasions, physical examination and ultrasound evaluation of the patient in preterm labor reveals a fetus with a size larger than expected for the gestational age (Box 8-3). In these cases, an error in dating should be suspected, and amniocentesis performed to determine if the fetus is mature. Also, approximately 50% of fetuses between 32 and 36 weeks have adequate pulmonary maturity. If pulmonary maturity is demonstrated by amniocentesis, tocolysis should be interrupted and if the woman is stable, she may be discharged or allowed to labor if spontaneous preterm labor continues. Fetal lung maturity (FLM) before 36 weeks is a frequent finding in patients with preterm labor secondary to placental insufficiency.

Advanced cervical dilatation

Amon et al. (2000) demonstrated that inhibition of labor is frequently successful in women with advanced preterm labor. They showed that following aggressive tocolysis, 46% of women with cervical dilatation of 5 cm delivered after 48 hours as well as 19% of those dilated to 6 or more cm. The problem is that up to 50% of these women had severe side effects associated with their treatment. This study also demonstrated that when the cervix is dilated to 4–5 cm, more than 50% of the women will deliver in less than 48 hours despite aggressive tocolysis. For women with a cervical dilatation of 6 cm at admission, the incidence of delivery before 48 hours was 81%. It is clear that once the cervix is 100% effaced and dilated to 4 or more cm, it is unusual that pregnancy can be prolonged for more than a few hours and efforts to prolong the pregnancy to give steroids for fetal reasons are contraindicated because of the maternal morbidity associated with pregnancy prolongation.

Women in Advanced Preterm Labor and no Indication for Immediate Delivery

After selecting those women in advanced preterm labor who need to be delivered, the obstetrician is left with a small group of patients who may benefit from the prenatal administration of steroids. An attempt should be made to stop or decrease the frequency of their uterine contractions using nifedipine alone or combined with low doses of terbutaline. The dose of nifedipine is 20–30 mg orally every 4–6 hours and the terbutaline dose is 0.25 mg subcutaneously every 2–4 hours. The use of these tocolytic agents in patients with advanced preterm labor has to be monitored carefully because the possibility of side effects is large. Pulse oximetry and monitoring of the vital signs every 2 hours is mandatory. Maternal tachycardia above 120 bpm, blood pressure below 100/60, pulse oximetry < 95%, and fever are reasons for discontinuation of treatment and to allow preterm labor to continue.

Betamethasone or dexamethasone is given at the usual doses, 12 mg IM for two doses 24 hours apart or 6 mg IV or IM every 12 hours for four doses, respectively. In many occasions the treatment has to be interrupted because of continuous cervical dilatation and delivery or because of side effects associated with the simultaneous administration of tocolytic agents and steroids.

Delivery of the Preterm Infant

Labor and delivery may be a significant stress for the preterm infant. This has led to suggestions that cesarean section should be used to deliver infants under 1500 g. This is a controversial subject and there is no solid evidence that cesarean is a better way of delivering these babies although this is a suggestive proposition. The evidence about the effects of labor and cesarean delivery on the incidence of germinal matrix hemorrhage and intraventricular bleeding (GMH/IVH) is reviewed in Chapter 7.

There is no controversy about the need to give antibiotics for the prevention of group B streptococcal (GBS) infection. Screening for GBS is usually performed at about 36 weeks and the majority of women in preterm labor have not been screened. Therefore they should receive treatment with penicillin, 5 million units (mU) IV initial doses followed by 2.5 mU every 4 hours until delivery. For patients allergic to penicillin the best choice is cefazolin, 2 g IV initial dose followed by 1 g IV every 8 hours. Women with a history of anaphylactic reaction to penicillin should receive vancomycin, 500 mg IV every 6 hours.

Preterm infants tolerate hypoxia more poorly than infants at term due to the immature autoregulation of their vascular system and the increased sensitivity of the immature oligodendrocytes to hypoxia-ischemia. Therefore it is necessary to react promptly to electronic monitoring patterns indicating a nonreassuring fetal status in the preterm baby. The preterm infant is the perinatal patient with the greatest need for adequate monitoring, and significant damage to the fetus could be prevented by timely intervention at the early signs of fetal distress. If cesarean delivery is necessary for the delivery of a preterm infant and the lower uterine segment is not developed, the best incision in the uterus is a low vertical incision that may be extended upwards if necessary. Delivery of a preterm baby through a low transverse incision over a thick low uterine segment is as traumatic as a vaginal delivery.

EARLY PRETERM LABOR

The difference between advanced and early preterm labor is the degree of cervical dilatation. In women with early preterm labor the cervix is soft, 80% effaced or more, and dilated more than 1 but less than 3 cm. The absence of advanced cervical changes in women in early preterm labor has important prognostic implications. While prolongation of pregnancy for 1 or more weeks is uncommon in women with advanced preterm labor, 60–65% of women in early preterm labor will respond to tocolysis and will deliver at term or closer to term. This difference may be the result of a lower incidence of intra-amniotic infection in the early preterm labor group. In these patients amniocentesis will reveal bacteria in the amniotic fluid in approximately 10% of the cases, while this incidence doubles or triples in the advanced preterm labor group.

All women in early preterm labor should have ultrasound examination of the fetus, placenta, amniotic fluid, and umbilical, cerebral, and uterine arteries Doppler as well as determination of maternal serum CRP. Similar to the case of women with advanced cervical changes, these tests will help the clinician decide in which cases delivery is indicated and which will be candidates for tocolysis and pregnancy prolongation. Ultrasound will be useful to detect gross fetal malformations, oligohydramnios, significant differences between the gestational age and the ultrasound measurements, and abnormal umbilical artery Doppler indicative of placental insufficiency. An elevated maternal CRP will immediately raise the suspicion of intra-amniotic infection.

FFN is a valuable test in the evaluation of women in early preterm labor to determine more accurately the risk of preterm delivery. FFN is normally present in the cervicovaginal secretions before 22 weeks and after 37 weeks. It is a glycoprotein that acts as a cement or glue between the fetal membranes and the decidua. When the normal interrelation between the chorioamnion and the decidua is altered because of contractions or infection, FFN is released and appears in the cervicovaginal secretions. If the amount of cervicovaginal FFN is less than 50 ng/ml (negative result), the woman is at low risk of preterm delivery. A negative FFN result has a high negative predictive value and women with a negative FFN test have a 97% probability that they will not deliver within 2 or 3 weeks. If the FFN test is positive (more than 50 ng/ml), the likelihood of preterm delivery in the following 2 weeks is approximately 35%. In a study of women with symptoms and cervical dilatation less than 2 cm, Peaceman et al. (1997) found a sensitivity of 86.4%, specificity of 82.3%, positive predictive value of 12.7%, and negative predictive value of 99.5% for FFN in the identification of symptomatic women who delivered within 7 days of the test. The test is also valuable in asymptomatic women as shown by Goldenberg et al. (1997) who found a sensitivity of 63.2%, specificity of 97.8%, positive predictive value of 14.7%, and negative predictive value of 99.7%. Several meta-analyses have confirmed the value of FFN in the prediction of preterm birth in symptomatic and asymptomatic women (Faron et al., 1998; Honest et al., 2002).

In summary, a negative FFN indicates that delivery will not occur in the next 2 or 3 weeks, while a positive result will increase markedly the possibilities of preterm delivery. It is important to know that sexual intercourse, speculum or digital pelvic examinations, and endovaginal ultrasound exams interfere with the accuracy of the test. Therefore, in most symptomatic patients in early preterm labor, it is not appropriate to obtain a sample for FFN in the initial evaluation because usually they have had examinations or tests that invalidate the test. In these cases it is necessary to wait for 24–48 hours before the test is performed.

Management

Tocolysis

The majority of women in early preterm labor are candidates for tocolysis and respond well to oral nifedipine (30 mg orally initial dose followed by 20 mg orally every 6 hours). Only a few cases continue with contractions and develop additional cervical changes. In these cases it is necessary to suspect the presence of an underlying condition causing the contractions that was not identified in the initial evaluation and repeated testing and amniocentesis may be indicated. A few cases will require oral terbutaline (2.5 mg every 6 hours) given concomitantly with nifedipine. The concomitant administration of terbutaline and nifedipine increases the possibility of side effects and interactions of the medications. As a result frequent monitoring of vital signs and pulse oximetry and frequent assessment for pulmonary congestion are necessary.

Nifedipine

Nifedipine is a calcium channel blocker that causes smooth muscle relaxation and is used for the treatment of chronic hypertension. The drug has been used for the inhibition of labor since 1980 and is found to be as or more effective than betamimetics. It is given by the oral route. The loading dose is 20–30 mg and the maintenance dose is 10–20 mg every 6 hours. Randomized trials have demonstrated that nifedipine is a better tocolytic agent than ritodrine and terbutaline (King et al., 2003). Nifedipine is the best first-line tocolytic agent available at this time. The problem is that the doses commonly used to stop labor (10 mg orally every 6 hours) are frequently ineffective. The initial dose should be 30 mg and subsequent doses 20 mg every 6 hours. With this regimen most women stop having contractions. Headaches are the main maternal side effect but overall the drug is well tolerated and has no apparent fetal effects.

Magnesium sulfate

Magnesium sulfate has been for many years the drug of choice for the prophylaxis of convulsions in women with preeclampsia. The use of this drug for the treatment of preterm labor originated in the observation that it causes a decrease in frequency and intensity of contractions in preeclamptic women in labor. Overall, the medication is poorly tolerated and women who have been treated with magnesium sulfate frequently refuse to receive the same drug if they have a recurrence of their problem. The main problems with the use of magnesium sulfate have to do with its effectiveness and with maternal and fetal side effects. The main subjective maternal complaints are related to the mental effects ("out of it" or "felt like a zombie") and the overall muscular weakness produced by the drug.

The most frequent side effects of magnesium sulfate are pulmonary congestion, respiratory depression, hypothermia, and neuromuscular toxicity. Intravenous magnesium sulfate causes a significant increase in plasma osmolarity that is compensated by mobilization of fluid into the intravascular space. This expansion of plasma volume is dangerous in patients with other factors predisposing to pulmonary edema such as chorioamniotic infection, twin pregnancies, and underlying cardiac disease. It is desirable to monitor with pulse oximetry women receiving maintenance doses greater than 2.0 g/hour of magnesium sulfate. The pulmonary congestion secondary to magnesium sulfate usually reverses promptly with the administration of furosemide and limitation of the total fluid intake. Women treated with magnesium sulfate or any other tocolytic agent that develops pulmonary edema frequently have subclinical chorioamnionitis. The neuromuscular toxicity of magnesium sulfate is well known and can be reversed quickly by intravenous administration of calcium gluconate (10 ml of a 10% solution or 1 g IV).

Magnesium concentration in the fetus and the neonate are similar to maternal levels. This translates clinically in decreased fetal heart variability during labor and in central nervous system depression in the neonate. Infants of mothers treated with IV magnesium sulfate shortly before delivery are frequently hypotonic at birth and require respiratory support until the magnesium is eliminated. Long-term administration of magnesium sulfate causes fetal/neonatal hypocalcemia.

Recent investigations have suggested the existence of an association between the use of magnesium sulfate in women with preterm labor and the incidence of neonatal adverse effects, particularly intraventricular bleeding (IVH). In a randomized clinical trial the incidence of neonatal adverse effects in newborns from women treated with magnesium sulfate was 32% versus 19% in those who received placebo ($p = 0.07$), leading the authors to recommend abandoning magnesium sulfate as tocolytic therapy (Mittendorff et al., 2002).

In summary, magnesium sulfate is an ineffective tocolytic agent as shown by a Cochrane systematic review of the available information (Crowther et al., 2002; Cox et al., 1990). Therefore, there is no valid reason to expose patients to the toxic effects of this medication.

Beta-adrenergic agents

Intravenous beta-adrenergic agents are the second choice for the treatment of patients in established preterm labor (Anotayanonth et al., 2004). These powerful medications are contraindicated in several conditions and have bothersome and potentially dangerous effects (Box 8-4). One of

BOX 8-4

Problems associated with the intravenous administration of magnesium sulfate for the treatment of preterm labor

- Subjective complaints (nausea, blurred vision, generalized weakness, obtunded sensorium)
- Muscular weakness
- Pulmonary congestion
- Respiratory depression
- Neurotoxicity
- Neonatal depression
- Neonatal hypotonia
- Neonatal hypocalcemia
- Increased frequency of IVH

the most frequent contraindications is the presence of maternal cardiac disease. The decrease in afterload and the positive inotropic effect of these agents may precipitate cardiac failure in the pregnant woman with heart disease. Also, signs and symptoms of cardiac failure and anginal pain may complicate therapy with beta-adrenergic agents if the mother has a hyperdynamic circulation caused by hyperthyroidism or sickle cell disease.

Pulmonary edema is a serious complication of all tocolytic treatments including beta-adrenergic therapy. This complication occurs in patients receiving oral or intravenous treatment, although it is more frequent in the latter group. It occurs more frequently in patients who have excessive plasma volume expansion, such as those with twins or those who have received generous amounts of intravenous fluids. It also occurs more frequently in patients who have chorioamnionitis. The clinical picture is one of respiratory distress, bilateral rales on auscultation of the lungs, and pink frothy sputum. The chest x-ray is characteristic. Ideally, patients receiving IV beta-adrenergic drugs should be monitored continuously with pulse oximetry to anticipate the development of pulmonary edema.

It is a good idea to measure the hematocrit/hemoglobin values of patients in preterm labor before initiation of IV beta-adrenergic therapy. These drugs cause retention of water and electrolytes and cause further decrease in hematocrit/hemoglobin if anemia is present with marked decrease in blood viscosity that may be an important contributory factor to high-output cardiac failure. Also, a significant drop in hematocrit/hemoglobin levels during IV beta-adrenergic therapy suggests that a significant increase in plasma volume has occurred, which may precede the development of pulmonary edema.

In the majority of cases, treatment of pulmonary edema associated with beta-adrenergic therapy is simple and produces excellent results. As soon as the diagnosis is made, the medication should be discontinued, and the patient given oxygen by mask or nasal prongs and intravenous furosemide, 20 mg initially, to be repeated every 4 or 6 hours for several doses depending on the clinical response. With these simple measures, the majority of patients have a brisk diuresis followed by a dramatic improvement in their respiratory status. It is important to remember that pulmonary edema commonly is associated with subclinical amnionitis.

The plasma glucose concentration increases after initiation of IV beta-adrenergic therapy. A mild elevation to levels below 200 mg/dl is almost universal. This elevation is more marked in patients with gestational and insulin-dependent diabetes. Persistent elevations above 200 mg/dl require treatment with subcutaneous or IV insulin. Women with insulin-dependent diabetes are at high risk of complications with beta-adrenergic therapy. They may develop significant hyperglycemia, glycosuria, and ketonuria and require considerable increases in the amount and frequency of insulin administration. This effect of beta-adrenergic agents is the consequence of exaggerated glycogenolysis and accelerated lipolysis. Women with diet-controlled gestational diabetes usually require subcutaneous insulin and patients with insulin-dependent diabetes require intravenous insulin to maintain adequate blood sugar control. Beta-adrenergic agents are contraindicated in the unstable pregnant diabetic. In stable pregnant diabetic patients, they may be used but frequent monitoring of blood sugar and electrolytes and aggressive insulin therapy are necessary.

Serum potassium usually drops 0.5–1.0 mEq/L in the first few hours of treatment with IV beta-adrenergic agents and remains at this level or decreases another 1.0 mEq/L during the following 24 hours. There is no agreement as to the need to treat the drop in potassium levels. Some authorities believe that it is unnecessary to give potassium and restore its plasma concentration to normal values. We prefer to maintain the potassium serum concentration close to normal and give 40–80 mEq of potassium in one of the IV fluids bottles if the potassium concentration falls below 3.0 mEq/L.

The administration of beta-adrenergic agents is contraindicated in patients with chorioamnionitis. Also, patients receiving monoamine oxidase inhibitors for the treatment of psychiatric disorders have difficulties in metabolizing these agents. Finally, asthmatic patients already taking beta-adrenergic agents for the treatment may develop tachyphylaxis when receiving increased dosage of the medication. There is evidence that prolonged use of these agents leads to destruction of beta-adrenergic receptor sites and production of drug resistance. A summary of relative contraindications to beta-adrenergic agents is shown in Box 8-5.

BOX 8-5

Contraindications to the use of intravenous beta-adrenergic agents for the treatment of women in preterm labor

- Symptomatic cardiac disease, especially ventricular outflow obstruction
- Symptomatic cardiac rhythm or conduction disturbances
- Hyperthyroidism
- Sickle cell disease
- Uncontrolled insulin-dependent diabetes
- Chorioamnionitis
- Eclampsia or severe preeclampsia

For intravenous administration, 5 mg of terbutaline is dissolved in 500 ml of Ringer's lactate solution (10 µg/ml) and started at 5 µg/minute (0.5 ml). The initial dosage is increased gradually by 5 µg/minute every 10–20 minutes until a dosage adequate to stop uterine contractions is found or until side effects are intolerable. The maximum dose is 30 µg/minute. Continuous subcutaneous administration of low-dose terbutaline using precision minipumps is a controversial therapeutic modality. Some evidence about its effectiveness is suggestive of a beneficial effect (Lam et al., 2001), but other is not (Wenstrom et al., 1997). This mode of therapy has similar side effects to those observed with IV administration of the drug.

Another beta-adrenergic drug used to arrest uterine contractions is ritodrine. It has the same side effects as those of terbutaline and has questionable effectiveness. For intravenous administration the initial dose is 100 µg/minute. This dose is increased by 50 µg/minute until the contractions stop, toxicity develops, or a maximum dose of 350 µg/minute is reached.

Indomethacin

Indomethacin is an excellent tocolytic agent but is not used as a first-line medication because of concerns over its fetal effects. One study found that 7 of 14 fetuses of mothers taking indomethacin had constriction of the ductus arteriosus (Moise et al., 1988). The presence of ductal constriction was inferred from Doppler measurements indicating increased ductal velocity, and there was no relationship between the ductal velocity and the concentration of indomethacin in fetal blood. The sensitivity of the fetal ductus to indomethacin increases with gestational age and for this reason the drug is not used after 32 weeks of gestation. Also, there are reports of increased incidence of necrotizing enterocolitis and grade III and IV intraventricular hemorrhage as well of pulmonary hypertension and persistent open ductus in neonates born after indomethacin therapy. Also, indomethacin may adversely decrease fetal urinary output and cause oligohydramnios. However, the fetal effects are rapidly reversible after discontinuing the medication, and most babies born to patients treated with indomethacin during pregnancy do not show significant cardiovascular complications. Decision analysis models to quantify the risks and benefits of the drug support its use (Macones et al., 2001).

The dose of indomethacin is 25–50 mg orally. This is followed by 25 mg orally every 4 or 6 hours. Treatment is usually continued for 3 days. At the end of this period, treatment may continue if the ultrasound examination shows normal fluid volume and no tricuspid regurgitation. If any of these abnormalities are present, a different tocolytic agent should be used for maintenance treatment.

Nitroglycerin

Nitroglycerin (glyceryl trinitrate) is a powerful smooth muscle relaxant that has been used to achieve rapid uterine relaxation and facilitate removal of retained placenta, breech extraction, and replacing of inverted uterus. Nitroglycerin belongs to a series of compounds known as nitrous oxide (NO) donors. After intravenous injection or transdermal or sublingual absorption, nitroglycerin undergoes a series of biochemical reactions that lead to its conversion to NO. Nitrous oxide interacts with the enzyme guanylyl cyclase, promoting the synthesis of guanosine 3'-5'- monophosphate—a substance that activates protein kinases and ultimately causes dephosphorylation of myosin light chains and smooth muscle relaxation. Animal experiments have shown the effectiveness of nitroglycerin in arresting spontaneous labor. In humans the medication has similar cardiovascular side effects that the betamimetic agents have, although the effect of lowering the blood pressure is much more marked. A randomized trial of 245 women demonstrated that nitroglycerin and betamimetics are similarly effective in arresting preterm labor (Lees et al., 1999). A randomized clinical trial of only 30 women compared the effectiveness of nitroglycerin and magnesium sulfate in the treatment of preterm labor. They found that treatment failures happened more frequently in women receiving nitroglycerin and that up to 25% of women had to stop nitroglycerin treatment because of cardiovascular side effects (El-Sayed et al., 1999).

The preferred way to give nitroglycerin is by means of transdermal patches. They are manufactured to release a specific amount of medication, proportional to the size of the patch, that varies between 0.1 and 0.8 mg/hour. It is better to start with a low-dose patch (0.2 mg/hour) and add a 0.1 mg/hour patch every hour if there is no response. Cardiovascular side effects, particularly hypotension and severe headaches, happen often when the dose is 0.4 µg/hour or higher and are the main reason for treatment failure. Intravenous administration of nitroglycerin is associated with a high incidence of cardiovascular side effects, particularly hypotension. It is usually

started with a 100 µg bolus, followed by a continuous IV infusion at a rate of 1 µg/kg/minute.

Diazoxide

Diazoxide is a medication structurally related to the thiazide diuretics that is used in the treatment of hypertensive crisis. Diazoxide inhibits the contractility of arterial and venous smooth muscle. The drug also inhibits respiratory, gastrointestinal, and genitourinary smooth muscle and the latter action is responsible for its effectiveness as a tocolytic agent.

The most common maternal side effects of diazoxide administration are hypotension, tachycardia, hyperglycemia, and decreased uteroplacental blood flow secondary to maternal hypotension. The most important fetal side effects are hyperglycemia and fetal distress secondary to decreased uteroplacental perfusion. In order to avoid maternal and fetal side effects, it is desirable to expand the maternal intravascular volume before diazoxide administration. For most patients, 500–1000 ml of lactated Ringer's or normal saline solution constitutes adequate hydration before diazoxide administration.

The dosage of diazoxide is 5 mg/kg (300 mg for patients weighting around 130 lbs, 400 mg for patients weighting around 150 lbs). The medication should be given intravenously, slowly, in 15–30 minutes. For this purpose, one ampoule of diazoxide is dissolved in 250 ml of half-normal saline solution and given IVPB in 30 minutes. The medication can also be given in boluses of 50–100 mg every 5 minutes. The patient should be in the lateral recumbent or in slight Trendelenburg position while the medication is being administered. Continuous monitoring of maternal blood pressure and heart rate, uterine activity, and fetal heart rate is necessary.

Diazoxide usually eliminates uterine contractions within 15 minutes following its administration. The duration of action of the medication varies from patient to patient and in many cases one single dose stops uterine activity indefinitely. If labor recurs, a second dose may be administered. If the effect of the second dose lasts shorter than the first dose, further efforts with diazoxide or with any other tocolytic agents are doomed to fail and it is better to allow the patient to deliver without further tocolytic therapy.

Prophylactic tocolysis

Continuation of tocolytic treatment after successful inhibition of the episode of preterm labor has been a matter of controversy. Meta-analysis of the evidence indicates that prophylactic treatment does not result in significant pregnancy prolongation (Sanchez-Ramos et al., 1999). However, these studies have not categorized cases on the basis of the cervical changes of the study population assessed by digital and endovaginal ultrasound examination. When women with preterm labor are grouped together, those with minor cervical changes will be the majority and a large proportion of them will deliver at term and have a good outcome. Tocolytic agents do not significantly change the outcome in women with minor cervical changes and any beneficial effect in women with more advanced cervical changes will be diluted and difficult to detect. Since there are no studies demonstrating lack of effectiveness of maintenance tocolysis in women with advanced cervical changes who respond to the initial treatment, we continue the administration of uterine contractions inhibitors, usually nifedipine 10–20 mg orally every 6 hours, until preterm delivery is imminent or the woman reaches 36 weeks of gestation. One advantage of the prophylactic use of tocolytic agents is that they provide symptomatic relief. A continuous complaint of excessive uterine activity despite the use of tocolytic agents demands reassessment of the situation.

Steroids

The original purpose of the administration of steroids to women at risk of preterm delivery was to prevent neonatal respiratory distress syndrome. Analysis of large series of pregnant women treated with steroids revealed another significant benefit, the prevention of neonatal IVH. These benefits of steroid administration are so important that they overcome most theoretical objections about their use, and significant reasons must be present to justify withholding this treatment particularly if the preterm birth is going to occur before 30 weeks. A mixture of betamethasone phosphate (6 mg) and betamethasone acetate (6 mg) must be given intramuscularly in two consecutive doses, 24 hours apart, to women with established preterm labor and no contraindications to the use of steroids. Some obstetricians prefer to use dexamethasone 4 mg IM every 6 hours for four doses.

Meta-analysis of randomized clinical trials (Crowley, 1995) suggests that the effect of glucocorticoids on the fetal lung lasts no longer than 1 week. Because of this finding, many adopted the practice of administering a "booster" dose of betamethasone every week to those women who remained undelivered 7 or more days after their initial treatment. However, it has been demonstrated that this practice is associated with significant fetal and neonatal side effects and it should be abandoned (Debbs et al., 1997; Jobe et al., 1998; Banks et al., 1999; French et al., 1999; Vermillion et al., 1999).

Antibiotics

The main reason to use antibiotics in women in advanced preterm labor is the prevention of neonatal GBS infection. Pregnant women are usually screened for GBS colonization

at 36 weeks of gestation, and the GBS status of the majority of cases of preterm labor is unknown. In view of the seriousness of this complication and since it occurs more frequently in preterm infants, treatment with antibiotics is mandatory. The antibiotic of choice for the prevention of GBS infection is penicillin. The recommended dosage is 5 mU IV as initial dose, followed by 2.5 mU every 4 hours until delivery. Penicillin is an irritant to the veins receiving the solution and there are occasional periods when the medication is not easily available, and therefore many practitioners prefer to use ampicillin, 2 g IV every 6 hours. For women allergic to penicillin, the antibiotics more frequently used are clindamycin, 900 mg IV every 8 hours and erythromycin 500 mg IVPB every 6 hours. Unfortunately, the transplacental delivery of erythromycin to the fetus and the amniotic fluid is poor and there is growing number of reports indicating high degrees of resistance of GBS to both erythromycin and clindamycin. Because of these concerns it seems that the best choice for women with penicillin allergy is cefazolin. The placental transfer of cefazolin is similar to ampicillin and therapeutic levels of the antibiotic in amniotic fluid and cord plasma are achieved or exceeded in 30 minutes and sustained for more than 7 hours (Mitchell et al., 2001). The only concern is that there is a risk of cross-allergy between cefazolin and penicillin in approximately 5% of penicillin allergic patients.

A second reason for the use of antibiotics in preterm labor is the substantial evidence indicating an association between infection of the products of conception and preterm labor. This evidence fulfills the requirements necessary to define a cause–effect relationship. The association between intrauterine infection and preterm labor is more important when the preterm labor occurs before 30 weeks. This has led to the generalized and indiscriminate use of antibiotics in women in preterm labor. However, multiple trials of antibiotic therapy in women with preterm labor have produced contradictory results. While randomized trials with a relatively small number of subjects have shown that antibiotic treatment results in significantly greater prolongation of pregnancy than treatment with placebo (McGregor et al., 1986; Morales et al., 1988; Winkler et al., 1988; McGregor et al., 1991), studies with a larger number of subjects have shown negative results (Romero et al., 1993; Kenyon et al., 2001). Unfortunately, even the trials with large number of subjects have defects that cast doubt about the reliability of their conclusions. The patient population in these trials was significantly skewed toward women with a gestational age of 32 weeks or more where the incidence of infection as cause of preterm labor is small, probably no more than 5%. Since antibiotics should not alter the course of preterm labor in women who are not infected, their potential effect in the minority that is infected will be diluted. Similarly, the majority of women in both trials were in early preterm labor with cervical dilatation of less than 2 cm in approximately 90% of subjects in the ORACLE II trial (Kenyon et al., 2001), a population that has a lower incidence of intrauterine infection than that in those with advanced cervical dilatation. This fact also dilutes the potential effect of antibiotic treatment. Studies with stricter subject selection criteria that include a positive FFN test will increase the number of women having preterm labor as a result of infection and will provide a more satisfactory answer to this issue.

Inpatient versus outpatient management

Once the episode of preterm contractions has been controlled with tocolytic agents, women in early preterm labor may be managed on an outpatient basis with the exception of those with a positive FFN test. In these cases the risk of preterm delivery is substantial and the best probability of prolongation of pregnancy is with continuous bed rest in the hospital. The test should be repeated every 2–3 weeks while the patients remain in the hospital. If the test becomes negative they become candidates for outpatient management.

Women with an episode of early preterm labor and negative FFN test results may be managed as outpatients since very few will deliver within 2–3 weeks of the test. These women should stop working and limit their activities at home. They should be followed with frequent nurse contact via telephone and weekly office visits. Although several studies have demonstrated that continuous administration of tocolytic agents following the initial treatment of an episode of preterm labor is ineffective in improving the outcome of pregnancy, in many cases continuous administration of nifedipine or terbutaline is necessary to decrease the frequency and intensity of contractions and avoid unscheduled office or hospital visits.

THREATENED PRETERM LABOR

A large number of women admitted to the hospital with frequent uterine contractions have no effacement or dilatation of the cervix by digital examination. Most of them have spurious or false labor and will deliver at term. The risk of preterm delivery in this group of patients cannot be judged by the frequency or intensity of their uterine contractions. In the past, the traditional approach to the diagnosis of preterm labor in women with no apparent cervical changes was to observe them for variable periods of time and repeat the digital examination looking for changes in effacement and dilatation. This approach to the diagnosis of women with contractions and minimal or no cervical changes by digital examination has changed radically. At present, to determine who among them are

destined to deliver prematurely, it is necessary to perform an examination of the cervix with transvaginal ultrasound and a determination of FFN.

Cervical Assessment by Endovaginal Ultrasound

Endovaginal ultrasound allows the clinician to visualize the total length of the cervix including the internal cervical os and determine, based on this observation, if women with regular uterine contractions and without apparent cervical effacement or dilatation are or not at high risk for preterm delivery. For the performance of endovaginal ultrasound of the cervix, the woman should be in recumbent position with her bladder empty. The equipment used is a 5-MHz or 7-MHz vaginal probe transducer. The probe is inserted in the vagina and advanced until the cervix is visualized in the sagittal plane with the echogenic endocervical mucosa along the endocervical canal. Then the probe is moved back in the vagina and reapplied against the cervix using minimal or no pressure. The length of the endocervical canal, the length of the funnel, if present, the width of the internal os, and the relationship between the funnel length and the total length of the cervix (cervical index) are the measurements most commonly used in the sonographic assessment of the cervix. The most important measurement is the cervical length. If there is no funneling, the cervical length is measured from the internal os to the notch made by the external os. If a funnel is present, the cervical length is the distance between the upper and the lower ends of the closed segment of the endocervical canal (Figure 8-4). The width of the internal os is measured from the anterior to the posterior lip of the cervix and the funnel length will be the distance between the imaginary line used to measure the width of the internal os and the upper end of the closed segment of the endocervical canal . The examination usually takes no more than 5 minutes and causes minimal or no discomfort to the patient.

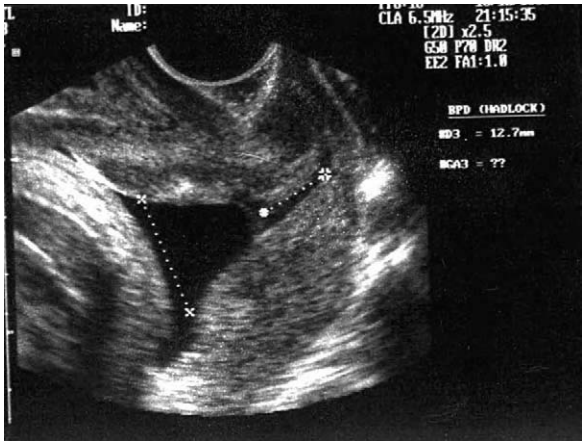

Figure 8-4. Sonographic cervical changes in preterm labor. "Y"-shaped cervix with opening of the internal os and funneling of the membranes into the upper two-thirds of the endocervical canal in a patient with threatened preterm labor. The cervical length is the distance between the upper and the lower ends of the closed segment of the endocervical canal.

The assessment of the cervix using a vaginal probe is not technically demanding but requires training and experience to obtain consistent results. One feature found in some women is dynamic cervical changes at the time of the examination. In these cases at the beginning of the examination, the cervix has a normal appearance with no funnel or with a small funnel. Suddenly a funnel develops and the length of the endocervical canal decreases. Sometimes these dynamic changes can be elicited by application of fundal or suprapubic pressure, maneuvers that should be integral part of all sonographic cervical evaluations. In these cases the cervical length corresponds to the shortest measurement obtained when the dynamic changes are present.

A problem with cervical length measurements is the difficulty in properly visualizing the external cervical os. In these cases, it is useful to place the woman in Trendelenburg position and inject 20–50 ml of sterile saline solution or 10–20 cc of water-soluble methyl cellulose in the vagina using a plastic catheter. The probe is reinserted and the external os will be clearly seen. There are also occasional problems with the visualization of the internal os. Usually this occurs (a) when the cervical length is measured before 16–18 weeks when the lower uterine segment has not developed (b) or in women who have a uterine contraction, myoma, or placenta implanted in the lower uterine segment impeding adequate identification of this anatomic landmark.

The normal length of the cervix has been studied extensively in both nulliparous and multiparous women, and there is preliminary evidence suggesting that measurements using three-dimensional endovaginal ultrasound are more precise and permit a better assessment of the cervix than those obtained with the standard two-dimensional ultrasound (Bega et al., 2000). The cervical length slowly decreases from a mean of 4.0 cm at 16 weeks to 3.0 cm at 40 weeks and there are no significant differences caused by the women's parity. Iams et al. (1996) did a longitudinal study of cervical length in women at high risk of preterm delivery and in a control group of normal women and found that the relative risk of preterm birth increased with decreasing cervical length. If the cervical length at 24 weeks was at the 10th percentile (26 mm), the relative risk of preterm delivery, before 37 weeks, was 3.84. When the cervical length was at the 5th percentile (22 mm), the relative risk increased almost 10 times. When the cervical length was at the first percentile (12 mm), the relative risk was almost 14 times greater. Since the risk of preterm birth increases markedly when the cervix is less than 2.5 cm, this measurement has been widely accepted as the

threshold to define the risk of premature birth. The possibility of preterm delivery (positive predictive value) when the cervix is less than 25 mm is 17.8%. This risk is significantly greater than the normal risk, and hence these women require additional diagnostic tests and special care. The negative predictive value (probabilities of delivery at term) of a cervical length greater than 25 mm is high, 97%, and therefore these women can be reassured and have routine care.

It is apparent that visualization of the cervix with endovaginal ultrasound has modified the classical definition of preterm labor. In addition to women in advanced and early preterm labor who are diagnosed by digital pelvic examination (effacement 80% or more, dilatation more than 1 cm), endovaginal ultrasound allows the recognition of a third group of women with ultrasonic cervical length less than 2.5 cm who are at high risk for preterm labor and preterm birth. In contrast, if the endovaginal ultrasound shows a cervical length of 2.5 cm or more, the woman is in false or spurious labor and has a low probability of preterm labor/delivery. Women with uterine contractions and cervical length less than 2.5 cm are in *threatened* preterm labor and their risk for preterm delivery is even greater if the cervical length is less than 1.5 cm.

Women with cervical length greater than 2.5 cm

If the cervical length by transvaginal ultrasound is 2.5 cm or more, the risk of preterm delivery will not be greater than that in the overall obstetrical population. Women with a long cervix (>2.5 cm) have less than 3% risk of preterm delivery. Therefore, these women should be told that the episode of contractions is spurious or false labor and that they have no greater chance of premature delivery than any normal pregnant woman. They may be sent home after a period of observation during which the contractions usually become irregular and disappear. In general, there is no need to use tocolytic agents during the observation period or after they are discharged. However, some of these women will frequently return to the hospital with episodes of false labor or will call frequently because the contractions are uncomfortable and are interfering with their sleep. In these cases the administration of tocolytic agents for symptomatic relief may be indicated.

Women with cervical length between 1.5 and 2.5 cm

If the cervix is less than 2.5 cm but longer than 1.5 cm, the risk of preterm delivery is approximately 35%, similar to that in women in early preterm labor. This risk is substantially greater than the overall risk of prematurity and these women need further evaluation and close follow-up. Determination of CRP should be routine in these cases and if the result is abnormal, amniocentesis may be indicated. If amniocentesis demonstrates infection, they should be delivered. If the CRP is negative, determination of FFN is important. As it will be discussed later, a positive fibronectin test along with the abnormal cervical length indicates a greater risk of preterm delivery and these women must remain in the hospital until they reach a gestational age consistent with a good fetal outcome or until the FFN test becomes negative.

The customary practice is to hospitalize women with cervical lengths between 1.5 and 2.5 cm and positive FFN test until delivery or until the FFN test becomes negative. The benefits of this practice have not been demonstrated by randomized clinical trials but there is indirect evidence suggesting that admission to the hospital has little value. A recent randomized clinical trial (Goulet et al., 2001) compared home management against in-hospital management after successful treatment or spontaneous remission of preterm labor. Patients in the home management arm of the study had a daily 1-hour visit by a nurse who performed fetal heart rate and uterine activity monitoring. In addition, child care and homemaker services were made available to the women managed at home who required these services. It was concluded that home management had as good results as obtained with in-hospital management. However, this conclusion is questionable because most cases were women in threatened or early preterm labor, the mean gestational age at randomization was 30 weeks, and subjects in the study did not have cervical assessment by ultrasound or determination of FFN. Until more dependable studies are available in this regard, it seems a better option to keep these women in the hospital. When they go home they are more active and the usual outcome is delivery shortly after discharge.

After admission to the hospital, penicillin, ampicillin, or cefazolin in women with penicillin allergy should be given for the prevention of GBS infection. Antibiotics are not indicated for the treatment or prevention of preterm delivery in women with preterm labor since well-designed randomized clinical trials have shown that they are not useful (Romero et al., 1993). It is noteworthy that in this particular setting the use of antibiotics has the potential to select antibiotic-resistant bacterial strains capable of causing significant maternal and neonatal morbidity.

Women with threatened preterm labor, a cervical length between 1.5 and 2.5 cm, normal CRP or negative amniocentesis, and positive FFN should be treated with tocolytic agents for 48–72 hours so that their fetuses may receive the benefits of steroid administration (betamethasone 12 mg IM every 24 hours for two doses). Most of them do well with oral nifedipine (30 mg initial dose followed by 10–20 mg every 6 hours) or oral terbutaline (2.5–5.0 mg every 6 hours). If the FFN is negative the possibility of delivering within 2–3 weeks is minimal and they may be managed as outpatients if the gestational age is 28

weeks or more. They have a greater probability of preterm delivery than the normal population, but the negative FFN indicates that if this is going to occur it will happen after 30 weeks. If the gestational age is < 28 weeks and the FFN is negative they may still deliver at < 30 weeks, when the complications of prematurity are severe, and therefore they should remain in the hospital until they reach 28 weeks. They should have a repeated FFN test before discharge, at 28 weeks, and if the test is positive inpatient management should continue.

Several studies have compared FFN versus cervical length for the prediction of preterm delivery and produced varied results: some suggesting that FFN is a better predictor, others suggesting that cervical length is superior, and still others suggesting that they have similar value (Rizzo et al., 1996; Rozenberg et al., 1997; Goldenberg et al., 2000; Rozenberg et al., 2000). A literature review indicates that these tests are approximately equivalent in their ability to distinguish between high and low risk for preterm delivery in symptomatic patients but their combined use has a better predictive value than that obtained with the use of only one of the two tests. If a single test is to be used, the ultrasonic examination of the cervix is preferred to determine the likelihood of preterm delivery because it is a relatively simple test that gives an immediate answer and is less costly than the biochemical test. Also, most labor and delivery units have portable ultrasound equipment with vaginal probe capability, and availability of equipment is not an issue. We limit the use of FFN to the evaluation of women with early or threatened preterm labor to further define their risk of preterm delivery and to determine their eligibility for outpatient treatment.

Table 8-2. Risk of spontaneous delivery within 48 hours, 7 days, and 14 days for women in early preterm labor according to cervical length and vaginal fibronectin

	Delivery within 48 h (%)	Delivery within 7 days (%)	Delivery within 14 days (%)
Cervical length < 15 mm	36.7	56.7	56.7
Cervical length ≥ 15 mm	3.2	5.9	9.2
Cervical length < 30 mm	13.9	23.1	26.9
Cervical length ≥ 30 mm	1.9	2.8	4.7
(+) Fibronectin	19.2	34.6	42.3
(–) Fibronectin	4.3	6.1	7.4
Cervical length > 15 mm and (–) fibronectin	2.0	3.4	4.7
Cervical length > 15 mm and (+) fibronectin	8.3	16.7	27.8
Cervical length < 15 mm and (–) fibronectin	28.6	35.7	35.7
Cervical length <15 mm and (+) fibronectin	48.3	75.0	75.0
Cervical length >30 mm and (–) fibronectin	7.1	11.4	12.9
Cervical length >30 mm and (+) fibronectin	0.0	7.1	14.3
Cervical length < 30 mm and (–) fibronectin	2.2	2.2	3.2
Cervical length <30 mm and (+) fibronectin	26.3	44.7	52.6

From Gomez R, Romero R, Medina L, et al. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. Am J Obstet Gynecol 2005; 192: 350–9.

The study of Gomez et al. (2005) demonstrated that the combined use of cervical length by endovaginal ultrasound and FFN improved the value of both tests in the prediction of preterm birth when the cervical length was < 30 mm (Table 8-2). This study implies that women in early preterm labor or in threatened preterm labor can be screened first with vaginal ultrasound and determination of FFN is limited to those with a cervical length < 30 mm.

Women with cervical length less than 1.5 cm

If the cervical length is 1.5 cm or less, the risk of preterm delivery is substantial and approximately 50% of these women will deliver before 32 weeks and approximately 90% will deliver before 34 weeks of gestation (Hassan et al., 2001). In-hospital management is mandatory. Women with a cervix length less than 1.5 cm and positive fibronectin most probably will deliver within 1 or 2 weeks. If FFN is negative, delivery most probably will not occur within 2–3 weeks from the time of the test. Determination of CRP is mandatory in these cases because a significant number of these women will have subclinical amnionitis. If the CRP is elevated, amniocentesis is recommended and if the amniocentesis reveals intrauterine infection, the pregnancy should be interrupted. If the CRP or the amniocentesis shows no infection, management should be expectant and the woman should be treated with tocolytic agents, antibiotics, and steroids.

PREVENTION OF PRETERM LABOR

Prevention of preterm labor requires identification of the subjects at risk and effective preventative measurements to avoid the abnormal outcome. Unfortunately, we are far from fulfilling these two conditions. More than 40% of all women who deliver preterm because of preterm labor have no high-risk factors and there are no proven measures to prevent the outcome when a high-risk woman is identified.

Identification of Asymptomatic Women at Risk

The identification of women at risk of preterm labor has followed two different approaches. The first consists of

determining the woman's risk of preterm delivery on the basis of socioeconomic and past medical and reproductive risk factors. A second approach is the use of tests to determine the risk. Some of these tests are the measurement of cervical length by ultrasound and the determination of FFN in cervicovaginal secretions.

Sociodemographic risk factors

Some of the variables used in attempts to identify asymptomatic women at high risk for preterm labor are socioeconomic status, work environment, medical history, obstetrical history, history of spontaneous and induced abortions, maternal weight prior to pregnancy, weight gain during pregnancy, and drug and alcohol abuse. Some investigators have organized these clinical variables into high-risk scoring systems that are incorporated into the prenatal record. Unfortunately, the experience with the use of scoring systems to determine the risk of preterm labor/delivery is mixed and the majority of opinions are that they are not useful in identifying asymptomatic women at risk. Multivariate analysis (Mercer et al., 1996) shows that the presence of some of these variables increases the relative risk of preterm delivery but the increase is small and probably not useful for clinical use. In a recent investigation (Mercer et al., 1996) close to 3000 women were prospectively evaluated by univariate analysis and multivariate logistic regression and it was found that demographic factors such as race, socioeconomic status, and working conditions were associated with preterm delivery in nulliparous but not in multiparous women. In multiparous women the factor most strongly associated with preterm labor/delivery was a history of one or more preterm deliveries. A body mass index < 19.8 and a Bishop score of 4 or more were also associated with preterm delivery in both nulliparous and multiparous patients. Increased number of uterine contractions in the 2 weeks preceding delivery was an important association in nulliparous as was vaginal bleeding in multiparas. However, when the logistic regression equation was applied to 15% of the population under study it failed in identifying most of the women who delivered prematurely. Other studies (Wildschut et al., 1997) have concluded that sociodemographic factors have no substantial importance on the risk of preterm birth, both in nulliparous and multiparous women.

A variable that confounds epidemiologic studies on the prediction of preterm birth is that many of them do not separate the newborns between premature AGA (appropriate for gestational age) and premature SGA (small for gestational age). There is evidence (Zeitlin et al., 2001) indicating that the impact of demographic, socioeconomic, and medical factors for preterm birth is different if the newborn is AGA or SGA. Maternal age over 35, smoking, and high and low maternal body mass index have a stronger association with SGA than with AGA preterm infants. Also maternal hypertension is a variable associated with SGA, while diabetes is associated with non-SGA preterm infants.

Obstetrical risk factors

The identification of asymptomatic women at risk of preterm labor is different in nulliparous than in multiparous women. In the multiparous patients knowledge of the past reproductive performance is the best index to assess the probability of preterm birth. One study (Carr-Hill et al., 1985) demonstrated that in multiparous women the risk of preterm labor/delivery is 15% when there is a history of preterm birth in the first pregnancy. This risk increases to 24% if the fist pregnancy was delivered at term but the second was preterm and to 32% if both the first and the second pregnancy were preterm deliveries. The risk of preterm delivery is associated with the gestational age at the time of the preterm birth, and women with a history of preterm delivery between 23 and 27 weeks of gestation have a relative risk of 10.6 of delivering before 28 weeks in the current pregnancy (Mercer et al., 1999). Investigators have studied the probability of recurrent preterm birth in women with a prior preterm birth using logistical regression models including as variables the gestational age at the most recent preterm delivery and the results of cervical fibronectin and ultrasonic cervical length at 22–24 weeks (Iams et al., 1998). It was found that the risk of delivery before 35 weeks among fibronectin-positive women was 65% when the cervical length was < 2.5 cm, 45% when the cervical length was 26–35 mm, and 25% when the cervical length was > 35 mm at 24 weeks' gestation. Among fibronectin-negative women the recurrence risk was 25, 14, and 7% respectively. It is clear from all the studies that a history of preterm delivery because of preterm labor automatically classifies the patient as high-risk for another preterm labor/delivery.

A variable with some predictive value in both nulliparous and multiparous patients is the number of prior spontaneous or induced abortions. A retrospective cohort population study (Lumley, 1998) found an incidence of preterm birth in primiparous women of 5.9%. This incidence increased substantially with the number of prior spontaneous or induced abortions, reaching a relative risk close to 10 after four spontaneous or induced abortions. These data are in sharp contrast with the minimal relative risk after one to four prior normal births in women with no history of spontaneous or induced abortions. Similar observations in USA show a 2.5 times increase in the incidence of preterm birth in women with a history of at least one spontaneous abortion. With respect to voluntary terminations, studies indicate a 13% incidence of preterm birth after one termination and over 20% with three or more induced abortions.

Tests for the identification of women at risk

The tests most commonly proposed as screening tools for the identification of women at risk of preterm labor/delivery are home uterine contractions monitoring, assessment of cervical length by endovaginal ultrasound, determination of the concentration of fibronectin in cervicovaginal secretions, and testing for bacterial vaginosis, *Trichomonas*, group B streptococcus, and chlamydia colonization of the vagina.

Home uterine monitoring

Uterine contractions increase in frequency in the days before term or preterm birth (Iams et al., 2001). Home monitoring of uterine activity using data transmission devices was introduced for the early detection of excessive uterine activity in patients at risk of preterm labor. In the largest randomized study on this subject (Dyson et al., 1998) it was found that there was a higher number of unscheduled office or emergency room visits and that the diagnosis of preterm labor was made more frequently in women who had home uterine contraction monitoring than in control subjects. However, there were no differences between control and experimental subjects in the incidence of preterm birth and in neonatal outcomes. The results were similar in singleton and twins. The current opinion is that for most patients home uterine monitoring is not better than frequent nursing contact and support. However, patients who cannot recognize adequately the presence of contractions may benefit from home uterine monitoring. The inability to perceive contractions is particularly high in patients with multifetal pregnancies and with uterine overdistention due to excessive amount of fluid.

Cervical length

Cervical length measurement by endovaginal ultrasound examination is a popular screening test for preterm labor/delivery. A cervical length less than 25 mm conveys a relative risk of 6.9 (95% confidence interval 4.3–11.1). However, the positive predictive value of such a measurement in asymptomatic women is only 14% (Iams et al., 2001).

Screening of asymptomatic women with cervical length measurements has generated the interesting problem of the adequacy of prophylactic treatment of women with short cervix by means of cervical cerclage. It seems logical that the cause of preterm birth in women with short cervix is the inability of the cervix to support the pregnancy and that the solution is to reinforce the cervix surgically with a cerclage. However, the study of To et al. (2004) has definitely clarified this controversy. In this study cervical length was measured in 47,123 women between 22 weeks and 24 weeks and 6 days of gestation and 253 women with a cervical length of 15 mm or less were randomized between cervical cerclage and expectant management. The proportion of preterm delivery before 33 weeks was similar in both groups and there were no significant differences in perinatal or maternal outcomes. This study indicates that cervical cerclage is ineffective in the majority of women who present with short cervix in the midtrimester of pregnancy. Cerclage is an operation that should be limited to certain groups of women, as described in Chapter 10 of this book.

Fetal fibronectin

The accuracy of FFN in predicting preterm birth is different in symptomatic and asymptomatic women. The value of FFN in asymptomatic women is far from optimum with a positive predictive value of 14.7% and a negative predictive value of 99.7% (Goldenberg et al., 1996). Some have proposed universal screening on the basis of the high negative predictive value, but just telling low-risk women that they will not deliver prematurely will have a similar negative predictive value (95%).

The Preterm Prediction Study of the National Institute of Child Health and Human Development analyzed the sensitivity, specificity, and predictive values of a Bishop score ≥ 4, fibronectin test ≥ 50 ng/ml, and a cervical length ≤ 25 mm in the prediction of preterm birth in asymptomatic women (Iams et al., 2001). It was found that although the three tests were significantly related to the occurrence of birth before 35 weeks, they had low sensitivity and low positive predictive value to be considered suitable tools for primary screening of a low risk population. In another recent study (Goldenberg et al., 2001), investigators evaluated 28 potential biologic markers for preterm birth in a cohort of 50 women who delivered at less than 32 weeks because of preterm labor and compared their results with matched-term control subjects. In the univariate analysis they found that the most important predictors of preterm birth at 24 weeks' gestation were a positive cervical fibronectin and a cervical length < 10th percentile for the gestational age. The best serum markers were a concentration of alpha-fetoprotein and alkaline phosphatase above the 90th percentile and a concentration of granulocyte colony-stimulating factor above the 75th percentile. It was also found that there was little overlap among these biologic markers. The authors suggest the possibility of developing a multiple serum marker test at 24 weeks that in addition to the cervical length or the cervical fibronectin could be used as predictor of preterm birth. It is obvious that more research is necessary to validate this approach and determine the predictive values and the cost-effectiveness of this approach.

Vaginal infections

The search for and the treatment of vaginal/cervical infections was thought to be of fundamental importance in the prevention of preterm birth. Unfortunately, the results of therapeutic trials of women considered at risk because of the presence of vaginal infections have been disappointing. In one study (Carey et al., 2000) metronidazole treatment was effective for the treatment of bacterial vaginosis but was unable to prevent preterm delivery caused by preterm labor or preterm premature rupture of membranes. More disappointing, another randomized trial (Klebanoff et al., 2001) demonstrated that the incidence of preterm delivery was greater in women infected with *Trichomonas vaginalis* and treated with metronidazole than in women receiving placebo. A recent systematic review also concluded that treatment of bacterial vaginosis and infection by *T. vaginalis* does not reduce the incidence of preterm birth in low- or high-risk women (Okun et al., 2005).

Chlamydia trachomatis is a bacterium associated with short cervix, bacterial vaginosis, and preterm labor/delivery (Andrews et al., 2000). For that reason present prenatal care includes the performance of cervical cultures and the treatment of chlamydia infection early in gestation. However, there is no evidence that treatment of chlamydia infection decreases the incidence of preterm labor/delivery. Treatment is necessary anyway to prevent ophthalmologic infection in the neonate. In many women chlamydia colonization is asymptomatic and in others the only evidence of cervical infection is the presence of thick, yellow mucus that is very adherent to the endocervical glands, which bleed when the mucus is removed with a piece of cotton. Chlamydia responds well to erythromycin, 250–500 mg four times daily for 7 days. Alternative treatment is trimethoprim–sulfamethoxazole, 160 and 800 mg, respectively, twice daily for 10 days.

Another bacterium implicated in preterm labor/delivery is *Ureaplasma urealyticum*. This is the bacterium most frequently found in amniotic fluid and placental cultures of women who deliver preterm. However, women at high risk for preterm delivery and with cervical colonization by *Ureaplasma* who were treated with antibiotics had a similar incidence of preterm delivery than noncolonized high-risk women (Benito et al., 2001). In another study (Esenbach et al., 1991), pregnant women colonized with *Ureaplasma* were treated with erythromycin starting between 26 and 30 weeks' gestation and continuing until 35 completed weeks. There were no significant differences between women treated with erythromycin and women treated with placebo with respect to gestational age at delivery and incidence of premature rupture of membranes.

BOX 8-6

Warning symptoms and signs of preterm labor

- *Menstrual-like cramps* (constant or recurrent, just above the pubic bone)
- *Low, dull backache* (constant or recurrent)
- *Pressure* (feels like the baby is pushing down, feels heavy)
- *Abdominal cramping* (with or without diarrhea)
- *Increase or change in vaginal discharge* (may be mucous, watery, light, or bloody)
- *Fluid leaking from the vagina*
- *Uterine contractions that are 10 or less minutes apart* (may be painless, usually described as the baby "balling up")
- *Short cervix* (The distance between the insertion of the vagina in the anterior or the posterior aspect of the cervix (anterior or posterior fornix) and the external cervical os is less than 1 cm.)
- *Lower uterine segment* thinned (developed). Presenting part deep in the pelvis

In view of the disappointing results of clinical, laboratory, microbiologic, and sonographic screening in the identification of the asymptomatic low-risk women destined to develop preterm labor/delivery, the best approach available at this time is to provide intensive patient education in the recognition of early symptoms and signs of preterm labor. This implies systematic assessment during prenatal visits of the early warning signs and symptoms of preterm labor shown in Box 8-6. One or several of these symptoms and signs usually occur several days or even several weeks before the onset of regular contractions. These warning signs and symptoms of preterm labor are subtle, and pregnant women frequently ignore their importance. However, studies have shown that women are 75% accurate in their ability to recognize warning symptoms of preterm labor. The symptoms are unspecific and frequently are disregarded by the patient and by health care providers as a minor complaint or attributed to "round ligament pain," the baby "balling up," or to "gastrointestinal flu." All the pregnant patients, and especially those with high-risk factors for preterm birth, should be taught early in the course of their pregnancies to recognize these symptoms and to call their obstetricians when they occur. The obstetrician and his/her office personnel should not minimize the importance of these complaints and should consider as urgent matter the evaluation of women presenting with these minors complaints. It is also important to educate pregnant women about the dangers of self-diagnosis and the potential complications of attributing pelvic or abdominal discomfort to organs other than the uterus.

Management of Women at Risk

Women at risk for preterm labor/delivery (multiparous with history of preterm deliveries and nulliparous women

with early warning symptoms) should have endovaginal ultrasound examination of the cervix and determination of FFN in the cervical–vaginal secretions. Women with a prior preterm labor/delivery should have both tests performed at 24 weeks. However, the ultrasound of the cervix may be performed as early as 18 or 20 weeks if there are warning signs and symptoms or if the cervix appears to be short, less than 1 cm in the intravaginal portion, in the initial evaluation of the patient. Also, early ultrasound of the cervix at 18–20 weeks should be performed in women with a history of preterm delivery before 26 weeks. As mentioned before, the FFN test is not useful before 22 weeks. In nulliparous women the ultrasound examination and the FFN test should be performed as soon as warning symptoms or signs are detected.

Once a woman at risk is identified by her past obstetrical history, cervical length or fibronectin, or by a combination of these variables, then comes the frustrating task of attempting to prevent her preterm delivery. One of the first questions in the management of asymptomatic women at risk of preterm birth is whether or not they should continue working. There are studies (Henriksen et al., 1995; Walker et al., 1999) indicating that modification of working conditions is indicated in pregnant women who work 8 or more hours without interruption, work more than 5 days/week, work standing up on their feet most of the time, work with vibrating instruments, and perform monotonous, repetitive work such as in assembly lines or factories.

One question in the management of asymptomatic women at risk for preterm delivery is if they should be at bed rest. Most pregnant women at risk for preterm delivery notice a relationship between increased physical activity and the occurrence of preterm contractions. If this is the case, they should be counseled to avoid strenuous activities, to avoid exercise, and to rest in the lateral supine position every time that they have an opportunity to do so. However, complete bed rest should be discouraged.

Another frequent question in asymptomatic women at high risk for preterm delivery has to do with coital activity. There is some evidence suggesting the existence of a relationship between coital activity during pregnancy and preterm labor. One of these evidences comes from data from the Collaborative Perinatal Project (Naeye and Ross, 1982). This study showed that the frequency of amniotic fluid infection in women with intact membranes is significantly greater in subjects who had coitus once or more per week during the month before delivery than in those who did not have coitus. The implication of this finding is that coital activity during pregnancy may be a factor facilitating the production of preterm labor. However, recent investigations (Sayle et al., 2001) have not demonstrated an association between coitus and adverse outcome of pregnancy. This conflicting information should be given to the woman at risk for preterm delivery and to her husband. Discontinuation of coital activity is probably necessary if the woman notices strong contractions with coitus or at the time of orgasm.

Progesterone

The role of progesterone in the maintenance of pregnancy has been known for many years. It is known that this is a key hormone involved in maintaining uterine quiescence during pregnancy and in many mammalian species a decrease in progesterone levels is a prerequisite for the initiation of labor. The relationship between progesterone serum levels and initiation of labor is not clear in the humans and there is evidence suggesting that it is the density of myometrial progesterone receptors and not the changes in serum concentration—the phenomenon responsible for the uterus responsiveness to oxytocin and prostaglandins and to the onset of labor. For many years clinical trials on the effect of progesterone in preterm labor have mostly produced favorable results, but the reduced number of subjects has cast doubts about their accuracy and prevented wide acceptance of this therapy. More recently, two randomized clinical trials (Da Fonseca et al., 2003; Meis et al., 2003) and meta-analysis (Mackenzie et al., 2006) have reinforced the positive results of early trials. As a consequence, the Federal Drug Administration (FDA) of USA has recently approved the administration of weekly injections of 17-hydroxy progesterone acetate for the prevention of recurrent preterm birth. It is important to emphasize that the beneficial effect of progesterone has been demonstrated only for women with a well-documented history of spontaneous preterm birth and that the effect of treatment when prematurity is due to other causes such as multifetal pregnancies, clinical or subclinical infection or inflammation, bleeding in the choriodecidual membranes, etc., is unknown. The dose used by Meis et al. (2003) was 250 mg of 17-hydroxy progesterone caproate IM, every week, starting between 15 and 20 weeks of gestation and ending at 36 weeks. In Da Fonseca et al. (2003) trial the investigators used 100 mg vaginal suppository every night from 24 to 34 weeks of gestation.

INDIAN EXPERIENCE OF PRETERM LABOR

Preventive measures generally practiced in India to reduce the risks of preterm labor (PTL) include improvement of nutrition, correction of anemia so rampant in India, elimination of septic foci (urinary infection/bacteriuria, vaginitis, gingival infection), limit drug and substance abuse (tobacco, alcohol, tea and coffee, intoxicants), avoid heavy manual work, ensure adequate rest periods (2 hours afternoon and 8 hours at night), and provide regular antenatal care. Timely cerclage in patients with suspected cervical

incompetence. Working women advised to proceed on maternity leave by 32 weeks or earlier if there is a past history of PTL. Couples at risk advised to abstain from sexual intercourse in the last trimester of pregnancy. The practice of prophylactic administration of oral tocolytics (terbutaline/isoxsuprine HCl/duvadilan/ritodrine) has been of debatable value and is not widely practiced. Tocolysis to prevent threatened preterm labor has been practiced with a measure of success, but these patients need hospitalization and close monitoring.

Jayaram and Sudha (2001) from Guntur in Andhra Pradesh emphasized the role of tocolytics, antibiotics, steroids, and amnioinfusion in the management of PTL. Saha (2002) from Darjeeling (Hill district of West Bengal) reported on a series of 75 women of PTL with the magnesium sulfate regime. He was able to prolong the pregnancy by more than 72 hours in 90.7% of their patients. The onset was tocolysis was observed within 30 minutes of initiating treatment. No major side effects were observed and the fetal salvage rate was 89.3%. Pregnancy was prolonged beyond 32 weeks in 64%. The perinatal loss was 8/75, of which 2 died of respiratory distress syndrome. Sirohiwal et al. (2001) from Rohtak in Haryana reported an incidence of PTL of 9.3%. Of these 10.3% were selected for tocolytic therapy. A comparison of the efficacy of isoxsuprine and ritodrine revealed that whereas the mean period of prolongation of pregnancy achieved in the isoxsuprine group was 16.6 days, the pregnancy prolongation period in the ritodrine treated group was 23.6 days. Phadke et al. (2000) from Mumbai in Maharashtra reported on an experience of treating 65 patients with ritodrine tocolysis. Of these 15 patients were advised prophylactic ritodrine prophylaxis and 50 patients were treated with ritodrine tocolysis for PTL. The success rates of tocolysis in patients > 28 weeks gestation was 92.9% as against 38.5% in women with gestation periods of < 28 weeks. The pregnancy was prolonged by 1–4 weeks in 78% cases. Kumar et al. from Bhopal in Madhya Pradesh evaluated the efficacy of the "glyceryl trinitrite patch" in 100 patients with PTL. They reported a success rate of 95% in their series. The incidence of premature rupture of membranes was 4% as also the recurrence of PTL in 4%. The patch was well-tolerated by 88%. Common side effects reported included headache, dizziness, and local irritation at the site of the patch.

IMPORTANT POINTS

1. Preterm labor is a syndrome with multiple causes, characterized by the premature activation of the three components of the final pathway of parturition.
2. Preterm labor has different stages. *Advanced preterm labor* is characterized by cervical effacement ≥ 80% and cervical dilatation ≥ 3 cm. *Early preterm labor* is characterized by effacement ≥ 80% and cervical dilatation ≥ 1 cm but < 3 cm. *Threatened preterm labor* is characterized by regular and frequent (≥10/hour) uterine contractions, cervical dilatation < 1 cm, and short cervix (<2.5 mm) by endovaginal ultrasound examination.
3. Threatened preterm labor may be categorized in two groups with different prognosis according to the cervical length measured by endovaginal ultrasound. Women with cervical length < 1.5 cm have a 90% probability of delivery before 36 weeks. Women with cervical length between 1.5 and 2.5 cm have a 35% probability of delivering before 36 weeks.
4. The most common etiologies of preterm labor are chorioamniotic infection, maternal and fetal stress, and bleeding in the choriodecidual interface. The mechanism of labor for each of these causes involves different mediators that stimulate the final pathway of parturition.
5. Chorioamniotic infection causing preterm labor may be overt or subclinical. The main sign of overt infection is fever. Subclinical infection should be suspected in all women in preterm labor at < 30 weeks and with elevated (>0.9 mg/dl) CRP. The diagnosis is confirmed if the amniotic fluid analysis shows bacteria, elevated IL-6, decreased glucose, or elevated LDH.
6. Women in preterm labor with chorioamnionitis (overt or subclinical), with fetal disease, or with adequate FLM should be allowed to deliver. Women in preterm labor who do not need to be delivered should receive tocolysis and steroid treatment.
7. Tocolysis may decrease the frequency or temporarily abolish uterine contractions in women in advanced preterm labor with cervix dilated as much as 5 or 6 cm. However, maternal morbidity is high and it is preferable to allow them to deliver rather than attempting to arrest labor to give steroids.
8. The FLM test and the lamellar body count are rapid tests for FLM that require a small amount of amniotic fluid. They are quantitative and have predictive values similar to the L/S ratio (lethicin–sphingomyelin ratio). An FLM concentration ≥ 50 mg/g and a lamellar body count of 30,000 have a 95% predictive value for FLM.
9. Determination of FFN concentration in the cervicovaginal secretions is a useful complement to endovaginal ultrasound measurement of cervical length to assess the probability of preterm delivery.
10. The evidence that antibiotics prevent preterm birth or prolong gestational age in women in preterm labor is contradictory. The only indications for their use in women with preterm labor are (a) the presence of chorioamnionitis (overt or subclinical) and (b) for prophylaxis of neonatal GBS infection.

11. The agent of choice for the inhibition of uterine contractions in women in preterm labor is nifedipine. Tocolysis with intravenous magnesium sulfate and beta-adrenergic agents has the potential for serious maternal and fetal side effects.
12. The best predictor of preterm labor is a poor past reproductive performance. Unfortunately, more than 40% of all patients who develop preterm labor are nulliparous.
13. Endovaginal ultrasound and FFN have low sensitivity and specificity as screening tests for asymptomatic low-risk women and their use for this purpose is discouraged.
14. The majority of patients who develop preterm labor have early warning signs and symptoms. Patients should be taught to recognize these signs and symptoms and call for help when they occur.
15. For most patients at risk of preterm delivery (previous preterm birth, nulliparous with early signs and symptoms) home uterine monitoring is not better than frequent nursing contact and support for the prevention of preterm labor. However, patients who cannot adequately perceive the presence of contractions may benefit from home uterine monitoring. The inability to perceive contractions occurs frequently in women with multifetal pregnancies.
16. Randomized clinical trials have demonstrated that treatment of bacterial vaginosis, trichomonas, and ureaplasma infections have no value in the prevention and may increase the incidence of preterm birth. Chlamydia infections should be treated to avoid neonatal infection, but there is no positive effect of this treatment in the prevention of preterm labor.
17. The objectives of the management of patients with advanced preterm labor are to select patients who need to be delivered and to identify those who will benefit from tocolysis and glucocorticoid treatment.
18. There is no evidence indicating that the use of cervical cerclage in women in preterm labor is beneficial. The evidence about the use of cerclage in asymptomatic women with short cervix by endovaginal ultrasound clearly indicates that cerclage is of no benefit in the prevention of preterm birth.

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9

Premature Rupture of Membranes

CHAPTER OUTLINE

Premature rupture of membranes (PROM) is a syndrome characterized by rupture of the fetal membranes before labor. It occurs in approximately 10% of all pregnancies and in 70% of the cases it occurs in pregnancies at term. Although there is some morbidity when PROM occurs in term pregnancies, the fundamental clinical problem is preterm PROM (PPROM), a condition that occurs in 3% of all pregnancies and is responsible for approximately 30% of all preterm deliveries (Arias and Tomich, 1982).

Most Indian studies from Mumbai report an incidence of PROM between 7 and 12% (Bhalerao and Desai, 2000; Bhide 2001). Gunn et al. (1970) observed the incidence of PROM to range from 2 to 17%. Daftary and Desai (2006) correlated the incidence of premature rupture of membranes with the gestational maturity and reported that PROM before the onset of true labor occurs in 5–20% of all women in labor. About a third of these occur prior to 37 weeks (PPROM) and is associated with higher perinatal morbidity and mortality. There is an enhanced risk of cord compression/prolapse and infectious morbidity, particularly so if cesarean section becomes eventually necessary. Approximately two-thirds of the patients with PROM are delivered within the next 4 days and the rest within 1 week. The time between the rupture of membranes and onset of labor (latent period) may extend from hours to days. Generally the shorter the gestation period, the longer the latent period. Approximately 80% of *PROM at term* begin labor within 24 hours and 95% within 72 hours. In case of *PROM in preterm gestation,* labor generally sets in within 24 hours in 35–50% patients, and within 72 hours in 70% patients. Whereas in women with *preterm PPROM*, almost 90% deliver within the next two weeks.

MECHANISMS AND ETIOLOGY

As discussed in Chapter 7, PROM, preterm labor with intact membranes, and incompetent cervix are the clinical syndromes that result from the early activation of the final pathway of parturition. These three syndromes are

closely related and there is considerable overlapping in their etiology as well as in their clinical, pathological, and epidemiologic profiles. However, there are significant differences between preterm labor and PPROM, most importantly in the incidence of chorioamniotic infection and inflammation, making it necessary to treat and manage them as separate entities.

Theoretically, PROM may occur because of a reduction in membrane strength or an increase in intrauterine pressure or both. The possibility that excessive intrauterine pressure is an independent cause of PROM is not supported by clinical observations. Patients can tolerate constant or intermittent increases in intrauterine pressure secondary to polyhydramnios or to uterine contractions for prolonged periods without rupture of the membranes. Therefore, for all practical purposes, the cause of PROM is a reduction in membrane strength. Under normal circumstances, the tensile strength of the membranes increases until 20 weeks and then plateaus until week 39 when it starts to dramatically decrease (Pressman et al., 2002). The amniotic membranes are a connective tissue structure and their tensile strength depends on the synthesis, degradation, and quality of their collagen. An abnormal collagen structure may be responsible for PROM as evidenced by the high frequency of PROM in women affected by connective tissue disorders such as the Ehlers– Danlos syndrome (Barabas, 1966). Also, tobacco smoking and nutritional deficiencies of copper and ascorbic acid cause abnormal collagen cross-linking and may predispose to PROM.

Rupture of the membranes is the most distinctive clinical feature of membrane activation, one of the three components of the final pathway of parturition. One of the biochemical markers of membrane activation is an increase in collagenolysis. Collagen may be degraded as a result of the concerted sequential activity of several matrix metalloproteinases (MMP) that bind to specific tissue inhibitors (TIMP). When there is predominance of MMP over TIMP, collagenolysis occurs. The possibility that increased collagenolysis is a mechanism of PROM is supported by robust research data. The activity of MMP-9 is significantly elevated in the amniotic fluid of women with PROM at term as compared with women without PROM, is higher in women with PPROM, and is markedly elevated in women with bacterial invasion of the amniotic membranes regardless of the status of the membranes (Athayde et al., 1998). Similar evidence has been obtained for MMP-1 (Maymon et al., 2000a) and MMP-8 (Maymon et al., 2000b). In the case of MMP-8, a larger concentration of the enzyme is found in the forebag rather than in the upper part of the amniotic sac—a fact that may explain the predilection of the membranes to rupture in the lower pole of the sac. Also, fetuses with PPROM have greater plasma concentrations of MMP-9 as compared with fetuses with intact membranes (Romero et al., 2002).

There is evidence that genetic factors are of importance in the predisposition to PROM and may explain its higher frequency in the African-American population. Polymorphisms in the promoter region that control the transcriptional response of the MMP-1 were found more frequently in newborns of women who delivered after PROM (Fujimoto et al., 2002). Similarly, polymorphisms of the MMP-9 promoter region were found more frequently in newborns of African-American women who had PROM than in those who delivered at term (Ferrand et al., 2002).

Intra-amniotic infection may cause alterations in the tensile strength of the fetal membranes by mechanisms different than those involved in the increase in collagenolytic activity. Several of the microorganisms found in women with PPROM and amniotic infection produce proteolytic enzymes that can weaken the fetal membranes (McGregor et al., 1987). Furthermore, the host inflammatory response to intra-amniotic infection almost certainly plays a role in the mechanism of PPROM. This inflammatory response includes the production of cytokines that stimulate prostaglandin production by the amnion and chorion. Prostaglandins stimulate uterine contractility and cause increased collagen degradation. Also, the glucocorticoids produced in response to the stress of the intra-amniotic infection may be involved in facilitating rupture of the membranes.

There is evidence implicating that relaxin is a component of the mechanism of membrane rupture. Laboratory experimentation shows that relaxin induces collagenase activity when incubated with membranes in vitro (Qin et al., 1997). Also, the relaxin gene is overexpressed in the membranes of women with PPROM when compared with those from women in preterm labor with intact membranes or from women not in labor (Bojic et al., 1997). Other studies have indicated that the relaxin-mediated pathway of PPROM is independent of infection (Millar et al., 1998).

Infection

Infection is twice as frequent in PROM than in preterm labor with intact membranes. In term PROM the incidence of infection is approximately 20.0% (Romero et al., 1991) and in PPROM it is 38.3% (Romero et al., 1993). Also, women with PPROM and labor at the time of admission have a greater incidence of chorioamnionitis than women with PPROM admitted without labor (Romero et al., 1988c). Infection is also associated with gestational age and when PPROM occurs at less than 26 weeks, the incidence of chorioamniotic infection may be as high as 80%. The high frequency of infection in PROM has profound effects on the natural course, prognosis, and treatment of that condition. As it will be seen

later, a significant part of the initial assessment, diagnostic efforts and management plans in women with PROM are determined by the problem of infection.

The evidence implicating infection as an etiologic agent in membrane weakening and rupture is robust. Between 14.6 and 38.0% of women with PROM will have positive amniotic fluid cultures. The microorganisms isolated from amniotic fluid cultures (*Peptostreptococcus, Bacteroides, Fusobacterium, Lactobacillus, Ureaplasma urealyticum*) are similar to those normally found in the vagina, strongly suggesting that the source of infection is bacteria normally present in the vagina or the cervix. The mechanism of ascending infection is not clear. Under normal circumstances the membranes are separated from the vaginal flora by the cervix and the endocervical mucus. It is possible that unrecognized cervical changes facilitate the occurrence of ascending infections. Changes in the antibacterial properties of the cervical mucous (Hein et al., 2001) may also play an important role in facilitating ascending infection. The importance of factors that theoretically may increase the possibility of ascending infection such as sexual intercourse, pelvic digital examinations during pregnancy, and history of prior cervical dilatation for abortion or D&C has been disproved by clinical investigations. On the other hand, colonization of the lower genital tract by *Chlamydia, Neisseria gonorrhoeae,* group B streptococcus (GBS), *Trichomonas*, and bacteroid species has been shown to increase the risk of PROM, but the evidence that treatment of colonized patients prevents PROM is lacking.

Abnormal Placentation

Approximately 20% of the placentas of women with PPROM show abnormal trophoblastic invasion of the spiral arteries and another 20% show a combination of vascular and infectious lesions (Arias et al., 1993). Deficient trophoblastic invasion of the spiral arteries is not a phenomenon exclusive to women with PPROM and it is also found in cases of severe preeclampsia, fetal growth restriction, preterm labor, and unexplained fetal death. It seems that abnormal placental implantation is a fundamental mechanism of disease during pregnancy that has diverse clinical expressions. There are no adequate explanations to understand why and how the absence or deficiency of physiologic changes in the spiral arteries may have different clinical expressions or the specific mechanism leading to PROM in women with abnormal placentation.

Repetitive Stress

Toppozada et al. (1970) presented data indicating that repeated stretching of the membranes such as that occurring during labor causes decreased tensile strength. Lavery et al. (1982) demonstrated that uterine activity causes strain hardening of the membranes with development of microscopic flaws (tissue fatigue) that reduce their ability to tolerate normal increases in pressure. This mechanism of rupture may be operational during term labor where the fetal membranes, weakened by apoptotic changes, eventually break under the repetitive stretching and relaxation caused by uterine activity.

MATERNAL AND FETAL PROBLEMS ASSOCIATED WITH PROM

Maternal Problems

The maternal complications most frequently associated with PROM are acute chorioamnionitis, subclinical chorioamnionitis, premature placental separation, and postpartum endometritis.

Acute chorioamnionitis

Acute chorioamnionitis occurs frequently in women with PROM and a significant part of the women's surveillance is directed at the early recognition of infection. The occurrence of chorioamniotic infection following PROM seems to be greater in hospitals caring for low socioeconomic segments of the population than in institutions taking care of the affluent.

The diagnosis of chorioamnionitis is clinical. It requires the presence of fever (>100 F or 37.8°C) and at least two of the following conditions: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor of the amniotic fluid, or maternal leukocytosis (Gibbs et al., 1982). Amniocentesis is not necessary for the diagnosis of acute chorioamnionitis (Box 9-1).

The risk of acute chorioamnionitis is inversely related to the gestational age at the time of rupture of the membranes. Beydoun and Yasin (1986) found an incidence of chorioamnionitis of 58.6% in patients with PROM before 28 weeks. This is in contrast with an incidence of less than 10% when PROM occurs after 36 weeks. The data from the Collaborative Perinatal Project (Shubeck et al., 1966) show that definite clinical infection of the neonate follows a similar pattern: the incidence of culture-proven neonatal

BOX 9-1

Diagnosis of chorioamnionitis

Fever (>37.8°C or 100.4 F) *and two or more of:*
- Maternal pulse > 100 bpm
- Fetal heart rate > 160 bpm
- Uterine tenderness
- Foul smelling vaginal discharge
- Leukocytosis > 15,000
- C-reactive protein > 2.7 mg/dl

No other site of infection

sepsis was 2.0% for infants larger than 2500 g birth weight, 4.8% for those between 2000 and 2500 g, and 20% for those smaller than 2000 g birth weight.

The high incidence of acute chorioamnionitis and neonatal infection when PROM occurs in pregnancies remote from term may be related to decreased antibacterial activity of the amniotic fluid (Schlievert et al., 1976; Blanco et al., 1983). The antibacterial activity of the fluid is low in early pregnancy and increases with gestational age. Another factor is the immaturity of the fetal immunological system that limits the ability of the preterm infant to fight infection.

Acute chorioamnionitis may be apparent at the time of admission to the hospital. However, it may also develop during the latency period (time interval between rupture of the membranes and delivery) in women who are not infected at the time of admission. In these cases, the incidence of infection is related to the duration of the latency period. Burchell (1964) found that 1.7% of his patients with PROM developed fever within 24 hours, 7.5% between 24 and 48 hours, and 8.6% beyond 48 hours. In another study (Schreiber and Benedetti, 1980) the prevalence of chorioamnionitis was 2.7% before 12 hours, 6.3% between 12 and 24 hours, and 26.4% after 24 hours of latency. Histologic chorioamnionitis is found in 10% of the patients 12 hours after rupture of the membranes, in 30% after 24 hours, in 45% after 48 hours, and in 48% after 72 hours (Naeye and Peters, 1980). Other investigators (Ghidini et al., 1998) have found that the incidence of histologic chorioamnionitis does not increase with the duration of the latency period. Internal fetal monitoring is another factor that predisposes to chorioamniotic infection. Newton et al. (1989) determined by logistic regression analysis that the chance of developing chorioamnionitis was 20% for patients who had 20 hours of PROM and 3 hours of internal fetal monitoring. This probability increased to 40% if the latency period was greater than 20 hours and internal fetal monitoring lasted 12 or more hours.

Subclinical chorioamnionitis

Romero et al. (1988c) demonstrated by means of bacteriologic studies of the amniotic fluid that approximately 40% of patients with PPROM are infected at the time of admission to the hospital but only a minority of them had signs and symptoms of overt infection. On many occasions the only symptom of chorioamniotic infection is the presence of uterine contractions. Other signs of subclinical infection are a change from a reactive to a nonreactive pattern in the nonstress test (NST) and absence of respiratory movements in the biophysical profile (BPP). Desai BR from Belgaum, India (2001) reported that C-reactive protein estimation was superior to urine culture, cervical swab culture, placental culture, and histology in detecting subclinical infection in cases of PROM.

Placental separation

Patients with PROM have an incidence of abruptio placentae of approximately 6%, significantly higher than the 1 in 150 found in patients with intact membranes (Vintzileos et al., 1987). Abruption usually occurs within the setting of prolonged and severe oligohydramnios. The clinical picture is that of mild to moderate vaginal bleeding and preterm labor. Usually the abruption is not severe enough to cause fetal demise or disseminated intravascular coagulation. The reason for the high incidence of abruption in patients with PROM is a progressive decrease in intrauterine surface area, causing detachment of the placenta. Mukherjee (2003) reported a higher incidence of 30% in women with PTL and PROM suffering from antepartum hemorrhage.

Postpartum endometritis

Postpartum endometritis is a frequent maternal complication in women with PPROM, particularly if they develop chorioamnionitis and are delivered by cesarean section. The reader will find more information about this subject in Chapter 7.

Fetal/Neonatal Problems

Hyaline membrane disease

Several studies have concluded that hyaline membrane disease (HMD) is the greatest threat to the newborn when PROM occurs before term. The data from Mercer (2003) show that at all gestational ages the risk of respiratory distress is greater than the risk of infection (Figure 9-1). At 24 weeks 100% of the newborns will have respiratory distress

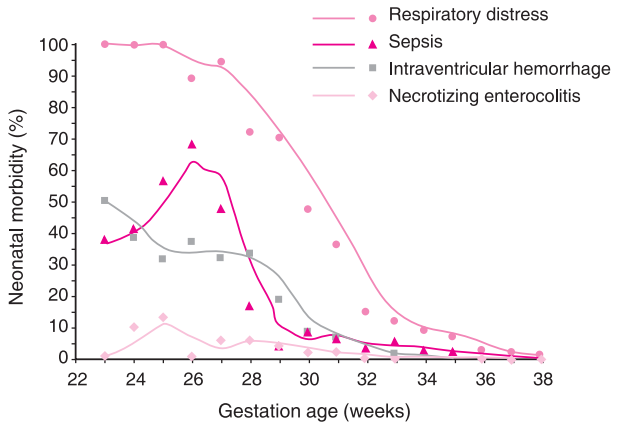

Figure 9-1. Neonatal morbidity in relation to the gestational age at the time of PPROM. (From Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol 2003; 101: 178–93).

Table 9-1. Perinatal survival and morbidity by birth weight

Birth weight (g)	Survival	RDS	Sepsis (%)	IVH (3–4)	NEC
500–749	65.4	100	34.6	23.4	23.1
750–999	87.3	92.9	14.3	9.8	3.6
1000–1499	98.6	86.3	15.1	3.6	9.6
1500–1999	99.0	36.6	3.0	0.8	4.0
2000–2499	97.6	27.8	1.6	0	0
2500–2999	99.2	28.0	3.0	0	0
≥3000	99.6	11.4	3.1	0	0

Data from the National Neonatal Database.

syndrome (RDS). At 28 weeks the incidence of RDS is 85%, at 32 weeks is 25%, and at 34 weeks is close to 10%. The risk of sepsis at these gestational ages is 40.0, 32.0, 4.5, and 3.0%, respectively. The National Neonatal Database (Table 9-1) gives an incidence of RDS of 100% at 24 weeks, 97.8% at 27–28 weeks, 58.1% at 31–32 weeks, and 30.9% at 33–34 weeks. The incidence of sepsis at these gestational ages is 36.4, 24.4, 1.6, and 0.8%, respectively. The data are consistent and the differences are probably due to variations in the populations being studied. It seems clear from these data that expectant management to improve fetal pulmonary maturity should dominate other considerations before 36 weeks, while infection is an important concern especially before 28 weeks.

Nonreassuring fetal status

Abnormal fetal heart rate (FHR) monitoring patterns occur in approximately 7.9% of patients with PROM as compared with 1.5% in patients with intact membranes (Oberg et al., 1984). The most common abnormality is variable decelerations, reflecting umbilical cord compression secondary to oligohydramnios. As a consequence, the rate of cesarean births in patients with PROM is high.

Pulmonary hypoplasia

A feared respiratory sequela of PPROM is pulmonary hypoplasia. This complication is frequent when PROM occurs before 26 weeks and the latent period is prolonged for more than 5 weeks. It is characterized by severe respiratory distress, requiring maximal ventilatory support and occurring immediately after birth. The lungs are small and clear on x-ray examination. The course is characterized by the development of multiple pneumothoraces and interstitial emphysema. The outcome is usually fatal and survivors frequently suffer from chronic bronchopulmonary dysplasia.

There are no methods by which an accurate diagnosis of pulmonary hypoplasia can be made prenatally. One of the first attempts to predict the occurrence of pulmonary hypoplasia was through the observation of the presence or absence of fetal breathing movements. Unfortunately, most investigations have concluded that absence of fetal breathing movements is not a good predictor of the condition. A popular method is the ultrasound measurement of the thoracic to abdominal circumference ratio, or T/A ratio (D'Alton et al., 1992). The thoracic circumference should be measured from a transverse view at the level of the four-chamber view. The abdominal circumference should be measured from a transverse view at the level of the bifurcation of the umbilical vein. The T/A ratio remains almost constant during gestation (mean approximately 0.92). Values below 0.80 are strongly suggestive of pulmonary hypoplasia. When the T/A ratio is 0.89 or greater, the probability of pulmonary hypoplasia is minimal (Johnson et al., 1987).

In a recent study (Laudy et al., 2002) the accuracy of clinical factors, sonographic measurements, and Doppler velocimetry of the pulmonary artery branches in the prediction of pulmonary hypoplasia was assessed in 42 pregnancies with severe oligohydramnios. It was found that no single factor had adequate positive predictive value. However, the presence of PROM before 20 weeks, severe oligohydramnios (largest pocket of fluid 1 cm or less) lasting for 8 or more weeks, T/A ratio in the 5th percentile or less, and peak velocity in a proximal branch of the pulmonary artery in the 95th percentile or greater had a 100% positive predictive value. In another investigation (Broth et al., 2002) Doppler was used to interrogate the first branch of the right or the left pulmonary arteries before and after maternal breathing of 60% oxygen by mask. Maternal hyperoxygenation decreases pulmonary vascular resistance and this is reflected in increased diastolic flow. They found that 11/14 (79%) of the fetuses that did not show a reaction to the oxygen challenge died of pulmonary hypoplasia. In contrast, only 1/25 (7%) of the fetuses that reacted to the maternal oxygen challenge died in the neonatal period. The false negative was a fetus with congenital cystic adenomatoid malformation of the lungs that died shortly after delivery. Two of the three false positive cases were fetuses with congenital diaphragmatic hernia and the third was an IUGR fetus with hemodynamic redistribution.

Cerebral palsy

Cerebral palsy is a long-term sequela of premature rupture of the membranes, particularly in cases complicated by acute or subclinical chorioamnionitis, severe intraventricular bleeding (IVH), or intrapartum fetal acidosis and hypoxia. Unfortunately, these complications occur rather frequently in PPROM. As explained in Chapter 7 the brain of the preterm fetus is unusually sensitive to the effects of antepartum or intrapartum hypoxia and the likelihood of long-term morbidity and death secondary to

asphyxia is greater than in the term infant. Cerebral ischemia in the premature results in decreased delivery of energy substrates to the brain tissue and in anaerobic metabolism with accumulation of lactate and inorganic phosphate. There is also intracellular accumulation of calcium and phosphorus in the neural cells and increased production of free radicals and cytokines. Hypoxia has more severe consequences in the preterm infant because of the increased vulnerability of the immature oligodendrocytes and the cerebral vascular system to hypoxia. The immaturity of the cerebral vascular system is reflected in the presence of a germinal matrix, the existence of border zones or watershed areas in the white matter, and poor autoregulation of the blood flow, factors that predispose to intracranial bleeding and eventually to cerebral palsy.

Congenital abnormalities

An important fact to consider when planning management strategies in women with PPROM is the high incidence of major congenital malformations occurring in PROM remote from term. In one study (Berkowitz et al., 1976) 4 out of 20 non-RDS deaths following PPROM were caused by congenital malformations. In another study (Gunn et al., 1970) 6 of 77 (8%) perinatal deaths in women with PPROM were caused by multiple congenital abnormalities.

Fetal deformities

Facial and skeletal deformities may occur as a consequence of prolonged PROM. Deformities in cases of prolonged PROM are the result of severe, prolonged oligohydramnios. With the lack of fluid the fetus loses the protective cushion against compression and has a severe limitation in the ability to move the limbs, factors that are responsible for the deformities. Similar to pulmonary hypoplasia, most of these cases occur with PROM before 26 weeks and after a latency period of 5 or more weeks (Nimrod et al., 1984).

DIAGNOSIS

The diagnosis of PROM is made when the membranes rupture in the absence of contractions. In many cases the diagnosis is obvious because copious amounts of amniotic fluid are seen in the vagina during speculum examination. If no fluid is present in the vagina, slight pressure on the uterus and gentle moving of the fetus may provoke leaking of fluid from the cervix. Sometimes the fluid comes out when the woman is asked to cough or strain down. If there are doubts about the nature of the fluid, a small amount should be collected over the lower blade of the speculum for Fern and Nitrazine testing.

Nitrazine Test

The normal vaginal pH is 4.5–5.5. The amniotic fluid has a pH of 7.0–7.5. The Nitrazine paper will turn quickly deep blue if the vaginal fluid has an alkaline pH. The membranes probably are intact if the color of the paper remains yellow or changes to olive yellow (pH 5.0–5.5). Antiseptic solutions, urine, blood, seminal fluid, bacterial vaginosis, and trichomoniasis alter the vaginal pH and cause false positive results. The Nitrazine test has 12.7% false negative and 16.2% false positive results.

Fern Test

Ferning results from the drying out of salts contained in the amniotic fluid. To perform the test, a sample of fluid is placed on a glass slide and allowed to dry. The preparation is observed under the microscope, looking for a crystallization pattern that resembles a fern plant. The accuracy of the test is affected by blood or meconium. The test may produce false positive results if the sample is obtained from the cervix because dry cervical mucus forms an arborization pattern that may be confused with PROM. The fern test gives 4.8% false negative and 4.4% false positive results (Tricomi et al., 1966). The diagnosis of PROM is close to 100% reliable if the vaginal fluid gives positive results with both the Nitrazine and the fern tests.

Intra-amniotic Injection of Indigo Carmine

The intra-amniotic injection of indigo carmine is occasionally indicated for the diagnosis of PROM. The main indication for this procedure is in women with a clinical history consistent with PPROM and negative Nitrazine and fern tests. In these cases a negative indigo carmine test may avoid a prolonged and unnecessary hospitalization. To perform the test, 2–3 cc of a sterile solution of indigo carmine is injected into the amniotic cavity and a tampon is placed in the vagina and examined visually 30 minutes to 1 hour later. The presence of a blue discoloration in the tampon is diagnostic of PPROM. It is not adequate to examine the tampon after more than 1 hour because that causes false positive results.

Fetal Fibronectin

Fetal fibronectin is a large molecular weight glycoprotein present in large amounts in the amniotic fluid. This substance can be detected in the endocervix or the vagina in 93.8% of women with PROM by means of an ELISA test. The test is highly accurate and is not affected by blood, but meconium may interfere (Lockwood et al., 1991).

Alpha-Fetoprotein

Alpha-fetoprotein (AFP) is present in high concentration in the amniotic fluid but does not exist in vaginal

secretions or in the urine. Therefore, determination of this substance in the vaginal secretions is an accurate test for the diagnosis of PROM. A study using a rapid colorimetric monoclonal antibody AFP test found a sensitivity of 98% for AFP, 77% for Nitrazine, and 62% for ferning. Specificity was 100% for the AFP test (Rochelson et al., 1987). The test may be unreliable at term because amniotic fluid AFP decreases with gestational age. Also, maternal blood contamination affects the accuracy of the test.

High Leaks

This is a term used to describe women with documented evidence of amniotic fluid losses who continue to leak fluid in small amounts for several weeks after the initial episode and maintain, at all times, an adequate amount of fluid inside the uterus. These clinical characteristics suggest that the loss of fluid is caused by a tear in the membranes above the lower uterine segment. High leaks may seal spontaneously, and usually are not associated with fetal or maternal complications. The diagnosis of a high leak is difficult.

Occasionally, patients with documented PROM show an intact sac at the time of delivery. These cases result from rupture of the amnion with an intact chorion, accumulation of fluid between the amnion and the chorion, and sealing of the amnion with formation of two sacs containing amniotic fluid (Schuman, 1951). When the first sac, or "chorionic cyst," ruptures, the clinical picture is that of PROM but the true amniotic sac is intact.

MANAGEMENT

Initial Assessment

The main objectives of the initial assessment are to confirm the diagnosis of PROM, to determine the gestational age of the fetus, and to identify the women who need to be delivered. Secondary objectives will be to determine fetal pulmonary maturity and to identify subjects colonized with *Chlamydia, N. gonorrhoeae*, and GBS.

Digital pelvic examination is not a part of the assessment of women with PROM unless they are in active labor as judged by the frequency and intensity of their uterine contractions. As shown in Table 9-2, it has been demonstrated that digital examination causes a significant decrease in the duration of the latency period (Lewis et al., 1992; Alexander et al., 2000), a variable that is of critical importance in the preterm fetus.

Speculum examination

The initial assessment of women with PPROM includes, in addition to the history and physical examination, a sterile speculum examination. The speculum examination is necessary to confirm the diagnosis of PPROM, to obtain amniotic fluid for determination of fetal pulmonary maturity, and to obtain samples from the endocervix for *Chlamydia and N. gonorrhoeae*. The speculum examination is also useful to determine the dilatation and length of the intravaginal part of the cervix. Before the speculum examination a swab from the outer part of the vagina and the anal area should be obtained to test for GBS.

Table 9-2. Effect of vaginal digital examination on the latency period after PROM

Gestational age (weeks)	Latency period	
	Digital examination	No digital examination
24–26	1.6 ± 0.7	20.5 ± 19.8*
26–28	3.8 ± 5.3	13.9 ± 14.1*
28–30	2.1 ± 2.9	14.2 ± 13.3*
30–32	1.5 ± 0.8	6.7 ± 6.8*
32–34	2.2 ± 5.7	5.5 ± 5.8*
34–35	1.2 ± 0.5	5.8 ± 3.6*

*≤ 0.001.

From Lewis DF, Mazor CA, Towers CV, et al. Effects of digital examination on latency period in preterm premature rupture of membranes. Obstet Gynecol 1992; 80: 630–4.

Laboratory assessment

The initial laboratory assessment should include a complete blood count, to determine the total number of white blood cells, a differential count, and determination of C-reactive protein (CRP).

Ultrasound examination

The initial evaluation of the woman with PROM should include a bedside ultrasound examination to determine or confirm the fetal position, measurement of the amniotic fluid volume, fetal biometry for estimation of gestational age and fetal weight, and cervical length by transvaginal ultrasound.

Ultrasound should not be used as the primary means of diagnosis of PROM. False positive findings may occur in patients with oligohydramnios from causes other than PROM and false negative results are common in patients having discrete amniotic fluid losses. However, it should be assumed that PROM has occurred if ultrasound examination shows little or no fluid in the uterus and a filled fetal bladder. In contrast, the presence of a normal amount of fluid makes the diagnosis of PROM unlikely.

Several techniques have been used for the ultrasound assessment of amniotic fluid volume. Some use the subjective qualitative impression of the individual performing the examination. For others the absence of a pocket of fluid with a vertical diameter greater than 2 cm indicates

oligohydramnios. However, the method most commonly used is the four-quadrant technique that consists in measuring the vertical diameter of the largest pocket of fluid present in each of the four quadrants of the uterus (Phelan et al., 1987; Sarno et al., 1990). The diameters are added and the result is the amniotic fluid index. In women with decreased fluid volumes it is important to use color Doppler to be certain that the pocket of fluid does not correspond to a conglomerate of umbilical cord loops. When color Doppler is used systematically to determine the diameter of the largest pocket in the four-quadrant technique, there is a tendency to the overdiagnosis of oligohydramnios.

Determination of gestational age

The duration of the latency period, the management of the patient and the fetal/neonatal prognosis are heavily dependent on the gestational age at the time of PROM. Therefore, a precise assessment of gestational age is an important part of the initial evaluation of women with PPROM. For a detailed discussion about assessment of gestational age see Chapter 1. An ultrasound examination in the first trimester of pregnancy is extremely accurate in the estimation of gestational age (Wisser et al., 1994). Similarly, an ultrasound-derived gestational age in the second trimester of pregnancy that does not differ by more than 7 days from the estimate based on the last menstrual period (LMP) confirms the diagnosis of the gestational age. If the ultrasound-derived and the LMP-derived estimations differ more than 7 days, the ultrasound-derived value is the most accurate and should be adopted for clinical management (Chervenak et al., 1998). It is important to consider that the lack of fluid affects the accuracy of ultrasound measurements and the gestational age is frequently underestimated (O'Keefe et al., 1985).

Identification of Women Who Need to be Delivered

One of the first steps in the initial management of women with PROM is to identify those requiring immediate delivery. The indications for immediate delivery may be maternal or fetal. These indications include women in advanced labor, women with acute chorioamnionitis, women with subclinical infection/inflammation, women at high risk for severe infection, fetuses with mature lungs, fetuses with nonreassuring well-being testing, and fetuses with lethal abnormalities.

Women in advanced labor

No efforts should be made to stop labor and prolong the pregnancy if the woman is having frequent uterine contractions and the pelvic examination shows a cervix[3] 80% effaced and dilated 5 cm or more. A significant number of these women have subclinical chorioamnionitis. The use of continuous intravenous infusion of tocolytic agents in this situation is not effective and may lead to pulmonary edema. Amon et al. (2000) demonstrated that although it is possible to arrest labor at advanced stages of cervical dilatation, there is high cost in maternal morbidity.

Women with acute chorioamnionitis

As mentioned before, acute chorioamnionitis is a severe complication of women with PPROM which has large implications in maternal and neonatal health. It is present at the time of admission in 1–2% of the cases and develops during the latency phase between PPROM and delivery in 3–8% of women (Yoon et al., 1996). The diagnosis of acute chorioamnionitis is clinical and the most important sign is fever. As it will be discussed later, antibiotic treatment and prompt delivery are the most important measures in the management of these patients.

The most commonly found bacterial isolates in women with acute chorioamnionitis are GBS and *Escherichia coli*, which are present in 20% of the cases but are responsible for 67% of the cases of maternal or fetal bacteremia. Particular attention has been given to GBS in its relation to PPROM. This organism may cause overwhelming neonatal infection resulting in death or severe neurological morbidity. Patients with GBS infection commonly have PROM at early gestational age and have a shorter duration of the latency period. Several tests have been proposed for the rapid diagnosis of GBS colonization of the genital tract. The most promising is a test using polymerase chain reaction (PCR) technology which has sensitivity greater than 97% and will be available soon for clinical use (Bergeron et al., 2000). Culture methods require a minimum of 18 hours to detect GBS. *E. coli* is an emergent clinical pathogen and there is evidence that it may have surpassed GBS as the predominant isolate in chorioamniotic infection in USA. Some E. coli strains are highly virulent and cause overwhelming sepsis in patients with poor inflammatory response.

Other bacteria frequently isolated in the amniotic fluid or placenta in women with PPROM and acute chorioamnionitis are U. urealyticum, Mycoplasma hominis, Bacteroides bivius, Gardnerella vaginalis, GBS, peptostreptococci, *E. coli, Fusobacterium sp.*, and enterococci. Most of these organisms are part of the normal vaginal flora. Some of them are more virulent than others. Anaerobes are active locally and rarely cause bacteremia.

The patient with acute or overt chorioamnionitis should receive antibiotic treatment and induction of labor immediately after the diagnosis is made if there are no contraindications for vaginal delivery and labor is not already in progress. Several studies have demonstrated a

lower rate of maternal and neonatal complications when antibiotics are given before delivery rather than postpartum (Sperling et al., 1987). There is no antibiotic treatment of choice and different types, number, and combinations of antibiotics are used. Since the infection in most cases is polymicrobial, it is necessary to use broad spectrum antibiotic coverage. Also, the antibiotic(s) should be effective against GBS, E. coli, anaerobic bacteria, and enterobacteria, which are some of the most frequent causes of severe infectious morbidity. Some prefer monotherapy with a third-generation cephalosporin (Cefizox, 1 g IVPB every 12 hours) or ampicillin–sulbactam 3 g IVPB every 6 hours. However, ampicillin–sulbactam has been associated with a high incidence of necrotizing enterocolitis in the newborns (Kenyon et al., 2001). Others use double antibiotic such as ampicillin 2 g IVPB every 6 hours plus Cleocin 900 mg IVPB every 8 hours. Still others use triple antibiotic therapy with gentamycin (0.5 mg/kg IVPB every 8 hours) or aztreonam 2 g IVPB every 8 hours, plus clindamycin 900 mg IVPB every 8 hours, plus ampicillin 2 g IVPB every 6 hours. All these methods of treatment provide adequate coverage for women with intrauterine infection.

There is broad consensus that women with acute chorioamnionitis should be delivered because the severity of the infection will become worse with the passage of time. If vaginal delivery is contraindicated (transverse lie, premature breech, etc.) a cesarean section should be performed after starting antibiotic treatment. Unfortunately, the optimum length of time to minimize maternal and fetal complications between the diagnosis of chorioamnionitis and vaginal delivery has not been defined. When the condition follows its natural course, more than 90% of these women deliver within 12 hours of the diagnosis (Gibbs et al., 1980). One study found that if delivery occurred between zero and 10 hours after the diagnosis, time period did not have an impact on neonatal outcome (Hauth et al., 1985). However, a common problem in achieving vaginal delivery shortly after the diagnosis is made is that women with chorioamnionitis frequently exhibit dysfunctional uterine activity that results in abnormalities in the progression of labor and prolongation of the interval between diagnosis and delivery. Another important consideration in attempting to define the optimum time between diagnosis of intrauterine infection and delivery is the well-known relationship between chorioamnionitis and cerebral palsy. Although it is possible that the damage to the fetal brain has already occurred when the diagnosis of overt chorioamnionitis is made, it is also possible that this damage may occur or be aggravated by keeping the fetus inside of the uterus. Until well-designed clinical trials come up with an answer to this problem, it is prudent to continue efforts to achieve vaginal delivery in patients with chorioamnionitis only if they are in advanced active phase or in second stage of labor and delivery is anticipated in a short time period.

Subclinical infection/inflammation

More than 40% of women with PPROM and without signs of overt infection have demonstrable signs of infection or inflammation by amniotic fluid analysis (Shim et al., 2004). All of these patients have elevated amniotic fluid MMP-8 and elevated cytokines but only one half of them are infected as shown by positive amniotic fluid cultures. Peculiarly, the outcome of pregnancy is worse in women without demonstrable infection. The most common microorganism isolated from the amniotic cavity is *U. urealyticum*. Fingerprints of the same bacteria are found by PCR in close to 40% of the cases of inflammation and negative bacteriologic cultures. Women with intra-amniotic inflammation and negative PCR reaction may have infection that is not detectable with the presently available bacteriologic techniques, infection outside the amniotic cavity or a noninfectious cause of inflammation.

Women with subclinical chorioamniotic infection/inflammation have none of the symptoms and signs of acute or overt chorioamnionitis. In some of them the only complaint is mild uterine contractions. Some present with subclinical infection at the time of admission to the hospital and others develop the infection in the course of expectant management. The diagnosis of subclinical chorioamniotic infection/inflammation is suspected if the maternal serum concentration of CRP at the time of admission to the hospital is twice or more the upper limit of normal (0.9 mg/dl). In this situation the woman should be informed about the possibility of infection/inflammation and the desirability of confirming the diagnosis by amniocentesis. The amniotic fluid should be sent to the laboratory for Gram stain and bacteriologic cultures, glucose, white cell count, and CRP. Unfortunately, methods for determination of interleukin-6 and MMP-8, the most sensitive indices of intra-amniotic infection/inflammation, are not readily available. The Gram stain, bacteriologic cultures, and the glucose concentration in the amniotic fluid are the indices of infection. The white cell count and the CRP are the indices of inflammation. The accuracy of these tests in the diagnosis of amniotic infection/inflammation can be found in Box 9-2.

Amniocentesis in women with PPROM is technically difficult because of the oligohydramnios. The rate of success varies between 15 and 95% in different studies. Some have found useful to place the woman in deep Trendelenburg position for several hours and administer a bolus of IV saline before the amniocentesis to increase the size of the amniotic fluid pockets. When

BOX 9-2

Accuracy of amniotic fluid tests in the diagnosis of chorioamnionitis (aerobic and anaerobic only) in women with PPROM

Test	Predictive value			
	Sensitivity (%)	Specificity (%)	Positive (%)	Negative (%)
Gram stain	75–80	97–99	85–92	96–97
Leukocyte esterase	80–91	84–95	78–95	85–91
Glucose (<16 mg/dl)	71–87	51–93	47–87	74–97
>50 WBCs	52–63	83–90	45–66	74–94
LDH (>419 mg/dl)	75	90	50	96

Lower and higher values taken from the following references: Carroll et al., 1996; Garry et al., 1996; Gauthier et al., 1992; Hoskins et al., 1987; Romero et al., 1993.

amniocentesis is not possible, the maternal serum CRP should be repeated in 12 and 24 hours and if a clear upward trend is detected, particularly if the woman is receiving IV antibiotics, the diagnosis of subclinical infection/inflammation is made and the patient should be delivered.

The accuracy of the amniotic fluid indicators of infection is different in PPROM than in preterm labor with intact membranes because the prevalence of amnionitis is different in the two syndromes. In both instances, the Gram stain of amniotic fluid is the most specific test for the detection of intra-amniotic infection with specificity of 98.56% (Romero et al., 1993). Unfortunately the sensitivity of the test is not as good and varies from 41 to 80% (Romero et al., 1988a). There are several possible explanations for the low sensitivity of the amniotic fluid Gram stain. Firstly, there is considerable interobserver variation. Secondly, the Gram stain does not identify *Mycobacterium*. Thirdly, the infection may be causing considerable maternal and fetal inflammatory response but may still be localized in the decidua and inaccessible to the amniotic fluid analysis. In women with PPROM, a positive Gram stain has a 93.3% positive predictive value and a negative Gram stain has a 85.4% negative predictive value for the diagnosis of intrauterine infection. We perform the Gram stain using a drop of the sediment obtained after centrifugation of the fluid at 3000 rpm for 10 minutes but others use fluid that has not been centrifuged. The presence of any bacteria is diagnostic of infection.

The presence of white cells in the fluid is a better predictor of inflammation than infection. These cells are fetal in origin and an index of the fetal inflammatory response (Sampson et al., 1997). A marked leukocytic reaction in the absence of bacteria is suggestive of mycoplasma or ureaplasma infection (Yoon et al., 1998). If the Gram stain is negative for both bacteria and white cells, the probability of infection is less than 5%.

There are several amniotic fluid tests that may be used to diagnose infection but whose value in the detection of inflammation has not been studied. Amniotic fluid glucose concentration equal to or less than 16 mg/dl has a 87% positive and a 90% negative predictive value for chorioamniotic infection (Gauthier and Meyer, 1992). Another sensitive indicator of amniotic fluid infection is the concentration of LDH (lactate dehydrogenase) (Garry et al., 1996). Amniotic fluid LDH values equal to or above 419 U/L have a sensitivity of 75% and a specificity of 90% in the prediction of a positive culture. Values equal to or above 225 U/L indicate a fivefold increase for delivery within 36 hours of amniocentesis. An amniotic fluid test for infection that may be used in situations where the laboratory facilities are not adequate is the leukocyte esterase assay (Romero et al., 1988b). This test is one of several quick diagnostic assays contained in the strips used for urine analysis. A positive test has 91% sensitivity and 95% positive predictive value for the diagnosis of chorioamnionitis (Hoskins et al., 1987).

Women at high risk for severe infection

A policy of expectancy is not adequate if the mother with PPROM is at high risk for severe infection such as those affected by sickle cell disease, rheumatic heart disease, autoimmune disorders being treated with immunosuppressive agents, etc. Therefore the past and present medical history of the mother should be meticulously reviewed in search of factors making her highly susceptible to infection or making it unusually dangerous for her to develop infection. Some of these factors are shown in Box 9-3. For the majority of these patients, the best management is treatment with steroids to accelerate fetal pulmonary maturity and delivery 24 hours after the last dose of steroids.

BOX 9-3

Conditions making women with PPROM at high risk for infection or for unusual severity of infection

- Receiving immunosuppressant drugs
- Infected with human immunodeficiency virus
- Heart valve prosthesis
- Rheumatic heart disease
- Sickle cell disease
- Insulin-dependent diabetes
- Multiple pelvic examinations following PPROM

Fetuses with mature lungs

Women with PPROM and adequate fetal pulmonary maturity demonstrated by fetal lung maturity (FLM), L/S (lecithin to sphingomyelin) ratio, or PG (phosphatidylglycerol), should be delivered. Assessment of fetal pulmonary maturity can be made with amniotic fluid

BOX 9-4

Amnioinfusion

1. Warm up a plastic bag containing 500 ml of normal saline solution. Do not use microwaves for warming.
2. Run the saline through a blood warmer, keeping the solution at 37°C.
3. Connect the saline solution with the side arm of a three-way stopcock placed in the external end of the intrauterine catheter used for the amnioinfusion.
4. Infuse 250 ml of saline in approximately 30 minutes.

Continuous amnioinfusion is not recommended unless it is obvious that the patient is losing significant amounts of the saline solution through the vagina. If continuous amnioinfusion is used, the intrauterine resting pressure should not exceed 25 mmHg at any time.

obtained during the speculum examination or by amniocentesis. In the majority of cases, the fluid obtained from the vagina is not suitable for L/S ratio or FLM but is adequate for PG determination. Up to 10% of fetuses with PROM before 32 weeks have positive PG. This increases to 25% between 32 and 35 weeks.

Fetuses with nonreassuring well-being testing

Umbilical cord compression and cord prolapse are relatively frequent complications of PPROM, especially in patients with unengaged breech presentations, transverse lies, and severe oligohydramnios. If the FHR monitoring shows a pattern of moderate or severe variable decelerations or episodes of fetal bradycardia associated with poor variability, the patient should be delivered. If the fetus is in vertex presentation, amnioinfusion (Box 9-4) should be performed before induction of labor. Cesarean section is the method of choice if the FHR pattern does not improve with amnioinfusion or for the delivery of fetuses in abnormal presentations.

Fetuses with lethal abnormalities

Conservative management with its inherent risk of maternal infection is inadequate and against maternal interest if the fetus has lethal abnormalities. Fetuses with nonlethal abnormalities should be treated as if they were normal but parental input into the management decisions is of great importance.

Management According to Gestational Age at the Time of Rupture

The management of PROM is dictated by the gestational age at the time of its occurrence. This is due to variations in the incidence of fetal/neonatal complications at different gestational ages.

PROM at 36 or more weeks

Women with PROM after 36 weeks should be delivered. There is little to be gained by conservative management when the pregnancy has advanced to a stage at which fetal pulmonary maturity is complete or almost complete and the incidence of severe RDS is minimal. The main question in these patients is the best method to induce labor and the answer will be provided by examining the cervix. Induction with intravenous oxytocin is probably necessary if the cervix is effaced 75% or more and dilated 2 or more cm. Lesser degrees of cervical ripening should be managed with endovaginal prostaglandins (dinoprostone or misoprostol) alone or simultaneously with a Foley catheter balloon inserted in the cervix for mechanical dilatation.

The probability that induction will fail and a cesarean section will be performed is high if the cervix is not ripe. Some obstetricians prefer to wait for several hours before induction of labor in the hope that natural ripening of the cervix will occur during the waiting period. Awaiting for spontaneous onset of labor for 24 hours usually does not result in maternal and neonatal infection, but longer expectancy brings a significant increase in the incidence of infection. It is important to determine, before adoption of an expectancy policy, that the fetal head is engaged and that FHR monitoring shows no abnormalities. Maternal temperature should be obtained frequently, the baby should be monitored twice daily, and ampicillin 2 g IVPB every 6 hours or cefazolin 2 g IVPB every 8 hours should be given for the prevention of GBS and *E. coli* infection. Antibiotic prophylaxis is still important in women who had a negative screening test for GBS before PROM, because GBS is not the only pathogen causing chorioamnionitis. For women allergic to penicillin the specific reaction to penicillin should be ascertained. If the reaction was anaphylactic shock penicillins and cephalosporins are contraindicated and the antibiotic of choice will be gentamycin 120 mg IVPB initial dose followed by 80 mg IVPB every 8 hours plus clindamycin 900 mg IVPB every 8 hours. Another combination will be gentamycin 120 mg IVPB initial dose followed by 80 mg IVPB every 8 hours and vancomycin 500–1000 mg IVPB every 12 hours. If the allergic reaction to penicillin was mild (hives, pruritus) cefazolin can be given because most of these patients will not have allergic cross-reactivity with cephalosporins. If labor does not start spontaneously within 24 hours of rupture in a patient with PROM at term, labor should be induced.

PPROM between 32 and 36 weeks

Approximately 50% of the fetuses of women with PPROM between 32 and 36 weeks of gestation will have adequate lung maturity. Therefore, if lung maturity is

unknown and all of them are managed expectantly, 50% will be submitted to unnecessary risks. Since the issue of FLM is important in the management of women with PPROM between 32 and 36 weeks, a decisive effort should be made to collect amniotic fluid for lung maturity testing. If it is not possible to collect an adequate sample of fluid by speculum examination, amniocentesis should be attempted after placing the patient in Trendelenburg position for a few hours to improve the accumulation of amniotic fluid.

The evidence favoring active intervention and delivery when PPROM occurs between 32 and 36 weeks and the fetal lungs are mature is strong. Spinnato et al. (1987) found significantly increased maternal infectious morbidity and no neonatal advantages by prolongation of pregnancy in this group of women. Mercer et al. (1993) did a randomized trial of women with PPROM between 32 and 36 weeks and with mature amniotic fluid and found increased frequency of chorioamnionitis, prolonged maternal and neonatal hospitalization, and more frequent and prolonged antimicrobial therapy in the neonates of women in the expectant management arm of the study.

The management of women between 32 and 36 weeks with PPROM with immature or unknown FLM is a matter of discussion among experts. One of the first studies favoring induction and intentional delivery of women with PPROM between 32 and 36 weeks was from Cox and Leveno (1995). These investigators randomly assigned 68 women between 30 and 34 weeks to expectant management and 61 to induction and delivery and found no difference in the incidence of neonatal sepsis, RDS, and length of stay in the NICU between the two groups. In another study, Naef et al. (1998) randomized 120 women at 34–37 weeks between oxytocin induction of labor and expectant management. They found that chorioamnionitis occurred more frequently in women in expectant management (16% versus 2%, $p = 0.007$). Also, culture-proven neonatal sepsis was more frequent (5% versus 0%) in the expectant management group, although because of small numbers the difference had no statistical significance. There were no differences between the two groups in the incidence of RDS (5% for each group) or in other indices of neonatal outcome.

Another argument in favor of induction and delivery is that the latency period when PPROM occurs between 32 and 36 weeks is short. In the work of Mercer et al. (1993) the median duration of the latency period from randomization to delivery in women assigned to expectant management was 36 hours. In the work of Neerhof et al. (1999) only 10% of women managed expectantly had a latency period greater than 48 hours and only 2.5% had latencies of more than 7 days. This evidence has been used to raise the question if it is adequate to risk maternal and fetal infectious morbidity in exchange for an insignificant prolongation of the latency phase. However, this evidence was collected before the generalized use of antibiotics and glucocorticoids in the management of patients with PPROM. The use of antibiotics and steroids has changed the natural course of PPROM because the latency period is prolonged and the incidence of maternal and neonatal complications decreases. Expectant management with antibiotics and steroids decreases the incidence of RDS/HMD, which is the most frequent neonatal morbidity in this group of patients. This was demonstrated by Neerhof et al. (1999) in a retrospective review of the outcome of women with PPROM between 32 and 36 weeks of gestation managed expectantly. They found an incidence of 19.2% and 2.5% for RDS and neonatal infection, respectively, in pregnancies delivered at 32 and 33 weeks; 8.1% and 1.5% when delivery occurred at 34 and 35 weeks; and 1.5% for both complications when delivery occurred between 36 and 37 weeks. Another group of investigators (Jothivijayarani et al., 2002) involving 79 women with PPROM between 32 and 36 weeks of gestation found a significant decrease in the incidence of RDS after 34 weeks. These data indicate that the most common neonatal pathology between 32 and 36 weeks is RDS and that at 34 and 35 weeks the incidence of RDS is 8.1%, much larger than the incidence of infection. The incidence of RDS between 33 and 36 weeks in the National Neonatal Database is 30.0% while the incidence of sepsis at the same gestational ages is 3.0%. It is clear that in this gestational age range, the risk of infection is lower than the risk of RDS and in the majority of cases infection can be detected early and delivery accomplished without severe maternal or neonatal infectious morbidity. Also, the use of antibiotics in women with PPROM reduces the incidence of maternal and neonatal infectious morbidity and results in significant prolongation of the latency period (Mercer et al., 1997; Kenyon et al., 2001).

Expectant management should not be adopted blindly for all women with PPROM and unknown FLM between 32 and 36 weeks. The care of these women needs to be individualized. Immediate induction and delivery or treatment with steroids and antibiotics and delivery 24 hours after the last steroid injection may be the best options under the following circumstances:

1. Leukocytosis greater than 16,000 with neutrophilia and CRP greater than 0.9 mg/dl and no bacteria in the amniotic fluid Gram stain
2. Severe oligohydramnios with the largest pocket of fluid less than 2 cm in diameter
3. Variable decelerations and poor variability in the FHR tracing
4. Cervical length by ultrasound less than 1.5 cm with funneling
5. Breech presentation or transverse lie

6. Cervical dilatation equal to or greater than 5 cm and effacement equal to or greater than 80%

If none of these conditions are present, management may be expectant. The woman should remain in the hospital until delivery. Antibiotics should be given intravenously for 48–72 hours to achieve adequate amniotic fluid and fetal levels and then orally for 5 days to complete 7 days of antibiotic treatment. The first choice is cefazolin that covers GBS and Gram-negative organisms. Electronic FHR monitoring should be performed once or twice daily. Patients should be assessed daily for fever, maternal or fetal tachycardia, uterine tenderness, and foul-smelling discharge. They should be delivered if there are nonreassuring signs in the FHR monitoring, there are clinical signs of infection, labor starts, or there is vaginal bleeding. Vaginal bleeding in women with PPROM and oligohydramnios should be considered to be due to placental separation unless proven otherwise.

The effect of glucocorticoids in preventing RDS in women with PPROM between 32 and 36 weeks is controversial. The work of Liggins and Howie (1972) shows little or no effect when steroids are given after 32 weeks. At less than 32 weeks, steroids are clearly indicated in women with PPROM not only because of their effect on the fetal lungs but especially because of their protective effect against IVH. However, IVH is rare after 32 weeks. Finally, steroids are immunosuppressive agents and their use in the setting of PPROM always raises the possibility that they facilitate the development of infection. Therefore, the weight of the evidence, at this time, casts serious doubts about the benefit of administering steroids to women with PPROM between 32 and 36 weeks.

The management of women with PPROM between 32 and 36 weeks is summarized in Figure 9-1.

PPROM between 24 and 32 weeks

The risks threatening the fetus affected by PROM between 24 and 32 weeks are multiple. The predominant risk is RDS usually due to HMD, affecting 30–100%. Other frequent morbidities are sepsis, affecting from 10 to 50%; IVH, affecting between 5 and 50%; necrotizing enterocolitis, affecting 1–10%; and chronic lung disease, affecting between 2 and 80%. All of these complications are directly related to the gestational age at the time of birth and are more frequent and severe when the pregnancy is less than 28 weeks (see Tables 9-1 and 9-3).

The obstetrical management of women with PROM between 24 and 32 weeks should be directed toward prolongation of the latency phase, prevention of RDS and IVH, and prevention of fetal/neonatal and maternal infectious morbidity. These objectives are achieved through the use of antibiotics, steroids, and tocolytic agents. Women with PPROM between 24 and 32 weeks should be admitted to the hospital and remain as inpatients until delivery. They should be on bed rest with bathroom privileges.

Table 9-3. Survival and morbidity by gestational age

Gestational age (weeks)	Survival	RDS	Sepsis (%)	IVH (3–4)	NEC
≤ 23	37.5	100	25.0	37.5	25
24	72.7	100	36.4	27.3	18.2
25–26	89.9	100	22.2	11.1	22.2
27–28	91.1	97.8	24.4	15.6	2.2
29–30	100	87.2	10.3	5.1	5.1
31–32	98.4	58.1	1.6	3.2	0
33–34	100	30.9	0.8	0.8	0
35–36	99.2	29.5	3.0	0	0
37–38	97.8	18.8	4.3	0	0
39–40	99.2	3.8	3.1	0	0
>40	100	0	5.9	0	0

Data from the National Neonatal Database.

Antibiotics

One of the most important objectives of antibiotic treatment in women with PPROM is the prolongation of the latency period. Prolongation of the latency period is important because FLM improves with advancing gestational age, resulting in fewer days in the ventilator and shorter stay in the NICU. It has been calculated that every day that the preterm fetus remains inside of the uterus is equivalent to 2 or 3 days less that the neonate will stay in the NICU.

The evidence indicating that antibiotics prolong the latency period and decrease fetal/neonatal and maternal infection is robust. Several randomized trials and meta-analyses have demonstrated that administration of antibiotics after PPROM prolongs the latency period and decreases the incidence of chorioamnionitis, IVH, fetal sepsis, and maternal postpartum infection. No effect of the antibiotics has been demonstrated with respect to the incidence of RDS. Several antibiotics have been used in these trials, including ampicillin IV plus amoxicillin orally for 7 days, Cephalexin IV until delivery, Mezlocillin IV until delivery, Piperacillin IV for 72 hours, ampicillin/gentamycin/clindamycin IV for 24 hours plus ampicillin/ clavulanate orally for 7 days, ampicillin/sulbactam IV for 48 hours plus ampicillin/clavulanate orally for 5–7 days, and ampicillin/erythromycin IV for 48 hours plus amoxicillin/erythromycin orally until delivery. The results with these different antibiotic regimens have been similar and there is no evidence that this allows the selection of any particular treatment over the others. However, the administration of ampicillin–sulbactam has been associated with a higher than usual incidence of necrotizing enterocolitis (Kenyon et al., 2001), and this

antibiotic is not recommended. There is no evidence to recommend a particular duration of the antibiotic treatment, although in none of the randomized clinical trials were the antibiotics given for less than 3 days. It is important that the antibiotic(s) be effective against GBS and E. coli and that additional antibiotics be added if the cultures obtained on admission reveal *Chlamydia* or *N. gonorrhoeae*. Azithromycin is added if *Chlamydia* is present and Rocephin if *N. gonorrhoeae* is present. A commonly used regimen is cefazolin 2 g IVPB every 8 hours for 48 hours followed by cephalexin 250 mg orally for 5 more days to complete 7 days of treatment. However, recent evidence suggests that results are similar with or without the additional 5 days of oral antibiotic therapy (Segel et al., 2002; Svena et al., 2002).

Steroids

The controversy about the use of glucocorticoids in patients with PROM was resolved by the recommendation of the National Institute of Child Health and Human Development (National Institutes of Health Consensus Development Conference Statement, 1995) that they should be given to women with PPROM at gestational age < 32 weeks. This recommendation was based on the evidence indicating that steroids decrease the incidence of IVH rather than on data suggesting a beneficial effect on the incidence of RDS. Women with PPROM should receive betamethasone 12 mg IM in two consecutive doses 24 hours apart or dexamethasone 6 mg IM every 12 hours for four doses. The administration of repeated, weekly doses to women who have a prolonged latency period is not recommended (National Institutes of Health Consensus Development Panel, 2001).

Tocolysis

Administration of tocolytic agents does not significantly prolong the latency period in patients with PROM. However, they may be useful in women with contractions at the time of admission who may deliver before receiving the benefit of glucocorticoid administration. The tocolytic agent of choice for women with PPROM exhibiting frequent contractions at the time of admission or developing frequent contractions during the first 72 hours of the latency period is oral Nifedipine. It is given using an initial dose of 20–30 mg, followed by 10–20 mg every 6 hours. Magnesium sulfate has been the tocolytic agent of choice for many years, but it is not better than Nifedipine and its side effects are severe. Most women having mild contractions will have an adequate prolongation of the latency period with Nifedipine. Aggressive tocolysis after PPROM does not prolong pregnancy or reduce neonatal mortality more than a limited treatment for a few days (Combs et al., 2004).

Fetal surveillance

Women with PPROM are at high risk for umbilical cord compression, and it is important to assess frequently the fetal well-being during the latency period. Both the BPP and the NST are commonly used for this purpose. The BPP is difficult to interpret in PPROM because oligohydramnios is frequently present and the fetal movements are decreased because of the lack of fluid. In addition, before 32 weeks the maturity of the CNS is inadequate to produce a reactive NST or adequate breathing movements. Therefore, it is not uncommon to obtain a numerical score of 4 or 6 for the BPP in situations where the fetus is healthy and delivery is not indicated. A similar problem occurs with the NST. To obtain a reactive NST at early gestational ages is uncommon and in many occasions accelerations of the FHR are only clearly detected after 28 or 30 weeks.

Under these circumstances the best way to assess the fetal well-being, particularly before 28 weeks, is by external monitoring of the FHR for 1 hour, once or twice daily, using the baseline frequency and the variability and the absence of decelerations, not the presence of accelerations, as criteria to judge the fetal well-being. If the FHR frequency and the variability are normal and there are no decelerations of the FHR, the fetal status is good. If there is tachycardia, bradycardia, decreased variability, and/or repetitive variable decelerations the fetal situation is not reassuring and further evaluation or delivery may be necessary.

Monitoring for infection

Laboratory and biophysical tests are widely used to predict the development of infection in women with PPROM. A commonly used test is the maternal leukocyte count (WBC) at the time of admission to the hospital. Hoskins et al. (1987) found that a white cell count equal to or greater than 12,000/mm^3 had a 67% sensitivity and an 82% positive predictive value for the diagnosis of amniotic infection. However, patients with PROM and without infection have a wide variation in WBC and frequently exhibit more than 12,000/mm^3 white cells with neutrophilia. Also, the administration of steroids to accelerate the fetal pulmonary maturity causes an immediate increase in the WBC count with neutrophilia. For these reasons the WBC is not a good predictor of intrauterine infection.

A useful blood test is the determination of CRP, a substance that increases markedly in patients with infection and inflammation. The upper limit of normal CRP concentration during pregnancy is 0.9 mg/dl with no variations due to gestational age (Watts et al., 1991). Women with acute chorioamnionitis usually have CRP values above 3.0 or 4.0 mg/dl and women with subclinical

infection/inflammation usually exhibit values between 0.9 and 3.0 mg/dl.

The usefulness of CRP in the prediction and diagnosis of intrauterine infection has been the subject of several studies. Unfortunately, they have used different methods and threshold values, resulting in a wide variation in results. The data of Fisk et al. (1987) indicate that CRP is highly specific for the diagnosis of intrauterine infection, with the CRP elevation usually occurring 1–3 days before the development of clinical signs. The CRP concentration is not altered by the administration of steroids to mature the fetal lungs. CRP is a much better predictor of infection than the WBC. However, it is prudent not to make the diagnosis of chorioamniotic infection on the basis of the CRP concentration alone but rather the diagnosis of acute infection requires the presence of fever and the diagnosis of subclinical infection requires amniocentesis.

The tests for assessment of fetal well-being have also been used for the prediction of intrauterine infection. Vintzileos et al. (1985) originally reported the value of the BPP as predictor of chorioamnionitis in patients with PROM. The absence of fetal breathing and gross body movements during a 30-minute period of observation was associated with chorioamnionitis in almost 100% of the cases. When fetal breathing movements were present for at least one episode lasting 30 or more seconds during a 30-minute period, the possibility of infection was less than 5%. Approximately 60% of the patients had amnionitis when the episode of breathing movements lasted only a few seconds. They also found that the first manifestations of impending fetal infection were a nonreactive NST and the absence of fetal breathing movements. No cases of fetal infections were found if breathing movements were present within 24 hours before delivery. In a subsequent study they found that the efficacy of amniotic fluid Gram stain was inferior to daily BPPs in predicting the development of amnionitis. They also found a better outcome for patients with PROM managed with BPP than for those managed expectantly or with amniocentesis at the time of admission (Vintzileos et al., 1986b) However, the value of the BPP in the early diagnosis of amnionitis has been questioned by other investigators (Miller et al., 1990), and a randomized clinical trial comparing NST versus BPP in women with PPROM failed in demonstrating that daily BPP provided more benefit than daily NST (Lewis et al., 1999).

The NST has also been used for the prediction of chorioamniotic infection. The sensitivity, specificity, and positive and negative predictive value of a nonreactive NST in predicting infection were 78.1%, 86.3%, 65.7%, and 92.1%, respectively (Vintzileos et al., 1986a). Patients with persistent nonreactive NST from the time of admission and those with an initially reactive NST that becomes nonreactive have the highest infection rates.

Delivery

The onset of labor after PROM is directly related to the gestational age at the time of the rupture. One study found that labor started within 24 hours of PROM in 81% of patients carrying babies larger than 2500 g birth weight (Gunn et al., 1970). The situation is different when PROM occurs early in gestation when only 48% of the cases develop labor within 3 days after PROM (Moretti and Sibai, 1988).

Women with PPROM between 24 and 32 weeks should be delivered if infection develops, labor starts, or if signs of fetal distress—mainly, variable decelerations and loss of variability—appear in the FHR tracing. The route of delivery will depend on the ripeness of the cervix and the FHR tracing. If the cervix is ripe, the head is deep in the pelvis, and a short labor is anticipated the patient should deliver vaginally. If the cervix is not ripe it is better to do a cesarean section.

When delivery is indicated because of the presence of variable decelerations in the FHR tracing, it is important to perform an amnioinfusion before the induction of labor (Box 9-4). We prefer to give boluses of 250–300 ml of normal saline rather than continuous infusion. When amnioinfusion is given by continuous infusion it is necessary to be sure that some of the fluid comes out of the uterus, because retained fluid may cause a significant increase in resting intrauterine pressure and abnormalities of the FHR tracing.

If the fetus is < 1000 g, serious consideration should be given to cesarean section as the preferred way of delivery in order to decrease the incidence and severity of intracranial bleeding. Germinal matrix hemorrhage (GMH) and IVH occur in as many as 35% of neonates < 1000 g, and depending on the severity and the further extension of the initial bleeding episode, there is a probability of cerebral palsy and developmental problems. When a cesarean is done at early gestational age, the low uterine segment should be assessed as soon as the abdomen is entered and a vertical incision performed if it is thick. To deliver a small baby through a low transverse incision in an underdeveloped low segment may be more traumatic than a vaginal delivery.

As mentioned in Chapter 7, approximately 50% of the cases of GMH/IVH occur within 12 hours of birth and many of them happen within the 1st hour of life. It is in these early cases where research has shown an association of GMH/IVH with intrapartum events. The rest of the cases occur usually after 2 or 3 days of life and are associated with neonatal events particularly with ventilatory support and variations in neonatal blood pressure. Early GMH/IVH frequently extends in the days following the initial episode. Most of the prospective and retrospective studies on mode of delivery and neonatal intracranial

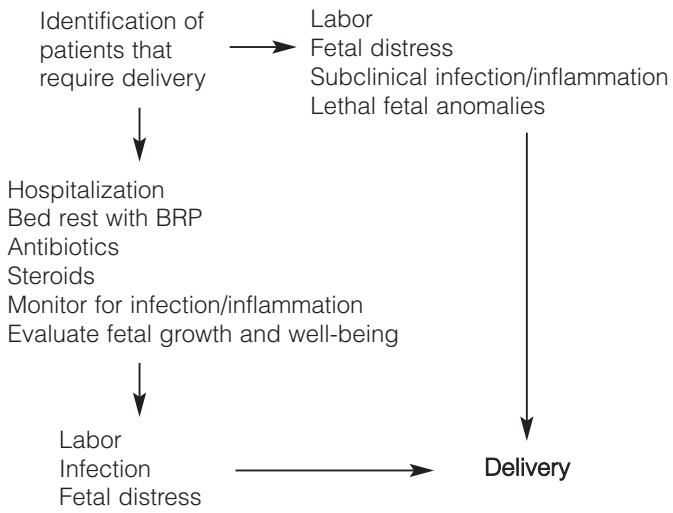

Figure 9-2. PPROM 24–32 Weeks.

bleeding indicate that the active phase of labor is the obstetrical event most closely associated with GMH/IVH. Cesarean, if performed before labor starts, reduces the incidence of early GMH/IVH and the extension of the initial bleeding episode. When the cesarean section is done in the active phase of labor, the beneficial effects of the procedure disappear. Therefore it is important to discuss this subject with women with PPROM when they are in the latency phase so that a planned cesarean can be performed before the active phase of labor begins.

The overall management plan for women with PPROM between 24 and 32 weeks is summarized in Figure 9-2.

PPROM before 24 weeks

The perinatal outcome of PPROM before 24 weeks of gestation is extremely poor. Forty-eight percent of these patients will deliver within 3 days, 67% within 1 week, and 83% within 2 weeks of PROM (Moretti and Sibai, 1988). Perinatal mortality is 60–90%. Approximately 50% of the mothers will have chorioamnionitis, 50% will be delivered by cesarean section, and 6.8% will have abruption. Sixteen percent of the surviving newborns will have severe long-term sequelae. Most of the survivors are patients who extend their latent period for 2 or more weeks. Some patients have their pregnancies prolonged for several weeks after PROM without evidence of infection and with little or no fluid in the uterus. They are at high risk for fetal musculoskeletal deformities and pulmonary hypoplasia. Deformities usually appear after 4 or more weeks of PROM.

No plan of management has been shown to improve the outcome of these pregnancies. If the pregnancy is less than 24 weeks the mother should be offered induction of labor and delivery of the fetus to avoid morbidity. If the parents choose to terminate the pregnancy it should be made absolutely clear to them that there is a 10–20% probability that the fetus will be born alive. Parents should know that in these cases the decision to give or not to give full neonatal support to the newborn will depend on the assessment by the neonatologist and not exclusively on the parental desire to terminate the pregnancy. If the mother declines termination and chooses expectant management, she will be treated with tocolytic agents, glucocorticoids, and antibiotics. If the pregnancy is less than 24 weeks the patient may be sent home and readmitted to the hospital for further expectant management after she completes 24 weeks.

Surgical approaches to the treatment of early PPROM

The site of rupture of the membranes can be visualized endoscopically (Quintero et al., 1998). The site is usually located above the internal cervical os in cases of spontaneous rupture while in traumatic rupture, following amniocentesis or fetal surgery, the site is far from the cervix. Shortly after rupture, the slit in the membranes has clean, sharp edges that become irregular with the passage of time. The size of the rupture varies between 0.5 and 3.0 cm.

Several experimental approaches have been used to seal the site of rupture. The first attempts were made using fibrin glue that results from mixing thrombin with cryoprecipitate. In 1999, Quintero reported the successful use in traumatic rupture of an "amniopatch" created by successive intra-amniotic injections of platelets and cryoprecipitate (Quintero et al., 1999). Unfortunately, this method is not useful in cases of spontaneous rupture. Also, sudden fetal death may occur in some cases most probably because of the release of substances toxic to the fetus by the activated platelets. More recently, Sciscione et al. (2001) reported transcervical application of a commercial fibrin tissue sealant made up by applying simultaneously cryoprecipitate and thrombin in 17 women with spontaneous rupture, 2 of them with twins. Six infants survived. There is a case report of an "amniograft" placed endoscopically over a spontaneous membrane defect, resulting in significant prolongation of pregnancy (Quintero et al., 2002). Another potential surgical treatment for PROM is the use of gelatin sponge embolization (O'Brien et al., 2002). After placement of a cervical cerclage and amnioinfusion of 200–300 cc of normal saline solution, small pieces of gelatin sponge are injected in the amniotic cavity using a 3-mm trocar or 12-gauge Angiocath. This technique was tried in 15 women, 14 with spontaneous rupture and 1 with rupture after fetoscopy. They had seven previable deliveries. Six of the eight fetuses that reached viability survived.

The surgical methods described above are experimental. The number of cases reported and the variations in case selection and treatment do not allow one to reach

meaningful conclusions about the validity of this approach. It should be noted that PROM is a syndrome with varied etiology and that most probably in only a minority of women with PROM the cause of the problem may be corrected by simply patching the membrane defect.

Special Situations in Women with PPROM

PPROM with cerclage "in situ"

PPROM occurs in 30–50% of cases of rescue cerclage and in about 5–10% of cases of prophylactic cerclage. When PPROM occurs in pregnancies at > 34 weeks, there are no substantial advantages of prolongation of pregnancy and the cerclage should be removed and labor induced if there is no spontaneous labor within 24–48 hours. In most of these cases cerclage removal is followed by spontaneous labor and delivery. The management problem occurs when PPROM occurs far from term in a woman with cerclage "in situ" because the literature in the era before antibiotic treatment for PPROM strongly suggested that the incidence of infection was greater when the cerclage remained "in situ" than when it was removed (Ludmir et al., 1994). The contemporary treatment with antibiotics of women with PPROM has modified the outcome of these patients, and most of the recent literature suggests that the cerclage should not be removed (Jenkins et al., 2000; McElrath et al., 2002). If the cerclage is left "in situ" and the mother is treated with antibiotics, the latency period will be prolonged without significant increases in fetal/neonatal morbidity and mortality. Exceptions will be cases with overt chorioamnionitis, active labor, or nonreassuring fetal status.

PPROM in multifetal pregnancies

The perinatal outcome of PPROM is worse in multifetal than in singleton pregnancies. PPROM in multifetal pregnancies is characterized by a high incidence of infection/inflammation as the primary etiology of the problem, short latency periods, increased number of maternal complications associated with tocolytics/glucocorticoids treatment, high incidence of cesarean delivery and poor neonatal outcome. There are no substantial differences in the management of PPROM in multifetal versus singleton pregnancies.

PPROM in women with herpetic lesions

Occasionally PPROM occurs in the setting of a recurrent herpetic infection in the vulvar and perineal areas and it is necessary to balance the benefits of prolongation of the latency period against the possibility of ascending fetal infection. Delivery by cesarean section is the best mode of management when the pregnancy is 34 weeks or more. In pregnancies under 34 weeks there is limited evidence indicating that expectant management is adequate, and fetuses do not become infected with HSV if the latency period is prolonged (Major et al., 1991).

PREVENTION OF PPROM

Prevention requires identification of women at risk for a particular condition and adequate means of treatment. Two studies have addressed the question of identification of risks. The first by Harger et al. (1990) was carried out before the incorporation of ultrasonic measurement of the cervical length and determination of fetal fibronectin in the vaginal secretions in the assessment of women at risk for preterm birth. This study identified three important high-risk factors: previous preterm delivery, vaginal bleeding during pregnancy, and cigarette smoking. The second study (Mercer et al., 2000) incorporated cervical length and fetal fibronectin among the variables that were analyzed and concluded that history of a preterm birth because of preterm rupture of membranes, short cervical length, and positive fibronectin were independent risk factors for PPROM. There is also evidence suggesting that colonization of the cervix and vagina by *Chlamydia trachomatis, N gonorrhoeae*, and GBS is associated with a higher incidence of PPROM than in individuals not colonized by these microorganisms. Also, it has been found that the risk of PPROM doubles in mothers who ingest three or more cups of coffee during the first trimester as compared with mothers who take two or less cups of coffee (Williams et al., 1992). Another important risk factor for PPROM is a history of a LEEP (loop electrosurgical excision procedure) or laser procedure in the cervix for the treatment of cervical intraepithelial neoplasia (Sadler et al., 2004).

Box 9-5 summarizes the correctable and noncorrectable high-risk factors for PROM. It is apparent that most of these factors can not be corrected. More

BOX 9-5

High-risk factors for premature rupture of the fetal membranes

Preventable

- Maternal smoking
- More than three cups of coffee per day in the first trimester
- Vaginal colonization by:
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhoeae*
  - Group B streptococci

Nonpreventable

- History of preterm delivery because of PROM
- Vaginal bleeding in the first and second trimesters
- Short cervix (<2.5 cm)
- Positive fibronectin

frustrating, once risk factors are identified, there are no adequate preventative treatments to modify the potential outcome.

INDIAN EXPERIENCE OF PREMATURE RUPTURE OF MEMBRANES

Premature rupture of membranes (PROM) refers to the membranes rupturing before the onset of true labor. This occurs in 5–20% of all labors. Indian Studies (Bhalerao and Desai, 2000; Bhide, 2001) report an incidence of PROM in 7–12% of all labors. If this occurs prior to 37 completed weeks of gestation (accounts for one-third of all cases), it is associated with an increased perinatal mortality. These women are prone to cord compression/cord prolapse and higher risk of infection. This risk may assume grave proportions in patients undergoing cesarean section. Approximately two-thirds of patients deliver within 4 days and the rest within a week. The longer the time interval between rupture of membranes and onset of labor (latent period), the greater the risk of ascending infection and chorioamnionitis. Almost 80% of patients close to term with PROM begin labor within 24 hours and 95% deliver within 72 hours. But in preterm gestations (prior to 36 weeks of gestation), labor generally follows within 24 hours in only 35–50% and 70% begin labor within 72 hours. Of patients with PROM prior to 36 weeks of gestation, almost 90% deliver within the next 2 weeks. Infection, cervical incompetence, trauma, antepartum hemorrhage, hydramnios, multiple gestation, and coitus in pregnancy contribute to PROM. It is often not possible to pinpoint the exact cause in an individual case. Jiwane (1991) observed that the incidence of PROM increased 4.4 fold in women undergoing routine pelvic examination in the third trimester of pregnancy. Kodkany and Telang (1991) observed that coitus in the last trimester led to a sixfold increase in PROM.

In women with PROM prior to 34 weeks of gestation, the chief factors contributing to high perinatal mortality are prematurity, hyaline membrane disease of the newborn, and infection. Therefore administration of antibiotics (Jayaram and Sudha, 2001; Khodke et al., 2000; Shenoy et al., 2000), tocolytics (Jayaram and Sudha, 2001; Saha, 2002; Sirohiwal et al., 2001; Phadke et al., 2000; Kumar, 2001), steroids (Jassawalla and Balsarkar, 2003; Venkat et al., 2002), and the employment of amnioinfusion (Jayaram and Sudha, 2001) need careful consideration to improve perinatal outcome.

IMPORTANT POINTS

1. The onset of labor following PROM is directly related to the gestational age at the time of rupture: after 36 weeks more than 80% of the patients will be in labor within 24 hours; before 28 weeks only 48% will be in labor within 3 days of rupture.
2. Most probably the cause of PROM is a reduction in membrane tensile strength due to the collagenolytic effect of metalloproteinases, the effect of bacterial proteases, or to repeated stretching by uterine contractions.
3. The method most commonly used for the ultrasound evaluation of amniotic fluid volume is the four-quadrant technique. It consists of measuring the vertical diameter of the largest pocket of fluid seen in each of the four quadrants of the uterus. The measurements are added and the result is the amniotic fluid index. An amniotic fluid index < 5 cm indicates oligohydramnios. Once the amniotic fluid index is < 5 cm, the fluid volume is measured using the largest diameter of a cord-free pocket of fluid.
4. The diagnosis of chorioamnionitis is clinical. It requires the presence of fever (>100 F, or > 37.8°C) and two of the following conditions: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor of the amniotic fluid, or maternal leukocytosis.
5. The risk of chorioamnionitis is inversely related to the gestational age at the time of PROM: it is greater than 50% when it occurs before 28 weeks, decreases to approximately 25% between 30 and 32 weeks, and remains between 12 and 20% from 32 to 36 weeks.
6. A positive Gram stain of the amniotic fluid has a 93.3% positive and an 85.4% negative predictive value for the diagnosis of chorioamniotic infection.
7. The first biophysical manifestations of impending infection in patients with PROM are a nonreactive NST and absence of fetal breathing movements. These signs are associated with chorioamnionitis in almost 100% of the cases. Patients with persistent nonreactive NST and those with an initially reactive NST that becomes nonreactive have the highest infection rates.
8. The incidence of HMD is inversely related to the gestational age at the time of PROM: it affects more than 80% of babies born before 28 weeks, more than 30% between 28 and 31 weeks, 14.8% at 32 weeks, 3–4% at 33–34 weeks, and very few after 34 weeks.
9. The first step in the management of PROM is to identify those patients who require delivery. They are patients in labor, with mature fetal lungs, with lethal fetal malformations, with fetal distress, with overt infection, with subclinical infection/inflammation, and those at high risk for infection.
10. There are different opinions about the length of time that a patient with PROM and overt chorioamnionitis may be in labor. Some investigators have not

found a definite time after diagnosis of amnionitis when delivery is necessary to avoid maternal and fetal complications. However, persistence in attempts to obtain a vaginal delivery in these patients may be potentially dangerous. The best policy may be to deliver these patients in a few hours after the diagnosis of chorioamnionitis has been established.

11. The predominant risk for patients with PROM between 32 and 36 weeks is RDS/HMD. Therefore, management should be expectant unless an indication for delivery is present. The risk of expectancy is infection, but in the majority of cases infection is diagnosed early and has no serious effects on mother or fetus.
12. The predominant risks for patients with PROM between 24 and 32 weeks are RDS/HMD, sepsis, and GMH/IVH. Administration of glucocorticoids and prolongation of the latent phase with antibiotics are beneficial for these patients if they do not have clinical or subclinical chorioamnionitis.
13. Administration of tocolytic agents does not significantly prolong the latency period in patients with PROM. These agents may be useful in patients with contractions at the time of admission who may deliver before receiving the benefit of glucocorticoid treatment.

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10

Cervical Insufficiency

CHAPTER OUTLINE

Cervical insufficiency or incompetent cervix is an obstetric condition characterized by the inability of the cervix to retain a pregnancy in the absence of uterine contractions (painless cervical dilatation). The diagnosis and treatment of the incompetent cervix are areas of renewed interest because the reliability of well-established concepts and practices in regards to this subject is being questioned by recent clinical investigations and particularly by the results of randomized clinical trials.

CAUSES OF INCOMPETENT CERVIX

Cervical incompetence may be congenital or acquired (Box 10-1). The most common congenital cause is a defect in the embryologic development of the Mullerian ducts, causing bicornual, unicornual, or septated uterus. Similarly, the cervix may not be able to perform adequately if its collagen is deficient in composition due to a genetic abnormality such as Ehlers–Danlos or Marfan's syndrome. The most common acquired cause is cervical trauma such as cervical lacerations occurring during childbirth, cervical conization, LEEP (loop electrosurgical excision procedures) for the treatment of carcinoma "in situ," or forced cervical dilatation during uterine evacuation in the first or second trimester of pregnancy. However, most patients presenting with the typical findings of incompetent cervix do not have

BOX 10-1

Causes of incompetent cervix (primary cervical disease)

Congenital

- Mullerian tube defects (bicornual uterus, septated uterus, unicornual uterus)
- Diethylstilboestrol exposure in utero
- Abnormal collagen tissue (Ehlers–Danlos syndrome, Marfan's syndrome)

Acquired

- Forceful mechanical cervical dilatation
- Cervical lacerations
- Cervical cone or LEEP procedure

acquired or congenital factors causing the condition and in most of them the cervical changes are the result of infection/inflammation, causing early activation of the final pathway of parturition.

Cervical insufficiency may occur in nulliparous or in multiparous patients. Cervical incompetence due to congenital causes, surgical conization, or LEEP may occur in the first pregnancy. Incompetent cervix secondary to obstetrical trauma typically affects multiparous women. Cervical incompetence due to primary cervical disease is a recurrent problem. Cervical insufficiency secondary to early preterm labor is not necessarily recurrent. Cervical insufficiency seems to be more common in obese women. However, this association has not been reported in the literature and at least one study did not find a correlation between morbid obesity and incompetent cervix (Ratner et al., 1991).

PATHOPHYSIOLOGY

The cervix is made up of 90% connective tissue and 10% muscular tissue and its ability to retain the products of conception depends on the content and composition of its connective tissue. The changes in the cervical connective tissue commonly designated as "cervical ripening," characteristically occur at the end of pregnancy and are one of the components of the final pathway of parturition. Cervical incompetence is cervical ripening occurring far from term. This means that the cervical changes that occur in women with incompetent cervix are identical to those happening during term or preterm parturition. In each of these cases the cervical connective tissue undergoes significant changes consistent mainly of an increased synthesis of collagenases, increased production of hyaluronic acid, and infiltration by inflammatory cells particularly neutrophils and macrophages. These changes cause collagen degradation, disruption of the collagen structure, increased water content, and increased synthesis of proinflammatory cytokines. The final result is that the cervix becomes soft, easy to stretch, and progressively short and the endocervical canal then starts to dilate in response to uterine contractions. There is evidence suggesting that prostaglandins and estrogens are the triggers of cervical ripening at term, but it is not known if they are the mediators when cervical ripening occurs early in gestation.

The trigger of the biochemical changes necessary to produce cervical ripening in the second trimester of pregnancy is not known. In cases of primary cervical disease it is possible that the main activator of the biochemical mechanisms causing cervical ripening is the intrauterine pressure. Women who have lost a significant amount of cervical tissue as a consequence of a surgical procedure or who have an abnormal composition of the connective tissue of the cervix would have a decreased intrauterine pressure threshold for the activation of the biochemical reactions responsible for cervical ripening. In these cases, when the pressure threshold is exceeded, the cervix ripens prematurely, usually between 18 and 22 weeks of gestation. This hypothesis is not supported by experimental data and there are no studies determining the minimal amount of connective tissue necessary to maintain cervical competence or the uterine pressure threshold that needs to be exceeded to initiate cervical ripening.

In women with incompetent cervix secondary to early preterm labor, there is a preponderance of signs and symptoms of cervical ripening which is one of the three components of the final pathway of parturition, the others being myometrial activation and membrane activation. The preponderance of signs and symptoms associated with cervical ripening and the early gestational age, when cervical ripening occurs, differentiates cervical incompetence from preterm labor with intact membranes and premature rupture of the membranes. In incompetent cervix, signs and symptoms of activation of the other two components of the final pathway of parturition eventually will occur and preterm birth will be unavoidable.

The predominant activation of one of the components of the final pathway of parturition does not happen exclusively in early preterm labor. In many women destined to deliver prematurely, preterm premature rupture of the membranes and release of fetal fibronectin in the vaginal secretions, markers of membrane activation, frequently occur several days before cervical ripening and uterine contractions. In others, uterine contractions, a marker of myometrial activation, frequently occur before cervical ripening and membrane activation. The clinical preponderance of one component of the final pathway of parturition over the other two most probably depends on the nature of the agent causing activation of the pathway. Anatomic or functional abnormalities of the cervix will preferentially cause cervical ripening, endocrine factors or bleeding preferentially stimulate the myometrium, and infection predominantly will cause activation of the membranes.

DIAGNOSIS

The diagnosis of incompetent cervix is usually made in three different settings:

1. Women who present with sudden onset of symptoms and signs of cervical insufficiency (acute presentation)
2. Women who present with a history of second trimester losses consistent with the diagnosis of cervical incompetence (historical diagnosis)
3. Women with endovaginal ultrasound findings consistent with cervical incompetence (ultrasound diagnosis)

Acute Presentation

Characteristically, women with acute presentation of incompetent cervix present between 18 and 22 weeks' gestation with complaints of pelvic or rectal pressure of recent onset, increased mucous vaginal discharge, and no contractions. The digital or speculum examination reveals a cervix dilated 2 or more cm, effacement greater than or equal to 80%, and the bag of waters (BOW) visible through the external os or protruding into the vagina. In some cases, there is a history of congenital anatomic abnormality of the uterus, instrumental vaginal deliveries with cervical lacerations, or that of voluntary abortions with forced dilation of the cervix. In other cases, there is a history of a LEEP or cervical conization before the index pregnancy. Patients with incompetent cervix occasionally have connective tissue disorders manifested by their ability to hyperextend their fingers and adopt postures that require unusual mobility of the joints of the upper and lower extremities. However, in the majority of cases, there is no additional information supporting the possibility of primary cervical disease and the most likely cause is early preterm labor secondary to intra-amniotic infection/inflammation.

The fundamental differential diagnosis in women presenting with acute onset of signs and symptoms is between cervical insufficiency secondary to primary cervical pathology versus early cervical ripening secondary to early preterm labor secondary to intrauterine infection. Romero et al. (1992) performed amniocentesis in 33 women between 14 and 24 weeks' gestation with typical presentation of incompetent cervix, no contractions, and no evidence of acute chorioamnionitis. They found that 17 of the 33 women (51.5%) had microbial invasion of the amniotic cavity. All patients with subclinical infection aborted, presented with ruptured membranes, or developed overt chorioamnionitis, while the prognosis was good for women with negative amniotic fluid cultures. Although the number of cases in this study is small, it suggests that approximately 50% of the cases of acute presentation of incompetent cervix are due to intra-amniotic infection/inflammation and surgical treatment with a cerclage is destined to fail. As it will be seen later, this possibility is supported by other studies demonstrating a high number of failures and complications following "rescue" cerclage procedures.

One important feature in the diagnosis of incompetent cervix is the absence of uterine contractions. Some women with classical acute onset presentation of incompetent cervix may complain of uterine cramps or mild contractions in the days preceding the diagnosis. The lack of correlation between the reported mild uterine activity and the magnitude of the cervical changes influences the clinician's judgment to believe that cervical incompetence is secondary to intrinsic abnormalities of the cervix. However, the history of cramps or mild contractions is important because it indicates to the clinician that a second component (myometrial activation) of the final pathway of parturition has been activated. A large number of these women with incompetent cervix and cramping will be infected as demonstrated by elevated white cell count, elevated C-reactive protein (CRP), and amniocentesis. Even if they are not infected, the prognosis is guarded because a large number of them will have premature rupture of the membranes (membrane activation) a few days later or will continue having uterine contractions and deliver prematurely.

BOX 10-2

Differential diagnosis between primary cervical disease and early preterm labor

Primary cervical disease	Cervical ripening secondary to preterm labor
Multiparity	Nulliparity
Between 18 and 24 weeks	Before 18 and after 24 weeks
No contractions	Mild contractions
History of anatomic abnormality of the uterus or cervix	Negative history
History of cervical trauma or surgical procedure	Negative history
Normal C-reactive protein	Increased C-reactive protein
Normal WBC and neutrophils	Increased WBC and neutrophils

Most cases of cervical insufficiency secondary to primary cervical pathology occur between 18 and 24 weeks. When the clinical signs and symptoms occur early in the second trimester (14–18 weeks) or late in the second and early third trimesters of pregnancy (24–28 weeks), the most probable cause is cervical ripening secondary to preterm labor. In general, the diagnosis of primary cervical incompetence in patients presenting with the acute onset of symptoms is not reliable. Approximately 50% of these women have subclinical amnionitis, and surgical treatment by means of cerclage is destined to fail. Box 10-2 summarizes some of the variables that may be useful in the differential diagnosis between intrinsic and extrinsic causes of cervical ripening.

Historical Diagnosis

The diagnosis of cervical incompetence is frequently made on a historical basis. The most common situation is when a pregnant woman gives a history of painless cervical dilatation treated with cerclage in the second trimester of a previous pregnancy. A historical diagnosis of incompetent cervix is also frequently made when women present with a history of ruptured membranes

without contractions in the second trimester of pregnancy. Also, a diagnosis of congenital uterine abnormality, diethylstilboestrol (DES) exposure in utero, cervical laceration, and cervical trauma in women without previous pregnancy losses is frequently used as diagnostic evidence that the cervix is incompetent and requires treatment.

It has been known for long time that the historical diagnosis of incompetent cervix has a high probability of being incorrect, and follow-up studies of women diagnosed with incompetent cervix in a given pregnancy indicate that the majority of them will not show evidence of incompetence in a subsequent pregnancy. Dunn and Dans (1962) followed 30 women with cervical incompetence on the basis of previous obstetrical history through 61 subsequent pregnancies and found a spontaneous cure rate of 50%. Fejgin et al. (1994) compared the outcome of pregnancies with and without cerclage in 35 patients who had prior McDonald procedures. These women had 58 pregnancies with a cerclage and 52 pregnancies without cerclage. The outcome of pregnancies without cerclage was significantly better and resulted in larger infants. Socol et al. (1984) followed 40 pregnancies in 37 women who previously delivered a live-born fetus between 20 and 32 weeks. Fourteen of them were treated with cerclage and 26 were managed expectantly. Three in the expectant group required cerclage placement. Preterm delivery happened in 36% of women treated with cerclage and in 38% of those managed conservatively. Although this study was not specifically designed to compare the efficacy of cerclage versus expectant management, it suggests that cerclage is not useful in women with historical diagnosis.

The analysis of the control groups in randomized trials of cerclage versus expectant management is valuable to examine the reliability of the historical diagnosis of incompetent cervix. In a study of Rush et al. (1984) 67 out of 98 (68.4%) women at high risk of late abortion or preterm delivery randomized to the no-cerclage group gave birth after 37 weeks of gestation. In a French multicenter study (Lazar et al., 1984) 225 out of 238 (94.5%) women randomized to no cerclage delivered after 37 weeks. In a European multicenter trial (MRC/RCOG Working Party on Cervical Cerclage, 1993) 447 out of 645 (69%) women randomized to no cerclage delivered after 37 weeks. More recently, in a CIPRACT trial (Althuisius et al., 2001) 44 women with a previous preterm delivery before 34 weeks who met clinical criteria for cervical incompetence were randomized to expectant management and followed with cervical ultrasound examinations. They were secondarily randomized to cerclage or no cerclage if the cervical length by ultrasound was less than 25 mm. Of the 44 women 18 (40.9%) developed cervical length less than 2.5 cm. The other 26 women (59.1%) delivered after 34 weeks. These studies indicate that approximately 60% of women with history of incompetent cervix in a given pregnancy will have a normal outcome without treatment in subsequent pregnancies and that ultrasound of the cervix may be useful to differentiate those who need cervical cerclage from those who will not.

In summary, the historical diagnosis of incompetent cervix is erroneous in the majority of cases. The practice of performing cerclage exclusively on the basis of a historical diagnosis of cervical incompetence should be abandoned.

Ultrasound Diagnosis

Cervical length

A commonly used diagnostic criterion for incompetent cervix is the presence of cervical changes by endovaginal ultrasound during the second trimester of pregnancy. The cervical changes are diverse. Some women simply show a short cervix. Others exhibit shortening of the cervix and funneling of the amniotic sac in the endocervical canal. Others have dynamic changes with a normal looking cervix at the beginning of the examination but later on the internal os will open and the membranes will herniate into the upper endocervical canal spontaneously or after application of fundal pressure. In these cases the "T" that sonographically characterizes a normal cervix becomes a "Y" when the internal cervical os opens and the amniotic sac starts to herniate into the upper part of the endocervical canal. The "Y" eventually becomes a "U" with further herniation of the amniotic sac and further thinning of the cervix. The measurement with better correlation with outcome is the cervical length defined as the length of the unopened portion of the endocervical canal. Different thresholds (<25 mm, <15 mm, <10 mm) have been recommended to identify women with incompetent cervix. However, the finding of a short cervix by endovaginal ultrasound is not diagnostic of incompetent cervix and does not differentiate between primary cervical disease and early preterm labor. In other words, endovaginal ultrasound can detect alterations in the anatomy of the cervix but is not useful in detecting the underlying pathologic process causing the abnormality. The finding of a short cervix by endovaginal ultrasound is suggestive but not diagnostic of incompetent cervix only in women who are at high risk for this condition (Box 10-3).

Review of the evidence indicates that the studies on ultrasound diagnosis of cervical incompetence performed before 1994 have significant problems. They used different parameters to diagnose cervical incompetence such as width of the internal os, width of the endocervical canal, thickness of the anterior wall of the lower uterine segment, and cervical length. Most of them used abdominal rather than endovaginal ultrasound and in most of them

BOX 10-3

Women at high risk for incompetent cervix

- Cervical incompetence diagnosed in a prior pregnancy
- Cervical treatment for abnormal cervical cytology (freezing, cone, LEEP)
- History of voluntary pregnancy termination
- Deep cervical laceration(s)
- Congenital abnormality of the connective tissue (Marfan's syndrome, Ehlers–Danlos syndrome)
- Anatomical abnormalities of the uterus (bicornual, septated)
- History of ruptured membranes in the second trimester
- Short cervix (<1 cm in the intravaginal portion) found in the initial prenatal evaluation
- Short labors
- History of two or more second trimester losses

the diagnosis was followed by cerclage treatment, making it impossible to judge the validity of the diagnosis. Better studies performed after 1994 have demonstrated that a short cervix detected by ultrasound is not exclusive of women with incompetent cervix and occurs also in women destined to deliver preterm due to preterm labor (Iams et al., 1994) or to preterm rupture of the membranes (Kishida et al., 2003). Also, a significant number of women found to have a short cervix early in gestation continue with the pregnancy and reach full term without intervention.

Funneling

Funneling is the ultrasound finding of herniation of the fetal membranes into the upper part of the endocervical canal. This is a feature quite common in women destined to deliver prematurely but, similarly to a short cervix, it is not diagnostic of incompetent cervix. Funneling is a common finding in all of the conditions that trigger the final pathway of parturition. There are no uniform criteria to describe funneling of the cervix and investigators have used the length of the funnel, the width of the funnel, the relationship between funnel length and total cervical length, and that between the funnel length and the actual cervical length among many criteria to quantify this variable.

Due to the lack of agreement in the description of funneling, cervical length is the universally accepted variable to measure cervical changes. However, funneling is an important finding that should be reported as present or absent when the cervix is assessed by endovaginal ultrasound. Funneling is equivalent to dynamic cervical changes. Both ultrasound findings are evidence of uterine activity usually undetected by the patient. The presence of funneling significantly increases the risk for adverse perinatal outcome. Rust et al. (2005) compared the obstetrical outcome of 82 women with short cervix and 82 women with cervical shortening and funneling and found that the group with funneling had more readmissions because of preterm labor and had a higher incidence of chorioamnionitis, abruption, premature rupture of the membranes, and cerclage placement. The neonates in the funneling group delivered earlier and had significantly more morbidity and mortality.

Dynamic cervical changes

In 1994 Guzman et al. reported that the application of pressure in the uterine fundus during endovaginal ultrasound examination caused an opening of the internal os and descent of the fetal membranes into the endocervical canal in women at risk for cervical incompetence. These changes did not occur in women at low risk. These investigators postulated that this maneuver was useful in the sonographic identification of incompetent cervix, but the validity of this conclusion was questionable since all their patients with positive changes had a cerclage and there was not an untreated control group. A few years later the same investigators (Guzman et al., 1997) followed with serial endovaginal ultrasound examinations a group of 10 women who had positive response to fundal pressure. These women had their first ultrasound at a gestational age between 15 and 22 weeks (median 19.0 weeks). It was found that in a period of 1–3 weeks, there was a significant decrease in cervical length to less than 10 mm in all the cases, with 6 of the patients having the membranes at the external os before application of pressure at the time of the last examination. This work indicates that passive or dynamic sonographic shortening of the cervix between 15 and 22 weeks in women is a significant predictor of additional cervical shortening but does not differentiate between women with primary cervical disease from those with early preterm labor. Dynamic changes are evidence of myometrial activity and early preterm labor. They are the result of painless uterine contractions and their presence indicates to the clinician that the patient is having contractions and that the cervix is opening because of those contractions.

In summary, the evidence supporting the accuracy of ultrasound diagnosis of incompetent cervix is not robust and ultrasound criteria should not be used alone to make this diagnosis.

MANAGEMENT

Women who may have incompetent cervix and require treatment can be divided into four groups:

1. Women who present with a history of "painless cervical dilatation" and the BOW is visible through the external cervical os or prolapsed into the vagina

2. Women with cervical changes demonstrated by ultrasound examination
3. Women with high-risk factors for incompetent cervix
4. Women with an obstetric history consistent with incompetent cervix and failure of one or more cerclage procedures to correct the cervical abnormality

Acute Presentation

Most of the literature regarding treatment with urgent or rescue cerclage when the cervix is dilated and the membranes are at the external os or bulging into the vagina consists of small uncontrolled case series which amount to over 700 cases (Rand and Norwitz, 2003). These studies differ in multiple aspects such as patient selection criteria, type of surgery, preoperative evaluation for infection, degree of cervical dilatation, membranes at the os or bulging, use of antibiotics and tocolytic agents, neonatal care, etc. overall they suggest that success, assessed by neonatal survival, is achieved in approximately 50% (22–89%) of the cases. The median prolongation of pregnancy is approximately 8 weeks (0–22 weeks). The large variation in results is not only a consequence of the clinical heterogeneity of the groups but is also a reflection of the lack of predictability of the intervention. There are three controlled clinical trials involving a total of 64 women who had cerclage compared with 37 who had no intervention. Olatunbosun et al. (1995) compared 22 women who underwent emergency cerclage with 15 women who elected bed rest and they found more advanced gestational age at delivery, shorter hospitalization, less need for tocolysis, and fewer cases of ruptured membranes in women treated with cerclage. The perinatal mortality was not significantly different. In a study of Althuisius (2003) 13 women were randomly assigned to emergency cerclage and 10 women to bed rest. They found that the preterm delivery rate before 34 weeks and the neonatal morbidity rate were significantly lower in women undergoing emergency cerclage than those in women treated with bed rest. No significant difference was found in neonatal survival. Another study (Daskalakis et al., 2006) found significant differences in prolongation of pregnancy (8.8 weeks versus 3.1 weeks) in 29 women who had emergency cerclage when compared with 17 women treated with bed rest. Neonatal survival was 96% in the cerclage group versus 57.1% in the bed rest group ($P = 0.02$). This trial excluded women with white cell count greater than 14,000/ml and with elevated CRP.

In summary, the literature about emergent or "rescue" cerclage for the treatment of women with the acute presentation of incompetent cervix suggests that surgical intervention is more advantageous than bed rest. However, this advantage is limited and the number of poor outcomes is significant, indicating the need to develop criteria to identify the cases that would benefit from surgery and to avoid unnecessary intervention and serious maternal morbidity in those who will not respond to treatment. With these considerations, the most important decisions in the management of this particular group of patients are to categorize women that may benefit and women that will not benefit from a rescue cerclage operation and to select the best surgical method for those who may benefit from the intervention.

Selection of patients for surgical treatment

The problem in selecting women who may benefit from surgical treatment originates in the significant difficulties that exist in the differential diagnosis between primary causes of incompetent cervix, which will benefit from cerclage, and cervical ripening due to early preterm labor, which will not benefit from cerclage. There are clinical and laboratory variables that may help in this differential diagnosis (Box 10-2) but in many cases it is impossible to differentiate between these two possibilities. Studies have demonstrated that more than 50% of women with acute presentation have microbial invasion of the amniotic fluid (Romero et al., 1992) and other studies have shown that 41% of them are infected when the cervical dilatation is greater than 2 cm (Treadwell et al., 1991). In general, nulliparity, cervical dilatation > 4 cm, WBC ≥ 14,000/mm^3, CRP >3.0 mg/dl, and amniotic fluid indices (glucose, LDH, WBC count) suggesting infection/inflammation are indicators of poor prognosis and most probably these women will not benefit from surgical treatment.

Amniocentesis is useful to identify women with subclinical infection (Mays et al., 2000). A positive Gram stain for bacteria, a WBC count of > 50 cells per high-power field, glucose < 14 mg/dl, and LDH (lactate dehydrogenase) > 400 U/L are indicative of infection/inflammation and contraindicate a surgical procedure. In the future, determination of interleukin-8, a marker of infection/inflammation, in the cervical mucous may be added to the presently available indicators of success or failure of cerclage (Sakai et al., 2006). Bacterial cultures of the fluid require several days to be completed and are not useful in the initial evaluation.

Rupture of the membranes occurs more frequently when amniocentesis is carried out in women with a dilated cervix and exposed membranes than when the cervix is closed. Most probably the rupture is not a consequence of the amniocentesis but is a spontaneous rupture secondary to infection/inflammation of the fetal membranes that coincides with the amniocentesis. This should be explained to the patient before the amniocentesis is performed so that they understand that the procedure is not

the immediate cause of the rupture. When the membranes rupture, the only option is delivery.

The maternal WBC count and the CRP concentration are frequently used as indices of infection/inflammation in the evaluation of women with acute onset of cervical dilatation in the second trimester of pregnancy. Unfortunately, these indices are not specific and are associated with poor outcomes only when are markedly deviated from normal. A retrospective study with a small number of cases (Minakami et al., 1999) suggests that a preoperative CRP value of CRP ≥ 4 mg/dl or a WBC count ≥ 14,000/mm^3 were strongly associated with failure following rescue cerclage.

It is possible to categorize women presenting with midtrimester cervical effacement and dilatation in three groups. Women in the first group are multiparous, are at 16–22 weeks of gestation, show no contractions or uterine cramps preceding the onset of acute symptoms, present with history of previous mechanical dilatation or surgical procedures in the cervix or that of midtrimester losses, normal CRP, normal WBC count, membranes visible at the external os but not herniated in the vagina, and cervix dilated less than 3 cm. These women are the best candidates for cerclage and their outcome is usually good. Women in the second group are nulliparous, presenting before 16 or after 22 weeks of gestation, with no history of cervical trauma, feeling contractions or cramps preceding the onset of symptoms, membranes herniated in the vagina, cervical dilatation > 3 cm, WBC > 14,000/mm3 with left shift, and CRP > 4 mg/dl. These are not adequate surgical candidates and their outcome will be almost uniformly poor. The third group consists of women who do not belong to either of the two previous groups and have an uncertain diagnosis and treatment. A few of them will benefit from rescue cerclage and antibiotic and anti-inflammatory treatment and will be able to prolong the pregnancy after 30 weeks. However, the majority of them will have a minimal prolongation of pregnancy with the cerclage—enough to convert a previable fetus into an extremely premature newborn at high risk for CP and other devastating problems. Severe maternal sepsis is another complication of cerclage in this group of patients. Patients must be counseled that either no intervention or delivery are the best options.

Surgical treatment

Placement of a cervical cerclage when cervical changes are advanced and the membranes are herniated through the external cervical opening is a challenging task and selection of the surgical technique is of great importance. The tissues are thin and it is easy for the sutures to cut through. The best surgical techniques for the temporary closure of the cervix when a rescue cerclage is necessary are the Espinosa-Flores operation (Espinosa-Flores, 1966) and the Wurm procedure (Hefner et al., 1961).

Espinosa-Flores operation

The Espinosa-Flores operation is popular in Latin-American countries. The procedure avoids incisions into the thin cervical wall and uses two bites into the cervix at the 9 o'clock and 3 o'clock positions (Figure 10-1). In this operation, after displacing the herniated BOW inside the uterus with a Foley balloon, the anterior and posterior aspects of the cervix are grasped with ring forceps and the area of insertion of the cardinal ligaments at each side of the cervix is identified by visual observation and manual palpation. Then, a 5-mm Mersilene band, a #5 Mersilene suture or a double #1 prolene suture is inserted into this area going from the posterior toward the anterior aspect of the cervix. Then the procedure is repeated on the opposite site with the needle going this time from the anterior toward the posterior aspect of the cervix. The two ends of the suture are tied tightly over the posterior aspect of the cervix. This operation is simple, effective, and can be used for both prophylactic and rescue cerclages.

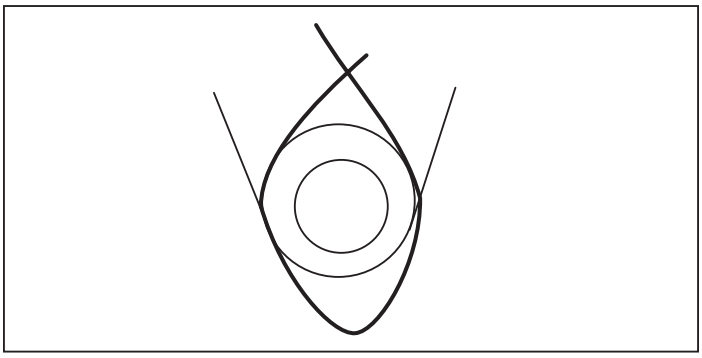

Figure 10-1. Diagrammatic representation of the Espinosa-Flores cerclage operation. The suture is inserted as high as possible using two bites, at 9 o'clock and 3 o'clock. The suture may be tied over the anterior or the posterior aspect of the cervix.

Wurm operation

In the Wurm procedure the BOW is displaced inside the uterus, using a Foley catheter's balloon, the lips of the cervix are grasped with ring forceps, and two "U" stitches of #1 prolene are placed, one vertically (from 12 to 6 o'clock and back to 12 o'clock) and the other horizontally (from 3 to 9 o'clock and back to 3 o'clock) through the whole thickness of the cervix and as near as possible to the internal cervical os. The entry and the exit points of each suture are separated approximately by 1 cm of tissue (Figure 10-2). This technique is relatively simple to perform in patients with cervical effacement greater than 80% and cervical dilatation of 3 or more cm.

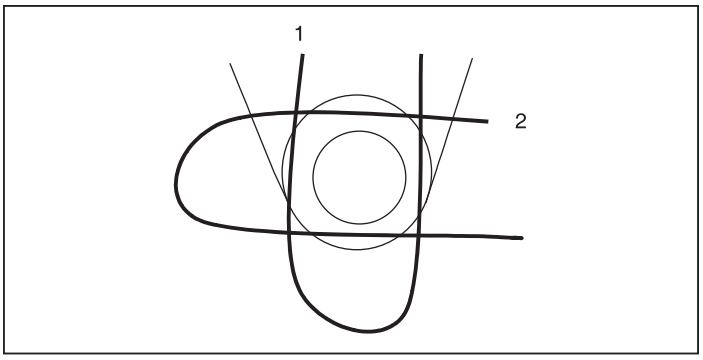

Figure 10-2. Diagrammatic representation of the Wurm cerclage operation. Suture 1 is a mattress suture placed in the cervix from 12 to 6 o'clock and back to 12 o'clock. Suture 2 is a mattress suture placed from 3 to 9 o'clock and back to 3 o'clock.

There are several measures that may contribute to the success of a rescue cerclage operation:

1. Proper placement of the patient on the operating table is important. To facilitate exposure during surgery, it is necessary for the perineum and the vulvar opening to be 1 or 2 in. beyond the border of the operation table.
2. To avoid contact of the exposed membranes with chemical irritants, the best preparation of the vagina for surgery is to wash with copious amounts of sterile saline or water dispensed with a syringe and removed by suction.
3. Good exposure is an essential condition for a successful cerclage placement when the BOW is protruding into the vagina. Ideally, two assistants are required to hold retractors, one at each side of the surgeon.
4. The best anesthesia for a difficult cerclage is general one with halothane. This anesthetic agent is a powerful uterine relaxant and facilitates repositioning of the BOW inside the uterus. However, due to haloxane toxicity anesthesiologists prefer regional anesthesia for this operation. A problem with general anesthesia is the increase in intra-abdominal pressure, and therefore on the cerclage suture, which occurs before removal of the endotracheal tube.
5. The best way to displace the membranes from the vagina into the uterine cavity is by means of an 18 French Foley catheter with a 30-cc balloon (Scherer et al., 1989). Depending on the degree of cervical dilation, the balloon is inflated with 5–25 cc of saline and a ring forceps is placed near the base of the balloon. The ring forceps placed in the cervix are used to pull the cervix toward the operator and the ring forceps with the Foley balloon are used to push the membranes inside the uterus. Once the membranes are inside the uterus, the balloon is filled up to 30 cc with normal saline. This keeps the BOW inside the uterus and facilitates placement of the suture.
6. A distended bladder may be also used to reposition a herniated BOW inside the uterus. The problem with this technique is that the distended bladder pulls the cervix upward, making placement of the cerclage difficult. A compromise may be to fill up the bladder until the BOW recedes into the uterus, grasp the anterior and posterior lips of the cervix with ring forceps, keeping the BOW inside the uterus with the help of an inflated 30-cc Foley balloon and then emptying the bladder to bring the cervix down and facilitate placement of the suture. In general, we have found the use of an overdistended bladder to reduce herniation of the membranes cumbersome and it complicates rather than facilitating the rescue operation. We prefer to work with an empty bladder and use a Foley catheter balloon to displace the BOW.
7. Some authors recommend draining 100–500 ml of amniotic fluid to collapse the amniotic sac and facilitate displacement of the BOW inside the uterus. This method is frequently associated with rupture of the membranes shortly after surgery.
8. The Shirodkar technique is not recommended in women with advanced cervical effacement and dilatation. The Mersilene band can easily cut through the thin cervical tissue when cervical changes are advanced and further complicate a difficult procedure.

There is no good evidence about the success rate regarding rescue cerclage operations. Old studies with few cases and no controls suggest a rate of success between 50 and 59%. One study (Olatunbosun et al., 1995) of a cohort of 43 women with cervix dilated ≥ 4 cm revealed longer mean gestational age at delivery, shorter antepartum hospitalization, less use of tocolysis, and fewer cases of premature rupture of membranes in 22 women who had rescue cerclage than in 15 women who elected conservative bed rest. A more recent study (Terkildsen et al., 2003) analyzed factors associated with delivery before or after 28 weeks of gestation in 116 women undergoing emergency cerclage operations. Cerclage placement was performed between 16 and 21 weeks in 64% of the cases. The univariate analysis revealed that nulliparity, cervical dilatation > 3 cm, cervical length < 0.5 cm, and prolapse of the fetal membranes were variables associated with delivery before 28 weeks. In the multivariate analysis only nulliparity and prolapse of the membranes continued to be associated with delivery before 28 weeks. A review of the literature (Cockwell and Smith, 2005) reported an average prolongation of pregnancy of 7 weeks plus 1 day, and 60% of pregnancies prolonged after 28 weeks and an average neonatal survival over 70% following rescue cerclage.

In conclusion, in about 50% of the cases rescue cerclage will result in a significant prolongation of pregnancy. Preoperative exclusion of women with high probability of failure (contractions, cervix > 4 cm, nulliparas, CRP ≥ 4.0 mg/dl, WBC ≥ 14,000) and careful selection of the surgical method will increase the rate of success.

Pessaries

Pessaries are an adjuvant treatment for obese women with incompetent cervix. In these cases the excessive weight of the abdomen causes an increase in the curvature of the spine, displacing the pressure vector on the pelvis in such a way that it falls perpendicularly on the internal cervical os. The pressure on the cervix will decrease considerably if the cervix is displaced posteriorly with a pessary. The Smith-Hodge and ring pessaries are adequate for this purpose. They should be inserted 1–2 weeks after surgery when the tissues have healed.

Women with Cervical Changes by Ultrasound Examination

As discussed before, cervical changes seen with endovaginal ultrasound are not diagnostic of incompetent cervix and do not permit differentiation between primary cervical disease and early preterm labor. Short cervical length by ultrasound examination is not equivalent to incompetent cervix, and many women with short cervix have normal pregnancies and deliver at term. In a few occasions the medical history and the physical examination will contribute information for the differential diagnosis, but in the majority of cases they are not contributory.

Endovaginal ultrasound gives the clinician a better assessment of the cervical anatomy than digital examination and ultrasonic cervical length is an important predictor of preterm delivery (Iams et al., 1996). From this initial observation it was extrapolated that cervical length during the second trimester could identify women with incompetent cervix before the dramatic changes associated with the acute onset presentation (Fox et al., 1996; McDonald et al., 2001). This assumption was incorrect because ultrasound can detect cervical changes but cannot identify the cause behind those changes. Specifically, endovaginal ultrasound cannot distinguish between primary cervical disease that will benefit from cerclage treatment from early preterm labor where cerclage is ineffective.

Randomized clinical trials in women at high risk for cervical incompetence and with cervical changes detected by ultrasound have failed in demonstrating benefit of cerclage. Rust et al. (2000) randomized 61 women between 16 and 24 weeks of gestation with demonstrable prolapse of the fetal membranes into the endocervical canal > 25% of the total cervical length or with a distal cervical length < 25 mm to receive or not cervical cerclage. It was found that the gestational age at delivery, the perinatal death rate, and the perinatal outcomes were similar in both groups. In a second publication the same investigators (Rust et al., 2001) expanded their patient population and randomly assigned 55 patients to cerclage and 58 patients to no cerclage and found again that cerclage did not affect perinatal outcome. The study of Althuisius et al. (2001) contradicted these findings. They selected 35 women with history suggestive of incompetent cervix and cervical length < 25 mm and randomized 19 women to cerclage and 16 to bed rest. They found that preterm delivery before 34 weeks was significantly more frequent in the bed rest than in the cerclage group and perinatal morbidity was significantly higher in the bed rest than in the cerclage group. More recently, Berghella et al. (2004) selected a population of 61 women at high risk for incompetent cervix and short cervix (<25 mm) or significant funneling (>25%) by ultrasound examination. The women were randomized to cerclage or no cerclage and it was found that cerclage did not prevent preterm delivery or cause differences in obstetric or neonatal outcomes.

The most probable explanation for the divergent results of randomized clinical trials on the effectiveness of cerclage in women with short cervix by second trimester ultrasound lies in the selection criteria for participation in the trials. The trial by Althuisius et al. (2001) selected patients at high risk for incompetent cervix, 71.4% with previous preterm delivery < 34 weeks and 34.3% with accepted gynecologic risk factors for cervical incompetence, while the trial of Rust et al. (2001) included 47% women with preterm delivery < 34 weeks and apparently none with gynecologic risk factors for incompetent cervix. The trial of Berghella et al. (2004) included 64% women with previous delivery at < 35 weeks and only 7 patients (11.4%) with gynecologic risk factors for cervical incompetence.

There is one meta-analysis on the use of cerclage in sonographic short cervix (Berghella et al., 2005). Unfortunately the authors added to the three randomized trials mentioned in the previous paragraph the study of To et al. (2004) where cerclage was used for the prevention of preterm delivery and women were scanned for the first time at 22–24 weeks of gestation, excluding the majority of cases at risk for primary cervical disease.

In summary, the randomized clinical trials suggest that cerclage may be valuable in women with short cervix by ultrasound examination in the second trimester if they have a history of second trimester delivery with characteristics suggestive of cervical incompetence (painless dilatation, short labor) or have accepted gynecological factors for primary cervical disease. The operation will be ineffective in women with short cervix in the second trimester and no risk factors, or with risk factors for spontaneous preterm labor.

There are three main surgical techniques for cerclage placement in women selected for intervention on the bases of vaginal ultrasound findings plus risk factors for primary cervical disease. They are the Shirodkar, the McDonald, and the Espinosa-Flores operations. The Espinosa-Flores method was already described for rescue cerclage in the treatment of women presenting in the acute phase of cervical incompetence.

Shirodkar operation

The Shirodkar operation is a procedure that requires incisions into the mucosa of the anterior and posterior aspects of the cervix, separation of the bladder and the rectum from the anterior and posterior aspects of the cervix, and placement of a purse-string suture as close as possible to the internal opening of the cervix. In the original Shirodkar procedure the vaginal mucosa is sutured over the cerclage suture which is buried in the cervical tissue, making its removal difficult and requiring delivery by cesarean. To avoid cesarean delivery one or both ends of the suture may be cut long and used to pull the suture, identify the knot, and remove the suture at the end of the pregnancy.

A popular modification of the Shirodkar procedure involves incision of only the mucosa of the anterior aspect of the cervix, separation of the bladder from the anterior aspect of the cervix, placement of the suture at the level of the internal cervical opening, and tying of the suture over the intact vaginal mucosa covering the posterior aspect of the cervix (Figure 10-3). The Shirodkar operation is not performed frequently because the obstetricians prefer the more simple McDonald procedure.

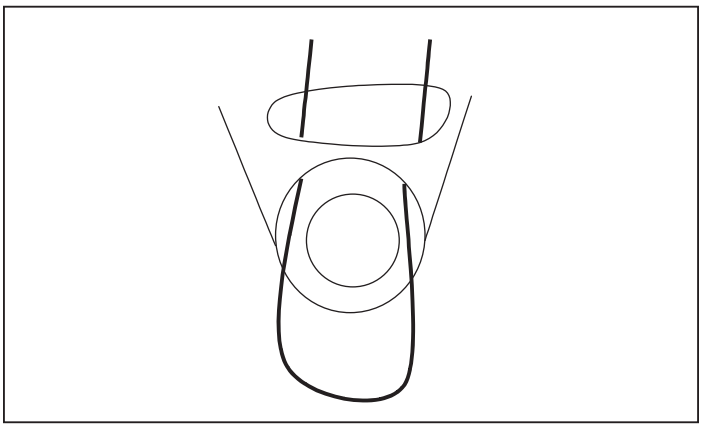

Figure 10-3. Modified Shirodkar operation. The vaginal mucosa covering the anterior aspect of the cervix is opened with a transverse incision to facilitate placement of the suture as high as possible, at the level of the internal cervical os.

McDonald operation

The McDonald operation is a simple procedure that avoids incisions into the vaginal mucosa. A purse-string suture is placed using four bites in each of the quadrants of the cervix including the vaginal mucosa and some of the cervical tissue (Figure 10-4). The suture, usually a double #1 prolene, is placed as high as possible into the vaginal fornices, although it never can be placed as high as with the Shirodkar method.

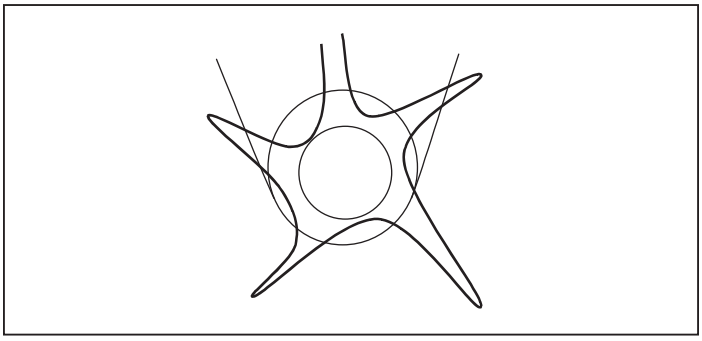

Figure 10-4. McDonald operation. Four bites are taken, one in each quadrant of the cervix. The suture is usually tied over the anterior aspect of the cervix.

There are no randomized studies comparing the results obtained with different cervical cerclage operations. Most patients undergoing cerclage because of short cervix or because of historical diagnosis of cervical incompetence do not need the operation and it is not surprising that the success rate is about 85–90%.

Postoperative endovaginal ultrasound may be useful to assess the possibilities of success after a cerclage operation. Althuisius et al. (2002) randomly assigned 35 women at high risk for cervical incompetence and cervical length < 2.5 cm to cerclage plus bed rest and bed rest alone. They found that postrandomization cervical length > 2.5 cm was more frequent in the cerclage group and was associated with a decreased risk of preterm delivery. Another useful test to predict outcome is fetal fibronectin which has similar predictive values for preterm delivery in women treated with cerclage than in women at risk for preterm delivery (Roman et al., 2003).

Women with Risk Factors for Incompetent Cervix

Box 10-3 summarizes several high-risk factors associated with incompetent cervix. The most frequent is a diagnosis of incompetent cervix in a prior pregnancy or a history of preterm premature rupture of the membranes in the second trimester of pregnancy. Also seen quite frequently is a history of conization of the cervix or LEEP for the treatment of cervical dysplasia.

The concept that cervical cerclage may be used prophylactically to prevent cervical incompetence in women at risk has been prevalent in obstetrical practice for the last 25 years. This idea was supported by studies using historical

controls that suggested a significant decrease in the rate of preterm delivery in women with risk factors treated with cerclage (Lazar et al., 1979). However, two relatively small randomized trials (Lazar et al., 1984; Rush et al., 1984) have demonstrated that cervical cerclage in women at risk does not prolong gestation or improve outcomes, while one large trial (MRC/RCOG Working Party on Cervical Cerclage, 1993) indicates that the potential benefit of cerclage in a high-risk population is limited to a specific patient's subgroup.

Lazar et al. (1984) randomized 506 women at risk for preterm delivery secondary to cervical incompetence to cerclage or no cerclage and found no improvement in outcomes with the use of cerclage. Furthermore, they found more morbidity, preterm deliveries, and cesarean sections in the group randomized to cerclage treatment. Similar results were obtained in South Africa by Rush et al. (1984). They randomized 194 women at high risk for incompetent cervix to have cerclage or to be managed without cerclage and found that cerclage did not prolong gestation or improve survival and resulted in increased morbidity. A large multicenter study of 1292 women (MRC/RCOG Working Party on Cervical Cerclage, 1993) produced slightly different results. The overall analysis demonstrated a 4% decrease in deliveries before 33 weeks in women randomized to cerclage treatment but more impressive was the subgroup analysis in women with at least three previous midtrimester losses, demonstrating a significant benefit (15–32%) of reducing delivery before 33 weeks. This benefit was not apparent in other subgroups with one previous second trimester abortion, with two previous second trimester abortions, with a history of cone biopsy or cervical amputation, with twin pregnancies, or with other indications.

A group of patients considered at high risk for "incompetent cervix" are women with multifetal pregnancies. The incidence of early opening of the cervix in women with twins is approximately 13.7% (Michaels et al., 1991) and it is a common assumption that the incidence is higher in triplets than in twins and higher in quadruplets than in triplets. Therefore, many protocols for the management of higher order gestation include prophylactic cerclage. Although there is some evidence supporting these assumptions (Goldman et al., 1989), the majority of women with multifetal pregnancies and early cervical ripening have no primary cervical disease and will not benefit from cerclage. The majority of these women are primigravidas and have no recurrence of the condition in subsequent singleton pregnancies—facts that are contrary to the natural history of primary cervical disease. Furthermore, there are controlled studies showing no difference in the rate of spontaneous preterm delivery or preterm premature rupture of membranes in women with multiple gestations and sonographic evidence of cervical shortening treated with cerclage when compared with a control group treated with bed rest (Newman et al., 2002; Roman et al., 2005). Women with multifetal pregnancies and early sonographic cervical changes are destined to have a poor outcome that will not be modified by a cerclage operation.

In summary, the evidence indicates that the majority of women with risk factors for cervical incompetence do not develop incompetent cervix and are able to reach term or near term without treatment. Therefore, it is erroneous to recommend prophylactic cerclage for women with risk factors. A better approach is to follow these women with serial endovaginal ultrasounds between 16 and 24 weeks and perform cerclage only if the ultrasound examination reveals cervical shortening. Kelly et al. (2001) studied 106 women at risk for incompetent cervix because of single unexplained second trimester loss, ≥ three first trimester abortions, history of cone biopsy or LEEP, DES exposure, or second trimester termination. Forty-five of these women had prophylactic cerclage at or before 15 weeks and 61 were followed with serial endovaginal evaluations of the cervix. Fifteen (24.5%) of the women followed with ultrasound required cerclage because of shortening or funneling of the cervix. The obstetrical and neonatal outcome was similar between the two groups. This and other (Groom et al., 2004; Higgins et al., 2004) investigations indicate that follow-up with endovaginal ultrasound of patients at risk for incompetent cervix avoids cerclage in 70–75% of this population without change in perinatal outcome. The conclusion from this evidence is that cervical cerclage should not be performed prophylactically in women with risk factors for incompetent cervix. Surgical treatment should be reserved for women with a history of three or more midtrimester losses and for women at risk who show cervical shortening or funneling of the cervix in ultrasound examinations between 16 and 24 weeks.

Women with Incompetent Cervix and Failed Vaginal Cerclage

There is a small group of women who present (a) with a history of repetitive midtrimester pregnancy losses following extensive conization or amputation of the cervix or (b) with extensive cervical lacerations following vaginal delivery who had one or more failed attempts to correct the situation by means of a vaginal cerclage. These patients are candidates for an abdominal cerclage.

Abdominal cerclage

The abdominal cerclage is an operation with significant possibilities of complications that require cesarean delivery for as long as the cerclage remains in the maternal pelvis. Since the morbidity is high, the indications for the surgery are few and the patients' selection criteria should be followed rigorously.

The main indication for abdominal cerclage is incompetent cervix due to severe trauma to the cervix such as deep lacerations following a difficult vaginal delivery, extensive conizations, or repeated LEEP for the treatment of carcinoma "in situ" (Davis et al., 2000; Zaveri et al., 2002). In addition to a clear history of trauma to the cervix the candidates for abdominal cerclage require a history of repetitive second trimester losses or failed vaginal cerclages. The history of previous midtrimester losses is important because many women with deep cervical lacerations or with complete amputation of the vaginal portion of the cervix can have a normal pregnancy without signs of cervical incompetence. It is not unusual that women who had extensive conizations or LEEP demonstrate a cervical length of 2.0 cm or less by endovaginal ultrasound but are capable of carrying the pregnancy to term.

In some cases the need for abdominal cerclage is evident in women who are not pregnant and the abdominal cerclage may be performed in anticipation of a future conception (Groom et al., 2004). Preconceptional surgery is easier to perform, can be done using a Pfannenstiel incision, and has a lower rate of complications. Abdominal cerclage can be performed preconceptionally or in pregnancies < 12 weeks using a minimally invasive laparoscopic approach (Lesser et al., 1998).

In pregnant women the best time to place the abdominal cerclage is between 16 and 18 weeks' gestation. At earlier gestational ages the pregnant uterus has not come out of the pelvic cavity and it is difficult to displace upward and laterally to place the suture. At more advanced gestational ages, a generous incision is needed for placing of the suture in the posterior aspect of the uterus. The best technique for placement of an abdominal cerclage was described by Mahran (1978). The abdomen is opened with a Pfannenstiel or with a vertical incision. The authors prefer the vertical incision, especially if the pregnancy is more than 14 weeks because manipulation of the pregnant uterus is easier. The peritoneum of the uterovesical reflection is open transversally and the uterine vessels at each side of the uterus are identified by palpation and in some cases by visual inspection. An area at each side of the cervix, just above the area of insertion of the uterosacral ligaments and at the level of the internal cervical os is selected for cerclage placement. The uterine vessels are displaced laterally by the fingers of the operator and a needle attached to a 5-mm Mersilene band or a #5 Mersilene suture is introduced from the posterior to the anterior aspect of the broad ligament very close to the cervix in the area previously selected. The needle is picked up anteriorly and inserted again in the opposite side of the cervix—this time going from the anterior to the posterior aspect of the broad ligament. The ends of the suture will be in the posterior surface of the uterus and will be tied tightly, cutting the suture 2–3 cm from the knot to facilitate removal of the cerclage by posterior colpotomy if necessary.

The postoperative course of women with abdominal cerclage is usually uneventful and most of them can be discharged 2–3 days after surgery. Contractions are not a problem and can be easily controlled with indomethacin. If complications requiring termination of pregnancy in the second trimester occur, the cerclage can be removed using a posterior colpotomy.

Box 10-4 summarizes the current recommendations for the performance of cervical cerclage in the prophylaxis or treatment of cervical insufficiency.

BOX 10-4

Indications for cervical cerclage

- **Acute presentation** (painless cervical dilatation with bulging bag of waters) after ruling out overt or subclinical amnionitis. Sixty percent of pregnancies prolonged to after 28 weeks; average prolongation 7 weeks; average neonatal survival 70%
- **Women with a history of three or more second trimester losses.** Fifteen to 32% reduction in the incidence of delivery before 33 weeks
- **Women with high-risk factors** (midtrimester pregnancy losses, history of LEEP, conizations, or cervical trauma, etc.) and progressive cervical changes by ultrasound examination

INDIAN EXPERIENCE OF CERVICAL INSUFFICIENCY

Shirodkar (1955) of Mumbai, India received worldwide acclaim for his operation of cervical os tightening for women who suffered from recurrent painless second trimester abortions due to incompetent cervix. Since those earlier days, many simplified procedures have been devised and successfully practiced.

Suman Sardesai and S Mittal (2001) from Solapur reported on their experiences of a modified Shirodkar technique for cervical encerclage performed in 25 cases of cervical incompetence (deep cervical tears, failed McDonald operation, and short cervix), 66% of these patients had at least two or more previous pregnancy losses. The procedure consisted of placing a transverse incision anteriorly at the cervicovaginal junction, mobilizing the bladder from in front of the cervix up to the level of the expected internal os. Thereafter, a black silk suture was passed through the substance of the cervix at either angles of the anterior incision, perpendicularly backwards out of the posterior wall of the cervix and tied posteriorly. The anterior vaginal mucosal incision was closed with fine interrupted catgut sutures. They reported a successful delivery rate at >37 weeks in 84%.

On occasions, the cervix is shortened following previous surgeries (conization, trachelorrhaphy, amputation in Fothergill's repair leading to repeated miscarriages, and pregnancy wastage). Occasionally, the infravaginal portion of the cervix is so shortened that it is not possible to tighten it by the vaginal route. In such cases an attempt at placing a suture at the level of the internal os at laparotomy has yielded rewarding results.

Tondare et al., from Mumbai were called upon to treat a 30-year-old gravida (G6) with history of four midtrimester miscarriages and no living child. She had undergone a Fothergill's repair for third degree uterine descent after her second delivery. She presented for antenatal care at 20 weeks of gestation. Pelvic examination at the first visit revealed that the cervix was flush with the vault of the vagina. Ultrasonography revealed a very short cervix of < 2.0 cm. Hence a decision was made to undertake an abdominal cerclage operation. The patient was delivered successfully (2.4 kg female baby) by an elective cesarean section at 37 weeks of gestation.

IMPORTANT POINTS

1. Cervical incompetence is the inability of the cervix to retain the pregnancy in the absence of labor due to congenital or acquired anatomic or functional defects of the cervix.
2. Cervical incompetence due to primary cervical disease may be easily confused with early preterm labor secondary to intrauterine infection/inflammation.
3. Cervical incompetence due to primary cervical disease characteristically occurs between 16 and 24 weeks of gestation. Outside of this gestational age window cervical incompetence is usually the consequence of early preterm labor.
4. Cervical incompetence due to primary cervical disease is a recurring condition that tends to occur earlier with each successive pregnancy. Women with "cervical incompetence" in one pregnancy and normal cervix in the following do not have cervical incompetence.
5. Cervical incompetence due to early preterm labor is usually the result of chorioamniotic infection/inflammation, causing early cervical ripening and dilatation.
6. Over 50% of women presenting with an open cervix and membranes visible in the external os or prolapsed in the vagina are in early preterm labor secondary to subclinical chorioamnionitis and their outcome will not be modified by a rescue cerclage.
7. The best surgical methods for rescue cerclage are the Espinosa-Flores and the Wurm techniques.
8. The most common factors associated with failure of a rescue cerclage are nulliparity, prolapsed membranes, cervical dilatation ≥ 4 cm, CRP ≥ 4.0 mg/dl, and WBC count ≥ 14,000/mm^3.
9. The finding of a short cervix by vaginal ultrasound examination in the second trimester is not diagnostic of incompetent cervix and does not allow to differentiate between primary cervical disease and early onset of preterm labor.
10. In the majority of cases, ultrasound shortening and funneling of the cervix in the second trimester are associated with poor perinatal outcome that is not modified by the performance of cerclage.
11. Only women with ultrasound shortening and funneling of the cervix, with a history of midtrimester losses, or with gynecologic conditions associated with primary cervical disease will benefit from cerclage.
12. The majority of women with risk factors for cervical incompetence will carry the pregnancy to term. The indiscriminate use of prophylactic cerclage in this population should be abolished.
13. Women at high risk for incompetent cervix should be followed with serial endovaginal ultrasound examinations between 16 and 24 weeks and cerclage should be limited to those exhibiting shortening and funneling of the cervix.
14. The preferred methods for prophylactic cerclage are the Espinosa-Flores, the modified Shirodkar, and the MacDonald procedures.
15. Abdominal cerclage is a procedure with significant morbidity that should be performed only in women with a history of second trimester losses and failed vaginal cerclages or with that of second trimester losses and anatomic impossibility to place a vaginal cerclage.

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11

Prolonged Pregnancy

CHAPTER OUTLINE

DEFINITION

Post-term pregnancy is a pregnancy that has reached or surpassed 42 weeks (294 days) of gestation. This definition is consistent with the names given to other stages of pregnancy like preterm and term. Other names commonly used in this context are "postdatism," postmaturity," "dysmaturity," and "prolonged" pregnancy. The term *postdatism* is inadequate because there is no definition of the dates the term refers to. *Postmaturity* is a specific syndrome of intrauterine growth retardation associated with a prolonged gestation. Some authors use the term *dysmaturity* to refer to postmature infants. In this chapter we will use the term *prolonged* to refer to those pregnancies advancing beyond the expected date of delivery (EDD) and *post-term* to designate pregnancies that reach or advance beyond 42 weeks.

The definition of post-term pregnancy generates the erroneous idea that 42 weeks (294 days) is the limit between normality and abnormality. More logical and more useful to the clinician and the patient is to define this limit as the time when the dangers of prolonging the pregnancy exceed the fetal and maternal dangers associated with delivery. Most of the information collected in the last 20 years indicates that this stage is reached prior to 42 weeks. Therefore, it seems reasonable to encompass in this topic all pregnancies extending beyond the EDD (prolonged pregnancies) and minimize or ignore the limit between term and post-term gestations.

INCIDENCE

Studies performed years ago indicated that about 11% of all pregnant women remain undelivered after 42 weeks. However, when ultrasound is used to verify the accuracy of the gestational age the incidence of post-term pregnancies decreases. Boyd et al. (1988) found an incidence of post-term pregnancy of 7.5% when the diagnosis was based on the menstrual history, 2.6% when the diagnosis was based on early ultrasound examination, and 1.1%

when the diagnosis was based on concurrent menstrual history and ultrasound examination. Prolongation of pregnancy beyond 40 weeks occurs more frequently, in about 1 out of every 10 pregnancies.

ETIOLOGY

The most common cause of a prolonged pregnancy is an error in the clinical estimation of the gestational age. Other causes are unknown and are probably associated with abnormalities in the biochemical and physiological mechanisms responsible for initiation of labor. One example is the prolongation of pregnancy associated with placental sulfatase deficiency. This enzyme plays a critical role in the synthesis of placental estrogens that are necessary for the development of gap junctions and increased expression of oxytocin and prostaglandin receptors in the myometrial cells. A second example is the prolongation of pregnancy associated with anencephaly. The lack of development of the fetal hypothalamus negates the production of corticotrophin-releasing hormone and the stimulation of the pituitary–adrenal–placental axis necessary for the initiation of parturition. These are rare examples of a cause–effect relationship between a biochemical or anatomic abnormality and prolonged gestation, and in the majority of cases the cause of this condition is unknown.

CHANGES ASSOCIATED WITH PROLONGED GESTATION

A series of changes occur in the amniotic fluid, placenta, and fetus which are associated with prolongation of pregnancy. Adequate understanding of these changes is essential for the management of patients with prolonged pregnancy.

Amniotic Fluid Changes

There are quantitative and qualitative changes in the amniotic fluid with prolongation of pregnancy. The amniotic fluid volume reaches a peak of about 1000 ml at 38 weeks of gestation and decreases to about 800 ml at 40 weeks. This reduction in volume continues and the amount of fluid is approximately 480, 250, and 160 ml at 42, 43, and 44 weeks, respectively. An amniotic fluid volume under 400 ml at 40 or more weeks is associated with fetal complications. The cause of oligohydramnios in prolonged pregnancy seems to be diminished fetal urine production (Trimmer et al., 1990).

Ultrasound is a reliable technique for estimation of amniotic fluid volume. Experienced sonographers can make a precise qualitative assessment of the amount of fluid. Others have proposed that the absence of pools of amniotic fluid measuring less than 1, 2, or 3 cm is indicative of oligohydramnios. These criteria are restrictive and patients with significantly decreased fluid may be classified as normal.

The four-quadrant technique (Phelan et al., 1987) is the most popular method to evaluate amniotic fluid volume. The four-quadrant technique consists of measuring the vertical diameter of the largest pocket of fluid found in each of the four quadrants of the uterus. The sum of the results is the amniotic fluid index (AFI). An AFI less than 5 cm indicates oligohydramnios. An AFI between 5 and 10 cm indicates a decreased fluid volume. An AFI between 10 and 15 cm is normal. An AFI between 15 and 20 cm indicates increased fluid volume. Finally, an AFI greater than 25 cm is suggestive of polyhydramnios. The problem with the AFI is the opposite of that with the 2-cm-diameter index, and pregnancies with low normal fluid may be classified as having oligohydramnios. For this reason, when the AFI is ≤ 5 cm the diagnosis of oligohydramnios should be corroborated by the ≤ 2 cm pocket of fluid rule.

In addition to the changes in volume there are changes in the composition of the amniotic fluid with prolonged gestation. After 38–40 weeks the fluid becomes milky and cloudy because of the presence of abundant flakes of vernix caseosa. The phospholipid composition changes due to the presence of a large number of lamellar bodies released from the fetal lungs and the L/S (lecithin to sphingomyelin) ratio becomes 4:1 or greater. The color of the fluid acquires a green or yellow discoloration when the fetus passes meconium. The presence of meconium, particularly if it is "thick," increases the probability of a poor outcome.

Placental Changes

The post-term placenta shows decrease in diameter and length of the chorionic villi, fibrinoid necrosis, and accelerated atherosis of the chorionic and decidual vessels. These changes occur simultaneously with or precede the appearance of hemorrhagic infarcts, which are foci for calcium deposition and formation of white infarcts. Infarcts are present in 10–25% of term and 60–80% of post-term placentas. They are more common at the placental borders. Deposition of calcium in the post-term placenta reaches up to 10 g per each 100 g of dry tissue weight, whereas it is only 2–3 g per 100 g in placentas at term.

The morphologic changes that occur with placental senescence can be observed by ultrasound and were originally described by Grannum et al. (1979). During the first part of gestation the ultrasonic appearance of the placenta is homogeneous, without echogenic densities, and limited by a smooth chorionic plate (grade 0 placenta). With progression of pregnancy the chorionic plate begins

to acquire subtle undulations, and echogenic densities appear randomly dispersed throughout the organ but sparing its basal layer (grade I placenta). Near term the indentations in the chorionic plate become more marked, echogenic densities appear in the basal layer, and comma-like densities seem to extend from the chorionic plate into the substance of the placenta (grade II). Finally, when the pregnancy is at term or post-term the indentations in the chorionic plate become more marked, giving the appearance of cotyledons. This impression is reinforced by increased confluency of the comma-like densities that become the intercotyledonary septations. Also, characteristically, the central portion of the cotyledons becomes echo-free (fallout areas), and large irregular densities, capable of casting acoustic shadows, appear in the substance of the placenta (grade III placenta). The correlation between ultrasonic signs of placental senescence and the functional capacity of the placenta is poor. The correlation between grade III placenta and fetal pulmonary maturity is excellent in pregnancies near term.

Fetal and Neonatal Problems Associated with Prolongation of Pregnancy

Perinatal mortality

Perinatal mortality has two components. The first is neonatal death, which is defined as the number of neonatal deaths per each 1000 live births. The second component is antepartum stillbirth death, which in numerous studies has been erroneously calculated as the number of stillbirths per 1000 live births or per 1000 total births. A correct assessment of the antepartum stillbirth mortality requires one to determine the number of stillbirths in a given week of gestation divided by the number of subjects that were "in utero" during that week, and therefore at risk for death. When this contingent risk of fetal death is estimated correctly, the week with the lowest risk is the 38th week. After 38 weeks the risk steadily increases with each week of gestation. There is general consensus that perinatal mortality increases severalfold when pregnancies are prolonged beyond 42 weeks.

The use of an incorrect denominator (deaths per 1000 live births or deaths per 1000 total births) is not the only problem with the estimation of the risk for stillbirth in prolonged pregnancies. The fetus is clearly at risk of antepartum stillbirth in the weeks preceding the week of delivery, and this cumulative risk is perhaps the best index of the risk of intrauterine death. Table 11-1 shows the contingent and the cumulative risks of fetal death from week 37 to week 43 (Smith, 2001).

Table 11-1. Contingent and accumulative risk of fetal death according to gestational age

Weeks of gestation	Conditional probability	Cumulative probability
37	0.0004	0.0004
38	0.0004	0.0008
39	0.0005	0.0013
40	0.0009	0.0022
41	0.0012	0.0034
42	0.0019	0.0053
43	0.0063	0.0115

From Smith GCS. Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies. Am J Obstet Gynecol 2001; 184: 489–96.

Intrapartum fetal distress

Approximately 25% of prolonged pregnancies are delivered by cesarean section because of nonreassuring fetal heart rate (FHR) patterns. The most common FHR patterns show moderate to severe variable decelerations with slow recovery and episodes of fetal bradycardia with loss of variability. Less common are repetitive late decelerations.

There are two main reasons for the occurrence of nonreassuring fetal heart patterns in patients with prolonged pregnancies. In the majority of cases they result from umbilical cord compression secondary to oligohydramnios (Leveno et al., 1984). In a minority of cases they are the result of placental insufficiency (Silver et al., 1988).

Meconium aspiration

Meconium aspiration syndrome (MAS) is a severe complication associated with prolonged pregnancy. The problem occurs more frequently when thick meconium, fetal tachycardia, and absence of FHR accelerations are present. Not only thick meconium is of concern. Patients with thin meconium at the beginning of labor may have thick meconium and MAS at the time of birth.

Fetal trauma

Difficult vaginal deliveries with varied degrees of fetal trauma occur commonly in prolonged pregnancies, especially in those complicated by fetal macrosomia. Shoulder dystocia is one of the most feared complications because it may result in brachial plexus injury, fracture of the humerus or clavicle, or severe asphyxia with neurological damage. Cephalic hematomas and skull fractures may also occur during the vaginal delivery of large babies.

Postmaturity syndrome

Postmaturity syndrome, also known as fetal dysmaturity, is one of the fetal complications associated with prolonged pregnancy first described in the medical literature. For many years it was thought that postmaturity was the most frequent complication of prolonged pregnancy when in reality, it occurs only in approximately 5–10% of the cases. Postmature fetuses have decreased amount of subcutaneous fat. Their skin is wrinkled because it has lost the vernix caseosa and may have a greenish or yellowish staining with prolonged exposure to meconium. Postmaturity is a complication that ideally should be discovered prior to the onset of labor because these fetuses are fragile, tolerate labor poorly, and frequently are acidotic at birth.

ANTEPARTUM MANAGEMENT

There are several studies indicating that fetal, neonatal, and maternal complications increase in frequency when the pregnancy is prolonged beyond the EDD. For example, in an analysis of 119,254 low-risk pregnancies (Caughey et al., 2007) it was found that the rate of primary cesarean section was 8.8, 9.0, 14.0, and 21.7% at 39, 40, 41, and 42 weeks' gestation, respectively. The increase in cesarean section was due to increases in the frequency of abnormal FHR monitoring patterns and cephalopelvic disproportion that at 39, 40, 41, and 42 weeks were 13.7, 19.6, 23.5 and 27.5%, and 14.9, 26.2, 31.4, and 38.0%, respectively. A similar trend was observed for the frequency of operative vaginal delivery, 3rd and 4th degree lacerations, postpartum bleeding, chorioamnionitis, endomyometritis, and prolonged labor. Similar information was obtained in another study involving 656,134 pregnancies (Divon et al., 2004) where the authors used life table analysis to calculate the cumulative fetal death rate per 1000 ongoing pregnancies and found rates of 0.7, 1.24, 2.08, and 4.36% at 39, 40, 41, and 42 weeks' gestation.

In view of the overwhelming evidence indicating that the outcome of pregnancy gets increasingly worse every week after 39 weeks of gestation, the question for the clinician is when the risk is high enough that delivery is mandatory. Most of the evidence, including a Cochrane review of 19 trials reporting on 7984 women (Gulmezoglu et al., 2006) and a meta-analysis of 16 studies (Sanchez-Ramos et al., 2003) indicates that women with prolonged pregnancies have better outcomes with a policy of labor induction at 41 weeks' gestation than with a policy of expectant management with serial fetal monitoring. This policy reduces not only perinatal mortality but also the cesarean section rate. Furthermore, a plan of management that mandates delivery of all women who reach or are beyond 41 weeks of gestation reduces the considerations about expectant management to a relatively small group of patients with gestational age between 40 weeks and zero days and 40 weeks and 6 days. Despite its apparent simplicity, adequate antepartum management of patients with prolonged gestations requires a sequential approach using clinical and laboratory information.

Reliability of the Gestational Age Estimation

The first step in the management of women with prolonged pregnancies is to determine the reliability of the gestational age using the criteria shown in Box 11-1. For this purpose it is necessary to review the information used to determine the EDD. The reliability of the EDD is excellent if the following conditions are met:

1. The patient was not using oral contraceptives, had three or more regular periods prior to the last one, and the last period was normal in duration and amount of flow.
2. The EDD calculated from the menstrual history was confirmed by an ultrasound examination performed between 12 and 20 weeks of gestation.
3. The pregnancy was achieved during infertility treatment following the administration of Clomid, Pergonal, or HCG and the date of conception is known.
4. The EDD was established by means of an ultrasound estimation of the fetal crown–rump length between 7 and 11 weeks of gestation.
5. The EDD was established by means of two or more ultrasound examinations, 3–4 weeks apart, obtained between 12 and 28 weeks of gestation.
6. The EDD corresponds to 36 weeks since the patient had a positive serum or urine pregnancy test.

BOX 11-1

Reliability of the expected date of delivery

1. Menstrual history (three or more normal, regular periods before the last, no oral contraceptives)
2. Pregnancy achieved during infertility treatment with known date of conception
3. EDD calculated from menstrual history coincides with EDD from ultrasound examination performed between 12 and 20 weeks of gestation
4. EDD established from ultrasound, crown–rump length between 7 and 11 weeks of gestation
5. EDD established from two or more ultrasound examinations 3–4 weeks apart between 12 and 28 weeks
6. EDD corresponds to 36 weeks since the patient had a positive serum or urine pregnancy test
7. Fetal heart tones documented 20 weeks before EDD by means of nonelectronic fetoscope or 30 weeks before EDD if the fetal heart was detected with Doppler

7. Fetal heart tones were documented 20 weeks before the EDD by nonelectronic fetoscope or at 30 weeks with Doppler.

Only patients who fulfill one or more of the conditions mentioned above have *reliable* dates. If none of these conditions are fulfilled, the dates are unreliable and the diagnosis of prolonged pregnancy is questionable. This is very important because the favorable results obtained with a policy of delivery at 41 weeks may disappear with a less rigorous estimation of the gestational age.

Patients with "prolonged" pregnancy and unreliable dates frequently present management difficulties. The obstetrician should use all information available at the time of this evaluation to determine if the pregnancy is closer to 40–41 weeks or to 36–37 weeks. In the majority of cases the management of women with "prolonged" pregnancy and unreliable dates is expectant with frequent maternal and fetal evaluations. Amniocentesis may be useful in these cases. An immature amniotic fluid L/S ratio suggests that the pregnancy is < 37 weeks, an L/S ratio that is mature but close to 2.0 suggests a pregnancy between 37 and 40 weeks' gestation, and an L/S ratio of 4 or more suggest a prolonged pregnancy. The presence of meconium in the amniotic fluid, especially if it is thick, is an indication for delivery. When thick meconium-stained amniotic fluid is known to be present, it is essential to have persons present for the delivery who are adequately trained in the management of neonatal meconium aspiration.

Once it has been determined that the dates are reliable, cases can be categorized according to the gestational age into those who have reached or are beyond 41 weeks and those who are between 40 weeks and zero days and 40 weeks and 6 days. Women who have reached or exceed 41 weeks should be delivered. The following steps are for women between 40 0/7 and 40 6/7 weeks and days of gestation.

Identification of Patients Who Need to be Delivered

The information provided by the history and physical examination, the ultrasound examination, fetal surveillance tests, and amniotic fluid analysis will identify patients who need to be delivered (Box 11-2).

High-risk pregnancies

Patients with high-risk pregnancies, especially those with diabetes and hypertension need to be delivered without consideration to the favorability of their cervix. Expectant management in these cases is not adequate because prolongation of pregnancy will place their fetuses at additional risk.

BOX 11-2

Patients with prolonged pregnancy who need to be delivered irrespective of the status of their cervix

1. Women with medical or obstetrical complications of pregnancy
2. Women with favorable cervix
3. Women with oligohydramnios
4. Estimated fetal weight ≥ 4500 g
5. Suspected fetal compromise
6. Fetal congenital abnormalities
7. Senescent placenta

Women with favorable cervices

The main objection to the universal delivery of all women who have reached or are beyond the EDD is the morbidity associated with induction of labor, especially the high incidence of cesarean deliveries. Multiple studies have shown that the risk of cesarean following induction of labor is directly associated with the status of the cervix. These studies have also shown that women with favorable cervices are at low risk for abdominal delivery. For this reason, the majority of investigators are in favor of induction and delivery of women with favorable cervices who have reached or surpassed their EDD. There are no randomized clinical trials supporting a policy of induction at or after the EDD when the cervix is favorable, but the possibilities of failed induction and cesarean delivery are low, and the morbidity associated with pregnancy prolongation will be avoided.

The classical method for evaluation of the cervix is the Bishop score (Box 11-3). A Bishop score ≥ 8 is a good index of inducibility. Others use cervical effacement ≥ 80% and cervical dilation ≥ 2 cm as the criteria to determine inducibility.

BOX 11-3

Bishop score

Factor	0	1	2	3
Cervical dilatation (cm)	Closed	1–2	3–4	5+
Cervical effacement (%)	0–30	40–50	60–70	80+
Fetal station	–3	–2	–1, 0	+1, +2
Cervical consistency	Firm	Medium	Soft	Soft
Cervical position	Posterior	Mid	Anterior	Anterior

From Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964; 24: 266.

Decreased amniotic fluid volume

The evaluation of amniotic fluid volume is of fundamental importance in prolonged pregnancies. Chamberlain et al. (1984) demonstrated that perinatal mortality increases dramatically with progressive severity of oligohydramnios. Leveno et al. (1984) demonstrated that umbilical cord compression secondary to oligohydramnios is the most common cause of intrapartum fetal distress in these patients. For these reasons, women with oligohydramnios need to be delivered.

Macrosomic fetuses

As many as 45% of the fetuses that remain undelivered after their EDD continue to grow in utero. With each additional week of gestation, more babies reach a birth weight greater than 4000 g, which is the most commonly used definition of fetal macrosomia. At 38–40 weeks the incidence of fetal macrosomia is 10% and at 43 weeks it is 43% (Arias, 1987). Fetal macrosomia is associated with an increase in cesarean, instrumental, and traumatic deliveries. The incidence of shoulder dystocia increases.

A significant part of neonatal morbidity associated with prolongation of pregnancy is secondary to fetal macrosomia. Thus, ultrasound estimation of the fetal weight (EFW) is an important component in the assessment of a pregnancy that extends beyond the EDD. The estimation of fetal size with ultrasound is not perfect, and the sensitivity and specificity of this method are low. An estimated fetal weight at term has a margin of error of approximately 1 lb, and in some instances the error is even larger. The error may be in either direction and babies thought to be large by ultrasound may be of normal size and, more frequently, babies thought to be of normal size are macrosomic. Despite the large margin of error, ultrasound is useful because it can confirm the clinical impression of fetal macrosomia and help the obstetrician in making decisions about the management of these patients. The technical quality of the measurements is important and when oligohydramnios is present or the mother is obese, visualization of fetal structures is difficult and measurements are frequently inaccurate.

The abdominal circumference (AC) is the most important measurement in estimating fetal weight and only examinations with high quality of the AC measurements must be accepted to calculate the EFW. There is a high probability that the baby is macrosomic even when the estimated fetal weight indicates a smaller size if the AC measurement is 2 or more standard deviations above the mean.

Measurement of the baby's subcutaneous fat layer thickness may be useful in the evaluation of fetal size. The majority of macrosomic babies have a subcutaneous fat thickness, measured at the anterior abdominal wall, that exceeds 10 mm. Babies with less than 6 mm of subcutaneous fat are rarely macrosomic.

The importance of the prenatal estimation of fetal weight in women with prolonged pregnancies is to determine the approach to delivery. Patients with estimated fetal weight of 4500 g or more should be counseled to have cesarean delivery because the possibility of traumatic vaginal delivery is substantial. Cesarean section should be offered also to women who have previously delivered infants with similar or larger birth weight, because prior delivery of a large baby does not guarantee an easy delivery of another large baby.

Patients with estimated fetal weights between 4000 and 4500 g should be counseled to have cesarean section if they are insulin-dependent diabetics, gestational diabetics, or they had abnormal diabetic screening and normal glucose tolerance testing, or only one abnormal value in the glucose tolerance test. Infants of mothers with abnormalities in carbohydrate metabolism have large subcutaneous pads in the shoulders and develop shoulder dystocia more frequently than babies of similar weight from mothers without carbohydrate intolerance. In one study (Nesbitt et al., 1998) it was found that the incidence of shoulder dystocia was 5.2 and 12.2% for newborns between 4000 and 4250 g, 9.1 and 16.7% for newborns with birth weight between 4250 and 4500 g, 14.3 and 27.3% for newborns with birth weight between 4500 and 4750 g, and 21.1 and 34.8% for newborns with birth weight between 4750 and 5000 g, for nondiabetic and diabetic mothers, respectively.

The counseling of non-diabetic patients with estimated fetal weight between 4000 and 4500 g and an unripe cervix is difficult. Studies have shown that the chance of a vaginal delivery is better when spontaneous labor occurs than when the labor is induced. Waiting for spontaneous labor is an option limited by the gestational age of the patient because once they reach 41 weeks, the perinatal outcome will be better by delivery than by expectant management. Induction of labor with an unripe cervix may increase the possibility of a cesarean delivery. In this situation other variables should be taken into consideration. One of these variables is parity. Induction will have greater chance of success if the patient is a multipara. Another variable is the frequency of uterine contractions. Women with frequent spontaneous contractions may initiate labor in a few days, and waiting for spontaneous labor may be an adequate option. Presence of risk factors will make induction a preferable option. Availability and experience in the use of prostaglandin preparations or mechanical means to achieve cervical ripening may also favor induction.

Fetal growth restriction

A fetal growth abnormality associated with prolonged pregnancy is poor fetal growth or dysmaturity.

Approximately 5–10% of fetuses delivered after their EDD show wasting of their subcutaneous fat characteristic of intrauterine malnutrition and are classified as small for gestational age by neonatal evaluation. The poor fetal growth does not occur exclusively after the EDD and most of these fetuses have been affected by inadequate nutrition and poor growth since early in gestation. Frequently, these fetuses exhibit abnormal FHR patterns before delivery or in the course of labor. The amount of amniotic fluid is reduced in most of these cases and meconium aspiration is a common problem. Fetal malnutrition is associated with multiple problems during the immediate neonatal period including hypoglycemia, hypocalcemia, and hyperviscosity syndrome. There is no advantage in prolonging pregnancy in these cases and these fetuses need to be delivered.

Suspected fetal compromise

Traditionally obstetricians have relied on the nonstress test (NST) for the evaluation of prolonged pregnancies. However, the NST was designed for the detection of placental insufficiency and is inadequate to diagnose oligohydramnios or to predict fetal trauma, which are both relatively frequent complications of prolonged pregnancies. Therefore, use of the NST as the only method of evaluating the fetus in prolonged pregnancy is not ideal. Theoretically, the biophysical profile (BPP) and the modified biophysical profile (MBPP) should be better than the NST for following patients with prolonged pregnancy because in addition to the NST, they include evaluation of the amniotic fluid volume. There are, however, problems with the use of these tests. One problem is that oligohydramnios is considered to be present only when the largest pocket of fluid found in the examination has a diameter less than 2 cm. This criterion is restrictive and patients with significantly decreased fluid may be classified as normal. Others use an AFI of 5 cm or less for the diagnosis of oligohydramnios. The problem with the AFI < 5 cm is the opposite of that with the 2-cm-diameter index and pregnancies with low normal fluid may be classified as having oligohydramnios. Also, the use of an AFI ≤ 5 cm instead of a largest pocket ≤ 2-cm diameter in the BPP and the MBPP has not been validated by prospective studies. Another problem with the BPP is that the result of the test is a numeric score resulting from assigning an equal number of points to the presence of breathing movements, fetal tone, fetal movements, normal amniotic fluid volume, and reactive NST. In prolonged pregnancies, a decreased amount of fluid, which is a variable of critical importance, will only cause a decrease of 2 in the total number of points and the test may be falsely interpreted as normal. To avoid this problem the authors of the test decided that the test is always abnormal when the amniotic fluid is decreased (Manning et al., 1990). A third problem is that fetal movements, fetal tone, and fetal reactivity are variables that are affected by relatively advanced fetal hypoxemia when an ideal test should detect early rather than late stages of fetal compromise. The problems associated with the use of the BPP have been the subject of a cogent review by Vintzileos et al. (1987).

In theory, the contraction stress test (CST) combined with an evaluation of the amniotic fluid volume may be the gold standard for fetal surveillance in prolonged pregnancies. The reason being that in the chain of events leading to fetal acidosis and hypoxia, late decelerations, demonstrable by the CST, are one of the first signs to appear. Also, the efficacy of the CST in post-term pregnancy has been clearly demonstrated (Freeman et al., 1981). Another advantage of the CST is that the contractions induced during the test will help to ripen the cervix and initiate labor. However, the CST is labor intensive, requires time, and has a high proportion of false positive results.

The umbilical Doppler waveform analysis has limited value in the fetal surveillance of prolonged pregnancies. Only a relatively small number of these pregnancies are affected by placental insufficiency, diluting the predictive values of the test.

A question of importance in patients with prolonged pregnancies is the appropriate interval between fetal surveillance tests. The classical concept has been that 1-week interval is adequate. However, the value of this concept is questionable because there is evidence (Clement et al., 1987) that in prolonged pregnancies the amniotic fluid may decrease from a normal volume to rather severe oligohydramnios in a 24-hour period. Also, there are case reports of fetal deaths occurring within 24 hours of a reactive NST. Therefore most practitioners test with a frequency of twice per week.

Fetuses with congenital abnormalities

Before the generalized use of ultrasound, some major congenital defects, particularly neural tube defects, were a relatively frequent finding in patients with prolonged gestations. Today, most of these defects are found early in gestation and these pregnancies do not become post-term. However, these defects should be sought in the rare patient with prolonged pregnancy who did not have an ultrasound examination early in gestation.

Advanced placental grade

Approximately 35% of all patients at term have a grade III placenta. The presence of a grade III placenta does not indicate fetal distress. However, poor outcomes are more frequent in patients with advanced degrees of placental

maturity than in patients with the same gestational age with less mature placentas. Therefore, the presence of a senescent placenta in a prolonged pregnancy is an indication for delivery.

Expectant Management

Expectant management of prolonged pregnancies was justified before the development of useful agents for cervical ripening, before good studies on perinatal morbidity and gestational age, and at times when achieving vaginal delivery was a dominant objective of obstetrical care. Today, expectant management of prolonged pregnancy is justified only in a small group of women who are less than 41 weeks of gestation, have an unripe cervix, a normal amount of fluid, normal size babies, and a normal CST, BPP, MBPP, or reactive NST. The main objective of expectant management in these cases is to see if spontaneous labor or cervical ripening occurs during a period of time that is usually limited to 1 and exceptionally to 2 weeks.

There is universal agreement that once the pregnancy reaches 42 weeks, delivery is mandatory because the cumulative risk of antepartum stillbirth and maternal complications is significant enough to justify the morbidity associated with induction and delivery. An increasing number of investigators believe that pregnancy should be interrupted at 41 weeks. This belief is based on solid evidence (Rand et al., 2000; Sanchez-Ramos et al., 2003; Gulmezoglu et al., 2006) indicating that prolongation beyond 41 weeks is associated with significant morbidity. In contrast, there are no clinical trials demonstrating advantages in delivering at 40 weeks. Although there is a small increase in fetal and maternal morbidity at 40 weeks when compared with 39 weeks, the difference is small and most probably without clinical value. Therefore, it seems that the only time when expectant management may be appropriate is between 40 and 41 weeks of gestation.

In the majority of cases, expectant management would last only for 1 week. In a few cases expectant management will be prolonged to 2 weeks, but there are no valid reasons to let the pregnancy go beyond 42 weeks. The best approach to this situation is to counsel patients about the potential problems associated with prolongation of pregnancy when they reach 39 weeks of gestation. At this time they should be counseled regarding the advantages and disadvantages of induction of labor. A plan for their delivery must be formulated. If they are candidates for expectant management, fetal assessment should be initiated when they reach 40 weeks and delivery planned at 41 weeks irrespective of the status of their cervices. The rationale to initiate fetal surveillance at 40 weeks is provided by the study of Divon et al. (2004), showing that the risk of fetal demise became significantly higher than the risk of neonatal death at any gestational age at or beyond 40 weeks and 3 days.

A necessary condition of expectant management is frequent assessment of cervical ripening, fetal status, and amniotic fluid volume. This assessment is to be done twice weekly. Induction of labor will be the best choice when the cervix becomes ripe or the amniotic fluid volume fluid decreases. Cesarean delivery will be the best choice if there are signs of fetal distress or the EFW is > 4500 g.

Induction of Labor

Induction of labor is the most common obstetric procedure performed in USA. The reasons for this popularity are multiple and include, but are not limited to, an increase in the number of indications for delivery, physician and patient satisfaction, social reasons, and more effective use of hospital and medical resources. However, induction of labor is a procedure not exempt of complications, some potentially serious, and in the particular case of prolonged pregnancy, there is a continuous debate about the week of gestation when the advantages of induction of labor clearly outweigh the advantages of expectant management.

The key factor for a successful induction is the status of the cervix. To attempt induction of labor with uterotonic medications in women with an unfavorable cervix is an exercise in futility and a good way to increase the cesarean section rate. Therefore most inductions of labor when the cervix is unripe should start with the use of a mechanical and/or biochemical method to achieve cervical ripening.

Vaginal ultrasound has an important role in the prediction of successful induction of labor and the likelihood of cesarean section. The study by Rane et al. (2004) in 604 pregnancies between 35 and 42 weeks' gestation indicates that vaginal ultrasound assessment of cervical length, posterior cervical angle, and occipital position is a better predictor of successful induction than the Bishop score. The same investigators demonstrated that the likelihood of cesarean section increases by about 10% with each increase of 1 mm in cervical length above 20 mm and that the odds of cesarean delivery are about 75% lower in multiparas when compared with nulliparas of the same cervical length.

Mechanical cervical ripening agents

The most commonly used mechanical cervical dilators are laminaria tents. Laminaria are long, thin pieces of a plant *Laminaria japonica* which swell, increasing their diameter severalfold, when placed in a moist environment. The main use of laminaria is for cervical ripening in the later part of the first trimester and beginning of the second trimester of pregnancy. However, it can be used and has

been used for cervical ripening at term. Laminaria comes in three sizes (small, medium, and thick). They are placed in the endocervical canal of the unripe cervix 12–24 hours before the scheduled induction. In early gestations the laminaria may be removed and replaced with new ones every 24 hours for 2 or 3 days prior to the procedure. In each application the practitioner should try to place the largest possible number of laminaria in the endocervical canal. After placement of the laminaria, one or two 4″ × 4″ gauzes soaked in water are placed in the vagina to facilitate swelling of the laminaria and dilatation of the cervix. The main concern with the use of laminaria is the development of chorioamnionitis, but this complication occurs in less than 1% of the cases.

A 24-French Foley catheter with a 30-ml balloon is a good mechanical agent to achieve cervical dilatation. The catheter is placed in the endocervical canal the day before induction of labor and the balloon of the catheter inflated with 30 ml of sterile saline solution. Many patients will pass the catheter with the inflated balloon spontaneously during the waiting period. Others may have the catheter removed, without deflating the balloon, with mild traction 12–24 hours after its insertion. In a few cases the procedure fails and the catheter cannot be removed without deflating the balloon. In successful cases the cervix will be dilated approximately 3 cm, but no effacement or descent of the presenting part will occur. Users of this method should be cautioned that the cervix frequently remains dilated 3 or 4 cm for several hours after the Foley catheter is passed and this should not be interpreted as a failure to progress in labor. Continuation of the induction will lead to further effacement, dilatation, and descent in the majority of cases. Also, the open cervix will allow rupture of the membranes and placement of internal monitors.

The Foley catheter may be used alone or with concomitant irrigation of the lower uterine segment with saline solution at 60 ml/hour. The saline solution will create a space between the membranes and the lower uterine segment and may help to accelerate the process of cervical ripening. Low-dose intravenous oxytocin induction is initiated after the extra-amniotic infusion is started. Others use the Foley catheter simultaneously with intravaginal misoprostol in an attempt to obtain not only cervical dilatation but also some degree of effacement of the cervix.

Chemical cervical ripening agents

Misoprostol

The most significant advancement in cervical ripening in the last 15 years has been the introduction of misoprostol (Sanchez-Ramos et al., 1993), an analogue of prostaglandin E1 that is licensed for the treatment of gastric ulcers caused by nonsteroidal anti-inflammatory drugs. Misoprostol has been found to be extremely useful for medical abortion in the first trimester of pregnancy, evacuation of the uterus in cases of anembryonic pregnancies or early fetal demise, ripening of the cervix prior to second trimester abortion, ripening of the cervix and induction of labor in term pregnancies, and for the treatment and prevention of postpartum bleeding. The effectiveness and safety of misoprostol for induction of labor was accepted by ACOG (1999).

In August 2000, the manufacturer of misoprostol issued a letter, warning about the use of this drug for conditions different from its approved indication, the prevention of gastric ulcers caused by nonsteroidal anti-inflammatory agents. This was followed by a quick reply by the American College of Obstetricians and Gynecologists (ACOG, 2000), emphasizing the safety of the medication when used in recommended doses for obstetrical procedures and its effectiveness for cervical ripening and labor induction. Two years later the Federal Drug Administration (FDA) approved a new label for misoprostol and revised the contraindication for the use of this drug in pregnant women and created a new labor and delivery section of the labeling, providing safety information related to that use (ACOG, 2003).

Misoprostol is rapidly absorbed from the gastrointestinal tract, reaching a peak plasma concentration approximately 30 minutes after its administration. The absorption through the vaginal route is slower and the peak plasma concentration is reached in 1–2 hours. The plasma level decreases rapidly after oral administration and slowly when it is given through the vaginal route. The drug is primarily metabolized in the liver and has no known drug interactions. Misoprostol is manufactured as 100-μg and 200-μg tablets. The medication is evenly distributed through the tablets, and it is possible to obtain an accurate low dose if the tablet fragments are weighted (Williams et al., 2002).

When misoprostol is used for cervical ripening and induction of labor, ACOG recommends an initial dose of 25 μg (one-quarter of a 100-μg tablet) inserted into the posterior vaginal fornix. It is not necessary to moisten the tablet with water or an acid medium before application (Sanchez-Ramos et al., 2002). The use of 50-μg tablet (half tablet) should be considered in women with a very unripe cervix and no evidence of spontaneous uterine activity. The 25-μg dose may be repeated every 4–6 hours. The use of larger doses or shorter intervals between doses frequently result in uterine hyperstimulation. Misoprostol can be administered by the oral route, 50 μg at 4-hour intervals, for a maximum of five doses. Oral misoprostol has not been shown to be as effective as vaginal misoprostol when vaginal delivery within 24 hours is used as the outcome variable (Shetty et al., 2001). Oral misoprostol has also the disadvantage of not being possible to remove

in cases of hyperstimulation. Better results are obtained when misoprostol is administered sublingually, 50 µg every 4 hours, and the medication can be removed in cases of hyperstimulation (Shetty et al., 2002).

The most significant complication associated with misoprostol administration for cervical ripening and induction of labor is uterine hyperstimulation. Uterine hyperstimulation is defined as uterine tachysystole with concomitant abnormalities of the FHR pattern. Uterine tachysystole is defined as six or more contractions in 10 minutes without concomitant abnormal FHR pattern. Uterine tachysystole may occur in as many as 30% of women receiving misoprostol for cervical ripening. Hyperstimulation affects between 5 and 15% of women treated with misoprostol. Uterine tachysystole and hyperstimulation are dose-dependent and are uncommon with low doses and long intervals between doses (25 µg every 6 hours). Because of the possibility of hyperstimulation, the use of misoprostol for labor induction or cervical ripening in women at term or close to term is limited to the hospital setting. Monitoring of FHR and uterine contractions is necessary during the entire procedure. The reason for these recommendations being the high incidence of uterine hyperstimulation associated with the use of misoprostol. The treatment of uterine hyperstimulation consists of the intravenous administration of 250 µg of terbutaline, a rapidly acting tocolytic agent, and if possible, the removal of the tablet fragment from the patient's vagina.

Misoprostol should not be used in women with previous uterine surgery, particularly cesarean section. Its use in these cases is associated with a high incidence of uterine rupture, especially when oxytocin is used following the administration of misoprostol.

Gastrointestinal side effects such as nausea, vomiting, and diarrhea are rare when misoprostol is used in the low doses necessary for induction of labor at term. These side effects occur more frequently when the medication is used in larger doses for cervical ripening in the second trimester of pregnancy.

Prostaglandin E2 derivatives

Prostaglandin E2 (PGE2) derivatives are also useful for ripening the cervix and inducing labor. Originally PGE2 was manufactured as a 20-mg vaginal suppository designed for the induction of second trimester abortions. To prepare the medication in doses safe and adequate for induction of labor at term, pharmacists used different methods such as dividing the original suppository into small fragments or chips, fabrication of low concentration suppositories, and preparation of liquid gel. These methods became obsolete with the availability of commercial preparations manufactured specifically for cervical ripening in term pregnancies. Dinoprostone, a PGE2 derivative, is available as a 10-mg vaginal insert ("Cervidil") which slowly releases the medication over a period of 12 hours. The effectiveness of "Cervidil" is enhanced with the simultaneous administration of low-dose oxytocin (Christensen et al., 2002) with no apparent adverse effects. However, due to the theoretical increased risk of hyperstimulation the simultaneous administration of dinoprostone and oxytocin is not recommended by the manufacturers. Dinoprostone is also available as a 0.5-mg gel for direct intracervical application ("Prepidil"). These medications are not better or safer than misoprostol and their cost is severalfold higher. The incidence of uterine hyperstimulation with "Prepidil" is 1% and with "Cervidil" is 5%. Uterine hyperstimulation may occur at any time after placement of the PGE2 derivatives and in the case of "Cervidil," continuous electronic monitoring should be used from the time the device is placed until at least 15 minutes after it is removed (ACOG, 1998).

Glyceryl trinitrate

A medication that can be used for the exclusive purpose of ripening the cervix without stimulating uterine contractions is glyceryl trinitrate (GT). GT is a nitric oxide (NO) donor, a free radical that plays a key role in multiple physiologic processes. Nitric oxide is produced by the enzyme nitric oxide synthase that has three isoforms, two expressed constitutively (endothelial and neuronal) and

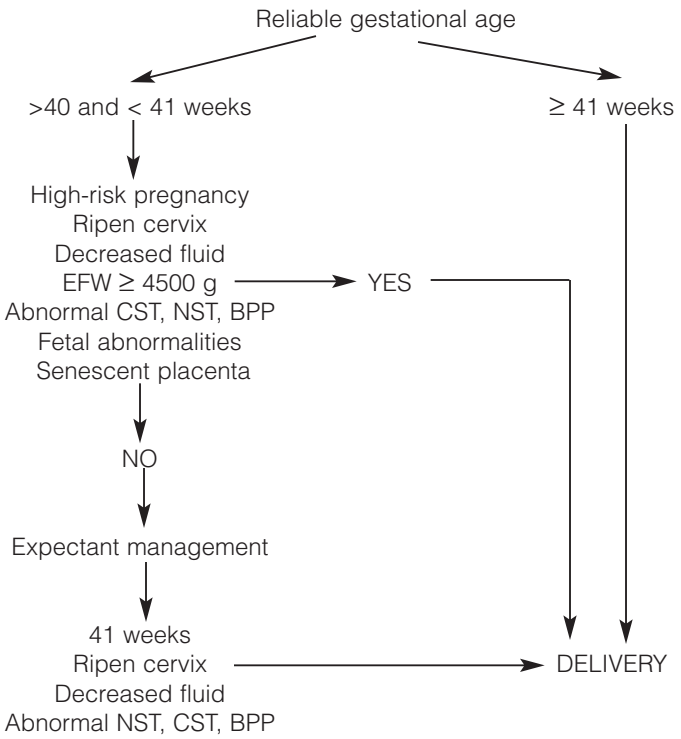

Figure 11-1. Antepartum management of prolonged pregnancy.

one that is inducible. All three isoforms are expressed in the human cervix, and the possibility that they play a role in cervical ripening is supported by animal (Chwalisz et al., 1997) and human (Thomson et al., 1997) investigations. Studies have shown that NO donors can induce cervical ripening but are less effective that PGE2 derivatives (Ledingham et al., 2001). Recently, it has been found that the combination of intravaginal GT and dinoprostone is more effective than dinoprostone alone for cervical ripening at term and reduces the incidence of side effects associated with the PGE2 derivative (Nunes et al., 2006).

A summary of the antepartum management protocol for patients with prolonged pregnancies is shown in Figure 11-1.

INTRAPARTUM MANAGEMENT

Once it has been determined that a patient with prolonged gestation must be delivered, the obstetrician should be ready to face potentially serious problems during the intrapartum period. The most common problems include nonreassuring FHR monitoring patterns, fetal trauma during delivery, shoulder dystocia, and meconium aspiration.

Nonreassuring FHR Monitoring Patterns

Nonreassuring FHR patterns develop frequently during labor in patients with prolonged gestation. Variable decelerations and decreased variability are the abnormal patterns most commonly observed. The initial treatment of this abnormal FHR pattern is amnioinfusion with 300–500 ml of warmed saline solution. If amnioinfusion fails in correcting the abnormal FHR pattern, the patient should be delivered by cesarean section.

In patients with prolonged gestation, decreased variability frequently is the only manifestation of fetal hypoxia. Decreased variability may be the only sign preceding the onset of fetal bradycardia that frequently ends in intrapartum or neonatal death. It should be noted that if variability is decreased using external monitoring, it will be worse with internal FHR monitoring. Also, it is important to know that the fetus at term and the healthy post-term fetus normally have *increased* variability. Cesarean delivery may be necessary in patients with minimal or absent variability even if variable or late decelerations are not present. Fetal tachycardia (190–200 bpm) has also been reported preceding fetal death in post-term pregnancies (Ron et al., 1980).

Fetal Trauma

Labor in a patient with prolonged pregnancy must be preceded by an evaluation of fetal size. If fetal macrosomia is present, close attention must be given to the development of labor abnormalities and cesarean section used liberally if arrest or protraction disorders occur. Traumatic vaginal delivery is 12 times more frequent in infants weighing 4500 g or more than in those with a birth weight of 3000–3999 g. Unfortunately, in many cases labor proceeds without detectable abnormalities until the moment when the fetal head is delivered and shoulder dystocia becomes apparent. Fetal trauma is common after shoulder dystocia but it may also occur in its absence, most commonly following the use of vacuum or forceps. The use of these devices may cause cephalic hematomas and skull fractures.

Shoulder Dystocia

The patients' care providers should be aware of the possibility of shoulder dystocia in every delivery of patients with prolonged pregnancy or with macrosomic fetus, even if their labor is completely normal. When shoulder dystocia is anticipated the obstetrician should mentally rehearse the sequence of steps necessary to treat this problem and be ready to act in a logical, step-by-step fashion. Lack of anticipation is the most common underlying reason for the confusion that usually occurs following the onset of shoulder dystocia.

The first step in the anticipation of shoulder dystocia is the recognition of patients at risk for this complication. The word DOPE may be used as a mnemonic to remember the most important risk factors associated with shoulder dystocia:

D is for diabetes.
O is for obesity.
P is for post-term (also for prior large baby).
E is for excessive weight gain during pregnancy.

Every time a practitioner is caring for a laboring woman he/she should ask: Does this patient have DOPE risk factors? If the patient does, the practitioner should mentally rehearse the following steps for the management of shoulder dystocia (Figure 11-2):

Step 1 (preparation)

A. Have the time noted when the problem is recognized and have minutes counted off by a designated individual.
B. Call anesthesia and alert the operating room.
C. Call for an assistant to help during the delivery.
D. Get the ultrasound machine at the bedside.
E. Do not pull the baby's head.
F. Do not apply fundal pressure.

Step 2 (diagnosis)

A. If necessary, enlarge the episiotomy.
B. Manually explore behind the baby's head and find out if the posterior shoulder of the baby is in or not in the hollow of the sacrum.

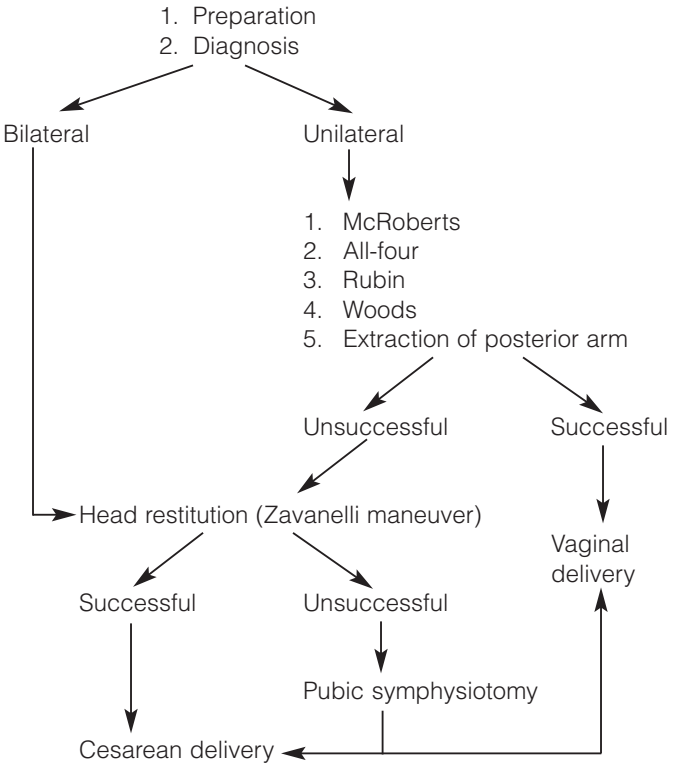

Figure 11-2. Sequence of steps for the management of shoulder dystocia.

If the posterior shoulder *is not* in the hollow of the sacrum the diagnosis is *bilateral* shoulder dystocia (both shoulders are above the pelvic inlet) and the best thing to do is to restitute the baby's head inside the vagina and perform a cesarean delivery (see step 6).

If the posterior shoulder is in the hollow of the sacrum the problem is *unilateral* shoulder dystocia (only the anterior shoulder is above the inlet) and vaginal delivery is possible. Then, the obstetrician should perform the following step.

Step 3 (McRoberts maneuver)

A. Remove the mother's legs from stirrups.
B. Abduct her legs and sharply flex them against her abdomen. This causes a cephalad rotation of the symphysis and often frees an impacted anterior shoulder without manipulation of the fetus.
C. Ask the assistant to apply firm *suprapubic* (not fundal) pressure directed laterally and inferiorly. This will help to force the anterior shoulder under the pubic arch.
D. The practitioner should apply constant, moderate traction on the fetal head for a count of 30 while suprapubic pressure is applied. Avoid intermittent pulling.

If the McRoberts maneuver and suprapubic pressure fail to solve the shoulder dystocia, the next step is as follows.

Step 4 (all-four)

The all-four or Gaskin maneuver (Gaskin, 1976) is a method for the solution of shoulder dystocia that is widely used by midwives and family physicians. The laboring woman is assisted onto her hands and knees (an all-four position) and downward pressure is applied to the fetal head to deliver the posterior shoulder. In a series of 82 cases (Brunner et al., 1998), 80% of the cases delivered spontaneously without the need for additional maneuvers. In the other 20% of the cases, rotation of the shoulders to the oblique diameter of the maternal pelvis or delivery of the posterior arm was used to complete delivery.

The mechanism of the all-four position in relieving shoulder impactation is unknown. It is possible that the maternal movement that occurs with the change of position may disimpact the shoulders and that the pelvic diameters increase by allowing posterior movement of the sacrum and increase mobility of the sacroiliac joints.

In many cases is difficult to move a woman laboring under epidural anesthesia from the dorsal lithotomy to the all-four position. In these cases this step may be bypassed and the practitioner should then proceed from the McRoberts to the oblique diameter rotational maneuvers.

Step 5 (oblique diameter)

Rotational maneuvers to move the fetal shoulders to the oblique diameter of the maternal pelvis can be performed with the woman in dorsal decubitus or in the all-four positions. In order to use the maneuvers to move the fetal shoulders into the oblique diameter of the pelvis, it is necessary to know precisely if the baby's spine is to left or to the right of the maternal abdomen. This information may be obtained by clinical assessment, but in obese patients a quick assessment with ultrasound may be necessary.

A. The first rotational maneuver to be used is the Rubin maneuver (Rubin, 1964), because the anterior shoulder is usually easily accessible. The woman should remain in the same position used for the McRoberts method, with her legs flexed and abducted, and manual pressure is exerted in the posterior aspect of the impacted anterior shoulder to promote adduction of the shoulders and overcome the impactation. Simultaneously an assistant applies suprapubic pressure in the same direction of the pressure applied by the operator's hand on the anterior shoulder.
B. The next maneuver to bring the fetal biacromial diameter into the oblique diameter of the pelvis is the Woods screw maneuver (Woods, 1943). In many patients this maneuver requires an episiotomy to obtain sufficient space in the posterior pelvis to introduce the operator's hand and manipulate the fetal posterior shoulder. In the Woods method the

fetal shoulders are the "screw" and the maternal pelvis is the "threads."

The shoulders are abducted by applying pressure on the anterior surface of the posterior shoulder. An assistant will help by applying suprapubic pressure in the opposite direction of the operator, on the posterior aspect of the impacted anterior shoulder. Once the anterior shoulder starts to move, maternal pushing and fundal pressure are used to facilitate rotation of the impacted anterior shoulder to an oblique position and eventually into the posterior pelvis. Maternal pushing and fundal pressure before the shoulder moves will not be helpful and may contribute to further impactation of the anterior shoulder. If the maneuver is successful the posterior shoulder will move into the anterior pelvis in front of the pubic symphysis and the anterior shoulder impactation will be resolved.

If the prior steps have been unsuccessful in resolving the shoulder dystocia, step 6 is performed.

Step 6 (extraction of the posterior arm)

A. Slide your hand into the vagina behind the posterior shoulder (the same side as the fetal spine) and along the posterior humerus and sweep the posterior arm of the fetus across the chest, keeping the arm flexed at the elbow. Grasp the fetal hand and pull the hand and the arm along the fetal head, delivering the posterior arm. When the posterior arm is extended and lies under the fetal body, it is difficult to deliver the arm without fracturing the humerus. In these cases, the fetal head is held upward by an assistant and the operator inserts both middle fingers into the fetal posterior axilla, one finger coming from the front and the other from the back. The fingers are overlapped and are used to pull the posterior shoulder downward and outward along the curve of the sacrum. Fractures of the humerus are frequent.

If extraction of the posterior arm is unsuccessful, proceed to step 7.

Step 7 (cephalic restitution—Zavanelli maneuver)

A. Turn the baby's head to the original position at the time of delivery [usually (OA) occiput anterior]. The fetal occiput should be approximately 90° from the fetal spine.
B. Flex the baby's head and apply upward pressure. The fetal head should move easily up into the birth canal.
C. Move the patient to the operating room and perform a cesarean section.

The step-by-step application of different maneuvers to solve shoulder dystocia should not take more than 5 minutes. The most serious risk to the fetus during the first 5 minutes is trauma. If the dystocia persists for more than 5 minutes, the next major potential risk is neurologic damage. The probability of serious fetal damage is minimized by this protocol because one of the first steps is the recognition of the most dangerous type of dystocia (bilateral dystocia) and the use in those cases of the Zavanelli restitution.

There are catastrophic shoulder dystocias where the baby cannot be delivered despite all the maneuvers previously described. In these cases, once the baby has lost muscle tone, delivery can be achieved but the outcome will be a dead baby or a newborn with significant neurologic damage. If all maneuvers fail and the baby is still alive, a cesarean can be performed to facilitate vaginal delivery. To do that the anterior shoulder is adducted and rotated into the oblique diameter of the maternal pelvis, applying pressure with the hand of the surgeon in direct contact with the posterior aspect of the fetal shoulder. In some terrible cases the baby cannot be delivered from above or from below and it is necessary to perform a symphysiotomy to enlarge the pelvic diameters and allow delivery.

Meconium Aspiration

One of the most serious neonatal complications associated with prolonged pregnancy is MAS. Until recently this problem had a mortality rate up to 60%. Fortunately, with the use of nasopharyngeal aspiration before the first breath the mortality and morbidity associated with MAS have substantially decreased.

In every delivery of patients with prolonged pregnancy, and especially in cases when meconium has been detected, the obstetrician must be ready to prevent the occurrence of MAS. For this purpose a suction device must be ready at the time of delivery. As soon as the fetal head appears on the maternal perineum, or in the open uterus in the case of cesarean section, and before the first fetal breathing effort, the nasopharynx should be completely aspirated. There is no difference in efficacy between a rubber bulb and a DeLee suction in clearing the meconium from the naso- and oropharynx of neonates (Locus et al., 1990). During this time the mother must be panting and avoiding expulsive efforts. Once the obstetrician feels certain that all or most of the meconium that was present in the oropharynx has been removed, the delivery is completed and the infant is taken to a radiant warmer where a person certified in neonatal resuscitation should observe the infant. If the infant is vigorous at birth, there is no need for further action. However, if neonatal depression is present and the baby needs respiratory support, the larynx should be visualized and tracheal suction and aspiration of meconium present below the vocal cords performed. The largest endotracheal tube compatible with the baby's tracheal size must be inserted in the infant's trachea and then removed slowly under continuous aspiration.

Endotracheal aspiration is not a benign procedure even in experienced hands. Endotracheal intubation and

suction causes pulmonary vasoconstriction. Also, laryngeal trauma characterized by stridor may occur. Hence most neonatologists abstain from laryngoscopy and endotracheal intubation if the newborn is vigorous at birth and had naso- and oropharyngeal suction on the perineum in cases of vaginal delivery or before delivery of the shoulders in cases of cesarean section. The better outcome of vigorous babies managed expectantly is well documented in the pediatric literature.

INDIAN EXPERIENCE OF PROLONGED (POSTMATURE) PREGNANCY

The terms prolonged pregnancy, postdated pregnancy, or post-term pregnancy are used to describe pregnancies exceeding a duration of 42 weeks (294) days. These pregnancies experience higher perinatal morbidity and mortality as compared to term gestations. In a postdated pregnancy, there is a 33% decrease in amniotic fluid volume per week. A decrease in fetal renal blood flow is the cause of oligohydramnios, which in turn predisposes to cord compression (variable deceleration and saltatory baseline on CTG, or cardiotocograph), predisposes to passage of meconium with its accompanying risk of meconium aspiration and neonatal respiratory distress. The higher incidence of fetal distress is not so much a result of placental insufficiency as it is the result of oligohydramnios causing cord compression. The liquor becomes milky/cloudy due to vernix caseosa, raising the L/S ratio. The liquor is often meconium stained due to hypoxia (Anjaria and Dastur, 2001). Certain ethnic groups such as Indians have a tendency toward early maturity. This may predispose them to a postmature state before the standard of 40 weeks, thus requiring antenatal surveillance tests before 40 completed weeks (Tambyraja, 1992).

Postdatism seems to run in families, suggesting genetic predisposition. In women with past history of postdatism, there is a 50% chance of recurrence in a subsequent pregnancy, suggesting that it is biologically determined. It is related with the lack of high levels of estrogen that characterize the onset of labor. Placental sulfatase enzyme deficiency, inherited as a sex-linked-recessive trait results in postdatism, disruption of fetal pituitary-adrenal axis in the form of absence of fetal pituitary, or fetal adrenal hypoplasia (fetal anencephaly) predispose to prolonged pregnancy. Extrauterine pregnancies are prolonged because of absence of the uterus. Lastly, oligohydramnios predisposes to postdatism (Anjaria and Dastur, 2001) .

Antepartum fetal surveillance includes sonographic evaluation of gestational age and fetal size, AFI, placental grading, BPP and excludes fetal anomalies. Intrapartum problems include failure of induction of labor, dystocia labor, fetal distress, meconium staining, abnormal CTG (variable decelerations) increased need for cesarean section and other obstetric interventions, shoulder dystocia, and fetal macrosomia (Kansaria and Gupta, 1999), leading to birth injuries (Anjaria and Dastur, 2001). After birth, neonatal problems include hypothermia due to poor subcutaneous fat, hypoglycemia, hypocalcemia, and birth injuries like brachial plexus injury. Post-term pregnancies are associated with a threefold increase in perinatal mortality. It is essentially due to intrapartum asphyxia (Anjaria and Dastur, 2001). In a report from Mumbai, Dastur (2003) remarked that oligohydramnios is commonly associated with postdatism, intrauterine growth restriction, fetal urinary tract anomalies, premature rupture of membranes, chromosomal anomalies, etc. Postdatism is associated with oligohydramnios in 20%, and with other obstetric problems like cord compression (variable decelerations), meconium-stained liquor, fetal compromise, and increased perinatal mortality. Treatment includes sonographic evaluation of fetal well-being, Doppler wave study of fetal circulation, oral hydrotherapy with hypotonic fluids or water, amnioinfusion. Transabdominal infusion of 250–300 ml normal saline under ultrasonographic control leads to increase in amniotic fluid volume and AFI to > 8.0 cm. Transvaginal amnioinfusion helps to decrease the severity of variable decelerations and end-stage fetal bradycardia and the need for obstetric interventions. There is a lowering in the cesarean section rates by almost 90%. In patients with evidence of fetal compromise, it is advisable to expedite the delivery (induced labor/cesarean section) (Dastur, 2003). In a study from New Delhi, (Malhotra and Deka, 2002), including a controlled clinical trial in two groups of 50 women, the authors compared the amniotic fluid volume before and 3 hours after instructing the first group to drink 2 L of water over 1 hour, and the control group were instructed to drink 100 ml of water over 1 hour. The results showed that the AFI increased by 2.01–3.73 cm (mean increase of 15.9%) in the first group as compared to only 0.51–1.12 cm in controls. It was concluded that maternal hydration status had a role to play in regulating amniotic fluid volumes. Clinicians should attempt to evaluate the role of oral hydration therapy in the management of oligohydramnios.

IMPORTANT POINTS

1. The incidence of prolonged pregnancy is 7.5% when the diagnosis is based on menstrual dating. It decreases to 2.6% when dating is based on early ultrasound examination and to 1.1% when the ultrasound and the menstrual history are in agreement. Therefore, the best prophylaxis of prolonged pregnancy is accurate dating.
2. The incidence of fetal macrosomia is approximately 10% for babies delivered between 38 and 40 weeks.

It increases to 23% between 41 and 42 weeks and reaches 42% between 43 and 44 weeks.

3. The main fetal problems associated with prolongation of pregnancy beyond the EDD are a high incidence of intrapartum distress mostly due to oligohydramnios, fetal trauma secondary to macrosomia, postmaturity syndrome, and meconium aspiration.
4. Evaluation of the amniotic fluid volume is of fundamental importance in patients with prolonged pregnancy. Umbilical cord compression secondary to decreased fluid is the most common cause of fetal distress in these patients and perinatal mortality increases directly with the severity of oligohydramnios.
5. The AC is the most important measurement in the sonographic estimation of fetal weight. If this measurement is 2 or more standard deviations above the mean, there is a high probability of fetal macrosomia.
6. The CST combined with evaluation of the amniotic fluid volume is the best test for fetal surveillance in post-term pregnancies. In patients with contraindications, the CST may be substituted with the NST. Fetal assessment should be initiated at 40 weeks.
7. Amnioinfusion does not improve the outcome of the infant when meconium is present in the amniotic fluid.
8. Patients with prolonged pregnancy who need to be delivered include those with medical or obstetrical complications of pregnancy, ripe cervix, decreased amniotic fluid, abnormal fetal surveillance tests, fetal congenital abnormalities, senescent placenta, and meconium-stained fluid.
9. Patients with decreased amniotic fluid should be admitted to the hospital and receive amnioinfusion before induction of labor.
10. The best method to ripen the cervix is with misoprostol. Other options are PGE2 derivatives and mechanical dilators, particularly a Foley catheter.
11. Amnioinfusion is the preferred treatment for patients with prolonged pregnancies who develop variable decelerations during labor.
12. The obstetrician should be prepared to manage shoulder dystocia in every patient with DOPE (D for diabetes, O for obesity, P for post-term, and E for excessive weight gain during pregnancy).
13. In cases of unilateral shoulder dystocia the following procedures should be performed sequentially: McRoberts maneuver, all-four maneuver, Rubin maneuver, Woods corkscrew maneuver, extraction of the posterior arm, and Zavanelli restitution.
14. With the use of naso- and oropharyngeal aspiration before the first breath, the morbidity and mortality associated with meconium aspiration have decreased substantially.

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12

Multifetal Gestation

*Carlos J Echeverry**

CHAPTER OUTLINE

Few topics in obstetrics have stimulated more interest than multiple gestation. Publications about twins and higher order gestations are abundant and reflect the multidisciplinary approach followed in the study of this biologic phenomenon. In this chapter the emphasis will be on the management of problems associated with twin gestations and the reasons behind the proposed management. Only a small section will be devoted to the study of gestations with higher fetal numbers. In fact, most of the problems associated with multifetal gestations with high fetal number are similar to those presenting in twins.

INCIDENCE AND EPIDEMIOLOGY

The frequency of twin pregnancy is approximately 1 per 80 live births, but there is significant variation among different countries and different populations. In USA in 2002 the incidence of twin pregnancies and pregnancies with three or more fetuses was 31.1 and 1.8 per 1000 live births, respectively (Martin et al., 2003). With the development of ultrasonic techniques for the early evaluation of pregnancy, it has become apparent that the incidence of multiple gestation in the humans may be more common than previously indicated and about half of these pregnancies fail to be recognized as twins gestations because one of the sacs spontaneously aborts or reabsorbs early in

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pregnancy (Dickey et al., 2002). Despite this relatively low incidence, multifetal pregnancies are responsible for 17% of all preterm births before 37 weeks of gestation, 23% of early preterm births before 32 weeks of gestation, and 24% of low-birth-weight infants (ACOG, 2004).

The incidence of monozygotic twins is uniform through the world, 3.5 per 1000 live births. In contrast, the incidence of dizygotic twins is affected by multiple factors and varies between 4 and 50 per 1000 live births. This wide variation in the incidence of dizygotic twins is due to multiple variables such as the use of assisted reproductive technology, ethnic differences, and maternal age.

Assisted Reproductive Technology

Assisted reproduction is responsible for 1% of all pregnancies and about 14% of all multifetal pregnancies in USA. In countries with high frequency of multifetal pregnancies, 30–50% of twin pregnancies and 75% of triplet pregnancies occur after the use of assisted reproductive technology (Blondel et al., 2002). In this study, women using in vitro fertilization (IVF) had a frequency of singleton, twins, triplets, and high order gestations of 58.1, 29.4, and 6.8%, respectively. The low frequency of higher order multifetal pregnancies is due to spontaneous or voluntary early pregnancy losses. The incidence of multifetal pregnancies when ovulation is induced with clomiphene is between 6.8 and 17.0%. When ovulation is induced with gonadotropins the incidence of multifetal pregnancies is larger, between 18 and 53%. In women treated with gonadotropins the incidence of multifetal pregnancies is greater in hypogonadotropic women (50.0%), followed by normogonadotropic women (32.0%), women with oligomenorrhea (18.4%), and women with corpus luteum deficiency (17.6%). Unfortunately, there is a narrow margin between the amount of gonadotropins necessary to achieve ovulation and the amount that is associated with multiple follicle formation and multifetal pregnancies.

Oral Contraceptives

There is evidence that pregnancy occurs in the 1st month after cessation of oral contraception. Also, when oral contraception has been used for more than 6 consecutive months, the possibility of a twin pregnancy is doubled.

Race and Geographical Area

The frequency of twinning is highest among the Black race (1 per 30 live births overall and 1 per 11 live births in Nigeria) and consistently lowest among Orientals (less than 1 per 100 live births). The White race is between these two extremes (1 per each 80 live births). In China there are 3 twins per each 1000 live births; in Scotland, 12.3 per 1000; and in Nigeria, 57.2 per 1000. In USA in 2002 the incidence of twin pregnancies was 31.1 per 1000 live births and the incidence of three or more fetuses was 1.8 per 1000 live births. The differences in frequency are the result of variations in double-ovum twinning because the rate of monozygotic twins is constant.

Advanced Maternal Age

Between 1990 and 2001 the incidence of twin pregnancies doubled in women between 40 and 44 years of age and increased more than sevenfold in women between 45 and 50 years of age. This is most probably due to the use of assisted reproductive technology and ovulation-inducing drugs.

Maternal Weight

Women with large body mass index (BMI) have increased frequency of twin pregnancies. In a study of 55,467 women who became pregnant without the use of fertility drugs, the frequency of twin pregnancies was 0.71% when the BMI was < 20 and doubled to 1.44% when the BMI was > 30 (Basso and Nohr, 2004). The increase was limited to dizygotic pregnancies. Another analysis of 51,783 pregnancies with 561 twins in USA (Reddy et al., 2005) indicated that the incidence of monozygotic twins was similar (0.3–0.4%) irrespective of the maternal BMI. In contrast, the incidence of dizygotic twins was 0.4% in women with BMI < 20, 0.5% when the BMI was between 20.0 and 24.9, 0.7% when the BMI was between 25.0 and 29.9, and 1.1% when the BMI was > 30.

CLASSIFICATION

By Zygocity

There are two types of twins: (a) monozygotic, identical, uniovular, or single-egg twins, and (b) dizygotic, fraternal, biovular, nonidentical, or two-egg twins. Monozygotic twins have identical genotypes and therefore are of the same sex. The similarity of their genetic composition is the result of the early division of an ovum fertilized by one sperm cell into two cell masses containing identical genetic information. In contrast, dizygotic twins are the result of the fertilization of two ova by different sperm, resulting in separate maternal and paternal genetic contributions to each infant. Multifetal pregnancies of higher order (≥ three fetuses) may result from any or by a combination of these mechanisms. Approximately two-thirds of all twin pregnancies are dizygotic and one-third are monozygotic.

Dizygotic twin pregnancies are dichorionic–diamniotic (Di–Di), indicating that they always have two placentas

and two amniotic sacs. In monozygotic twin pregnancies placentation is more complex and the number of chorions and amnions varies according to the timing of zygotic division. The finding of a monochorionic placenta is unequivocal proof of monozygosity. However, it is difficult in some cases to decide whether a single placenta is Mo–Di (monochorionic–diamniotic) or whether it is a fused Di–Di placenta. Also, the presence of a Di–Di placenta does not necessarily imply the existence of a dizygotic state, since up to 30% of monozygotic twins exhibit this type of placentation.

Therefore, because of the variation in monozygotic placentation, examination of the placenta is an imprecise method to determine zygosity.

In addition to the examination of the placenta several other methods have been used with varied success to determine twin zygosity. Among them, the study of blood groups and types (ABO, MNSs, Rh, Kell, Duffy, Kidd, etc.) is popular. A technique used with increasing frequency to determine twin zygosity is genetic fingerprinting using DNA probes to identify similarities or differences in restriction fragment length polymorphisms present in highly polymorphic areas of the genome.

By Chorionicity and Amnionicity

Multiple pregnancies can be classified by the number of placentas (chorionicity) and the number of amniotic sacs (amnionicity). To do that is necessary to examine a piece of the septum dividing the two fetal cavities. In Di–Di placentas there are two layers of chorionic tissue present between the two amnions (Figure 12-1). In Mo–Di placentas the septum consists of two amniotic layers and one chorionic layer. Examination of the placenta in the case of Di–Di twins will show whether the two placentas are fused or separated.

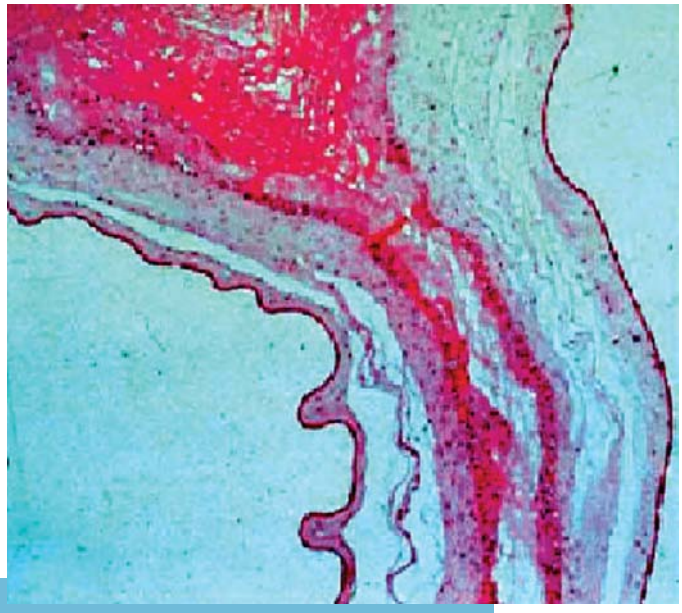
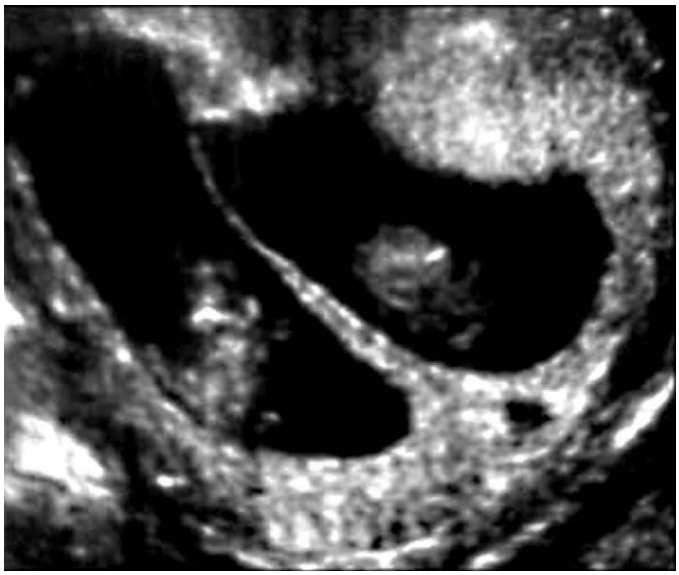


Figure 12-1. Histology of dichorionic pregnancy.

Pregnancies with dizygotic twins have two placentas and two amniotic sacs. Therefore, all dizygotic gestations are Di–Di but the placentas may be separated or fused. Placentation is more complex in monozygotic twins and the number of chorions and amnions varies with the time from fertilization until the zygotic division occurs. In about 25–30% of monozygotic twins the zygotic division occurs within 72 hours of fertilization, before the morula state, and the placenta will be Di–Di, similar to that of dizygotic gestations. In approximately 65% of monozygotic twins, the zygotic division occurs 4–8 days after fertilization, and in these cases the twins will share a single placenta but each will be in a separate amniotic sac (Mo–Di). In approximately 5% of monozygotic twin gestations, the zygotic division occurs more than 8 days after fertilization and they will share a single placenta and a single amniotic sac (monochorionic–monoamniotic, or Mo–Mo). In rare cases, 1 per 200 monozygotic pregnancies and one per each 50,000 live births, an incomplete division of the fertilized egg occurs more than 13 days after fertilization and the result will be conjoined twins. The factors responsible for the timing of division of the fertilized egg are not known.

The diagnosis of chorionicity is important because it is more specific than monozygosity as a risk factor for adverse perinatal outcome. Also, chorionicity may be determined antenatally and used for clinical management while zygosity cannot be assessed before birth in a large number of dichorionic pregnancies. Monochorionic twins are at higher risk than dichorionic twins for neurologic morbidity, birth weight discordance, and death. Also, 10–15% of Mo–Di twins develop twin–twin transfusion (TTT) syndrome. In addition, studies suggest that the poor obstetric and neonatal outcomes associated with monochorionic pregnancy persist even after exclusion of disorders unique to monochorionic placentation such as TTT syndrome and monoamnionicity (Leduc et al., 2005).

The number of amniotic sacs (amnionicity) also has clinical importance. Monoamniotic twin pregnancies are always monochorionic (Mo–Mo) and occur with a frequency of 1 per 10,000 live births. Mo–Mo twins have a high perinatal mortality rate of about 23%. Other complications include entanglement of their umbilical cords that affects two-thirds of the cases and may result in fetal death or in serious neurologic morbidity. Congenital abnormalities affect 26% of monoamniotic twins, the most frequent being defects of the abdominal wall and renal malformations. Other complication is birth weight discordance that affects 20% of monoamniotic twins. Because of the extremely high risk of a poor outcome, Mo–Mo pregnancies require intensive fetal surveillance and early delivery.



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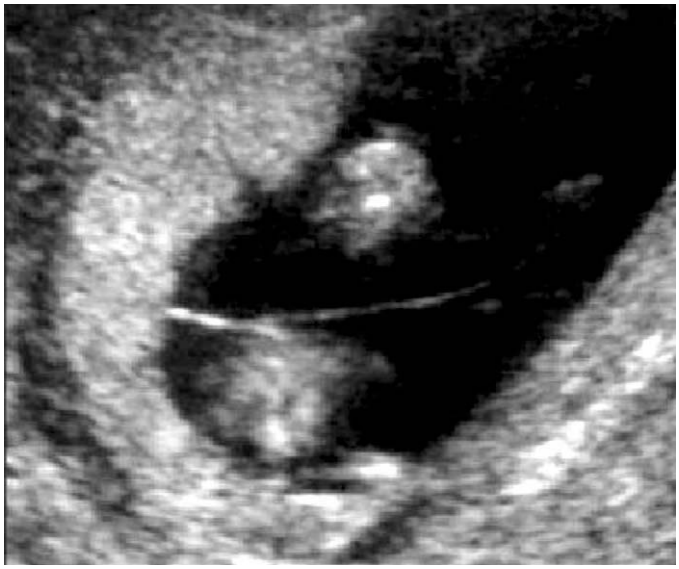

B

Figure 12-2. Ultrasound diagnosis of chorionicity.

The diagnosis of chorionicity and amnionicity is by ultrasound examination (Figure 12-2):

1. The identification of fetuses with opposite sex confirms the diagnosis of Di–Di pregnancy. This is particularly useful in pregnancies with advanced gestational age, but the method has no value when the twins share the same sex.
2. When two placentas are identified by ultrasound examination the pregnancy is Di–Di. This is difficult to evaluate at advanced gestational ages when the placentas are frequently fused.
3. Visualization of the membrane between the fetuses is of the largest importance in the ultrasound assessment of twin pregnancies. The membrane is thicker in dichorionic pregnancies because it is formed by four layers of tissue (two amnions and two chorions, Figure 12-1) while in monochorionic pregnancies it is formed by only two layers of amnion. The difference in the thickness of the membrane is less apparent with advances in the gestational age and the largest accuracy is when the examination is performed in the first trimester of pregnancy. The mean thickness of the interfetal membrane in a monochorionic pregnancy is 1.4 ± 0.3 mm and for a dichorionic pregnancy is 2.4 ± 0.7 mm. The threshold to differentiate monochorionic from dichorionic placentation is 2 mm. The accuracy of this method is 82% for monochorionic and 95% for dichorionic placentations.
4. In Di–Di pregnancies the ultrasound examination of the placenta frequently reveals the so-called "lambda sign" or "peak sign" that corresponds to a triangular projection of chorionic tissue between the membrane layers in the area of insertion of the membrane in the uterus (Figure 12-2).
5. Counting the layers of the dividing membrane is another accurate method for the determination of chorionicity. In most cases, counting of the layers can be achieved using 3.5–5.0 MHz transducers but it is more accurate with a higher frequency, 7.5–20.0 MHz, transducers (Vayssiere et al., 1996).

Ultrasound examination can determine chorionicity and amnionicity during the first and second trimesters of pregnancy with an accuracy of 95% (Stenhouse et al., 2002). The accuracy of ultrasound of chorionicity is excellent before 14 weeks and decrease significantly in the third trimester, particularly in the presence of oligohydramnios. The main problem with early ultrasound examination is the occasional difficulty in visualization of the interfetal membrane in some diamniotic pregnancies, leading to an erroneous diagnosis of monoamniotic gestation. Since this diagnosis has serious prognostic implications, the ultrasound examination need to be repeated several times until the sonographer is 100% sure of the presence or absence of the membrane.

In some cases it is necessary to use invasive methods for the diagnosis of monoamniotic pregnancies. When this is necessary, 30 ml of a radiological water-soluble contrast medium is injected into the amniotic cavity. An x-ray of the abdomen 24 hours after the injection will show the contrast medium in the gastrointestinal tract of both twins if the pregnancy is monoamniotic. When a monoamniotic pregnancy is suspected in a patient requiring genetic amniocentesis, the diagnosis can be made by injecting a mixture of 0.1 ml of air and 5.0 ml of amniotic fluid in the amniotic cavity after obtaining the amniotic fluid sample for genetic diagnosis. Ultrasound examination following this injection will show microbubbles around one or both twins depending on the amnionicity.

ETIOLOGY

The etiology of monozygotic twins is unknown. It has been suggested that a microscopic damage in the germinal cell layer may lead to the development of two separate points of growth, each one producing a separate individual. This mechanism occurs in some animal species, but there is no evidence of its occurrence in humans. The etiology of dizygotic twins is the ovulation of several follicles. The principal determinant of ovulation is the plasmatic concentration of follicle stimulant hormone (FSH), and it seems that this hormone is elevated in dizygotic twin pregnancies. Nigerian women of the Yoruba tribe who have a high incidence of dizygotic twin pregnancies have plasma FSH levels significantly higher than Japanese women who rarely have twin pregnancies. As mentioned before, ovulation stimulation with clomiphene or gonadotropins is an important etiologic factor for dizygotic pregnancies. The risk of multifetal pregnancy in women undergoing IVF has a reverse relationship with the maternal age and a direct relationship with the number of eggs being implanted. In a large retrospective cohort study the incidence of multiple pregnancies associated with the transfer of two fertilized eggs was 23, 20, 12, and 11% for women 20–29-, 30–34-, 35–39-, and 40–44-year-old, respectively (Schieve et al., 1999).

COMPLICATIONS

Multifetal gestations are associated with an increment in all complications of pregnancy with the exception of fetal macrosomia and post-term pregnancy. The main problems affecting the fetal and neonatal outcome are mortality, preterm labor, premature rupture of the membranes, TTT syndrome, fetal growth retardation, congenital abnormalities, umbilical cord problems, abruptio placentae, malpresentations, and other intrapartum complications. Overall, antenatal complications occur in approximately 83% of twin pregnancies compared with an incidence of 25% in singleton gestations (ACOG, 1998). Complications may be subdivided into maternal, fetal, and placental in origin (Table 12-1).

Maternal Morbidity

Maternal morbidity is increased three to seven times in multiple gestations. The main causes of maternal morbidity are increased incidence of hypertension during pregnancy (14–20% in twins versus 6–8% in singleton pregnancies), increased incidence of gestational diabetes, sepsis associated with premature rupture of the fetal membranes (three times more frequent in twins), and excessive postpartum bleeding (about 20% of all twin pregnancies).

Perinatal Mortality and Morbidity

Spontaneous reduction of one of the twins is one of the early complications of multifetal gestations. In a study of 549 twin pregnancies an ultrasound examination was performed between 3.5 and 4.5 weeks after ovulation and repeated every 2 weeks until 12 weeks of gestation and it was found that spontaneous reduction of one gestational sac occurred in 36% of twin pregnancies diagnosed before 7 weeks (Dickey et al., 2002).

Perinatal mortality in twins is five times greater than in singleton pregnancies (Table 12-2). A study (Kiely, 1990) found that the mortality is predominantly neonatal (51 per 1000) rather than fetal (28 per 1000). Perinatal mortality varies with birth order and the type of placentation. Second twins do not do as well as first twins with perinatal mortality, which is approximately 9% for the first and 14% for the second twin. Also, Mo–Mo twins have a poor prognosis with perinatal mortality, approximately 50%. Mo–Di twins have a perinatal mortality of approximately 26%.

Table 12-1. Maternal, placental, and fetal complications in twin pregnancy

Maternal	Placental	Fetal
Spontaneous abortion	Placenta previa	Fetal growth discordance
Anemia	Abruptio placenta	Fetal growth restriction
Hyperemesis gravidarum	Premature rupture of membranes	Fetal demise of one or both twins
Gestational diabetes	Umbilical cord entanglement	Congenital abnormalities
Preterm birth	Umbilical cord prolapse	Fetal malpresentations
Gestational hypertension	Postpartum bleeding	Twin–twin transfusion
Preeclampsia		Acardiac twins
Cesarean delivery		

Table 12-2. Causes of perinatal death in twins and singleton pregnancies in USA

Cause	Perinatal deaths per 1000 births	
	Twins	Singleton
Amniotic fluid infection with intact membranes	22.6	5.9
Premature rupture of membranes	15.9	3.5
Fetal hypoxia of unknown cause	15.1	2.6
Twin–twin transfusion	11.7	0
Congenital abnormalities	10.1	3.2
Large placental infarcts	10.9	2.1
Polyhydramnios	8.3	0.1
Overall perinatal mortality	138.7	33.4

From Naeye RL, Tafari N, Judge D, et al. Twins: causes of perinatal deaths in 12 United States cities and one African city. Am J Obstet Gynecol 1978; 131: 267.

The best prognosis is for dichorionic twins, although their perinatal mortality is high, approximately 9%, when compared with singletons, approximately 2.9%. The most common causes of perinatal mortality in twins are prematurity, usually due to preterm labor or preterm rupture of membranes, abnormal development, such as TTT syndrome, congenital defects, placental insufficiency, and traumatic delivery.

Perinatal morbidity is high in multifetal pregnancies. The largest threat is preterm birth, which affects between 22 and 54% of all twins pregnancies. Cerebral palsy, microcephaly, porencephaly, and multicystic encephalomalacia occur more frequently in preterm twins than in preterm singletons. Growth retardation affects 12–34% of twins. Trauma at delivery affects 5–10% and cord prolapse occurs in 1–5% of twin deliveries.

Hypertension

There is an increased frequency of hypertension during pregnancy in patients with multifetal gestations (12.9%). In an "ad hoc" analysis of prospectively obtained data in 684 women with twins and 2946 with singleton pregnancies, the incidence of gestational hypertension and preeclampsia in twins was twofold than that of singletons, 13 and 6%, respectively (Sibai et al., 2000). Early severe preeclampsia and HELLP syndrome happened more frequently in multifetal gestations. In a large number of these patients, hypertension occurs without proteinuria (gestational hypertension). Multifetal pregnancies resulting from assisted reproductive technology are at higher risk for the development of preeclampsia than spontaneously occurring multiple gestations, and pregnancies of higher fetal order frequently develop atypical forms of preeclampsia. It is possible that hypertension and edema develop because of an excessive expansion of intravascular volume. In these cases, the glomerular filtration rate is increased, proteinuria is absent, and serial hematocrit determinations show expansion of plasma volume. Gestational hypertension usually improves with bed rest but may also exhibit severe forms with increased maternal and fetal complications. Patients with multifetal gestations may also develop preeclampsia that could be extremely severe. In these cases, proteinuria is marked, and there is clinical and laboratory evidence of vasoconstriction and decreased intravascular volume. The risk of preeclampsia is greater when the twin pregnancy is the result of assisted reproductive technology, and the reasons for this are unknown.

The diagnosis, course, and management of gestational hypertension and preeclampsia are not modified in multifetal gestations with a few exceptions. Several studies have demonstrated that the uric acid plasma concentration increases with the number of fetuses with typical values of 5.2 and 6.4 mg/dl for singleton and twin pregnancies, respectively. Also there are case reports describing the resolution of early, severe preeclampsia following the demise of one of the fetuses.

The frequency of recurrent preeclampsia is less in multifetal than in singleton pregnancies. In an analysis of 550,218 women with singleton and multifetal pregnancies (Trogstad et al., 2004) was found a recurrence rate of preeclampsia when it happened in a twin pregnancy of 6.8% as compared with 14.1% when it developed in a singleton pregnancy.

Gestational Diabetes

Gestational diabetes occurs more often (a) in twins than in singleton and (b) in triplets than in twin pregnancy. The increased frequency of gestational diabetes in women with multifetal pregnancy is probably due to the large placental mass producing large amounts of human placental lactogen, a competitive inhibitor of insulin action. The diagnosis and management of gestational diabetes is similar to that in singleton pregnancies.

Fatty Liver of Pregnancy

Fatty liver of pregnancy is a rare complication that occurs more often in multifetal than in singleton pregnancies. Of all reported cases, 14.5% occurred in multifetal pregnancies, and it has been proposed that a large placental mass could be a factor in the development of this condition. Recently an association was found between acute fatty liver of pregnancy and fetal defects in the oxidation of fatty acids, in particular a deficiency in activity of long-chain 3-hydroxyacetyl CoA dehydrogenase. This association has been postulated as an example of fetal disease causing a maternal condition but the evidence in support of this hypothesis is weak.

Anemia

Maternal anemia is a frequent complication of twin pregnancy. It occurs in 9.4% of twin gestations compared with 4.1% in singleton pregnancies. It may occur in up to 70% of multifetal pregnancies of high order. During multiple pregnancy the iron requirements are increased due to the increase in red cell mass and the additional iron requirements of multiple fetuses. The iron demands may exhaust limited maternal iron storages and cause the development of iron-deficiency anemia. In addition, there is a physiological decrease in hemoglobin/hematocrit levels during multiple gestation, resulting from the large degree of intravascular volume expansion that occurs in these pregnancies. Since the predominant element in the intravascular volume expansion is the plasma volume, the net result is a drop

in hematocrit and hemoglobin levels, especially during the second trimester. However, these patients have an active hematopoiesis, and their total red cell volume is larger at the end than at the beginning of pregnancy. In many cases it is difficult to decide what proportion of the anemia is due to iron deficiency and how much is the result of the increase in plasma volume. For further discussion on the diagnosis and work-up of anemia in pregnancy, see Chapter 18, Hematologic disorders in pregnancy.

Postpartum Bleeding

Severe postpartum bleeding following the delivery of twins is usually the consequence of uterine atony. Postpartum hemorrhage is more common in twin pregnancies delivered near term when the muscle fibers have been stretched to their maximum. This complication may be prevented by the aggressive use of oxytocic agents immediately after delivery of the placenta. If excessive bleeding occurs in spite of adequate use of oxytocin, the intramuscular administration of prostaglandins (Hemabate) may be lifesaving. Many practitioners use prostaglandins as the primary oxytocic agent in these cases. Additional information about the management of postpartum hemorrhage may be found in Chapter 13, Bleeding during pregnancy.

Preterm Birth

Fifty-seven percent of twin pregnancies are delivered before 37 weeks of gestation, although not all preterm births occur spontaneously. Interestingly, male–male twin pairs are at higher risk of preterm birth. The single largest factor associated with fetal and neonatal mortality and morbidity in twin gestation is low birth weight. A review of 26 large series of twin pregnancies shows that 55.8% of twins have birth weights under 2500 g (Blondel et al., 2002). In most cases, this results from preterm birth secondary to preterm labor or preterm premature rupture of the membranes. However, in many other cases preterm birth is the result of problems specific to this type of gestation such as uterine overdistention. Twin pregnancies are the cause of 10.3 and 14.1% of preterm births in USA and Canada, respectively.

The gestational age at the time of birth decreases as the number of fetuses increases (Donovan et al., 1998). The mean gestational age at the time of birth was 35.4, 32.2, 29.6, and 29.1 weeks for twins, triplets, quadruplets, and quintuplets, respectively. The most frequent neonatal complications of preterm birth are hypothermia, respiratory difficulties, persistent ductus arteriosus, intracranial bleeding, hypoglycemia, necrotizing enterocolitis, infections, and retinopathy of prematurity. The risk of death, chronic pulmonary disease, and severe intracranial bleeding was similar between twins and singletons with birth weight between 401 and 1500 g. Twins had an increased incidence of respiratory disease and required surfactant treatment more frequently than singletons (62% versus 47%, respectively).

The reason for the increased frequency of preterm labor in twins is not completely understood. Most of the known risk factors for spontaneous preterm birth in singleton pregnancies are not associated with preterm birth in twin pregnancy (Goldenberg et al., 1996). Some investigators believe that overdistention of the uterus is the main cause. This hypothesis originated from observations of length of gestation versus litter number and size, which demonstrated a direct correlation between uterine stretching and initiation of parturition. The observation of increased frequency of preterm labor in patients with polyhydramnios supports this hypothesis. More research in this area is necessary.

Another hypothesis is that intrauterine infection is an important cause of preterm labor in twins. Some of the original data in this respect came from the Collaborative Perinatal Project. In this study autopsies were carried out on 171 twin and 1264 single-born infants, and the causes of death were analyzed (Table 12-2). Amniotic fluid infection with intact membranes or with preterm rupture of the fetal membranes was the single leading cause of perinatal mortality in twins. It seems that the excessive growth of the uterus in twin gestation results in an early opening of the cervix and exposure of the fetal membranes to the bacterial flora of the vagina, leading to amnionitis with intact membranes and, in more severe cases, to amnionitis with ruptured membranes. Variations in the virulence of the vaginal pathogens would account for differences in the severity and natural history of the process.

Discordant Growth

One of the problems more frequently found in the antepartum care of patients with twin gestations is discordant growth, a condition affecting between 15 and 29% of these pregnancies. Discordant growth causes a difference in the weight of the twins. The difference is expressed as a percentage of the larger twin's weight, and most authors consider a discrepancy of 20% or more to be significant. Some investigators classify discordant twins in two different categories depending on the magnitude of the weight difference. Grade I indicates a difference of 15–25%. Grade II is any discordance greater than 25%. Discordant twins are also classified as discordant-first and discordant-second, according to the birth order of the smaller twin.

The smaller twin is at high risk for perinatal complications. Many of them die as a result of congenital abnormalities or prematurity, and those who are born alive are often affected by neonatal morbidity with physical and

intellectual sequelae. The frequency of complications is greater and the prognosis is worse for second-discordant twins.

Several ultrasound criteria have been used to diagnose discordant twin growth before birth. Initially the diagnosis was based on the presence of a biparietal diameter difference of 6 mm or greater. Later, it was found that biparietal diameter measurements were inaccurate and a difference of 5% or more in head circumference was recommended as the criterion for diagnosis of discordant growth. Even later, it was proposed that a difference of 20 mm in abdominal circumference should be used. In the last few years, the criterion most frequently used is a difference of 15–25% in estimated fetal weight (EFW).

The causes of discordant growth are unequal placental mass, genetic syndromes, and TTT syndrome. Growth discordancy because of TTT syndrome is limited to monochorionic twins and will be discussed later in this chapter. Discordant growth because of unequal placental mass occurs in both monochorionic and dichorionic twins but is more common in twins with dichorionic placentation. Characteristically, ultrasound measurements in these babies are asymmetric, with elevated head to abdomen and femur to abdomen ratios. In most patients, the discordant growth is noticed after 24 weeks. If the placental insufficiency is severe enough, these babies show fetal heart rate (FHR) monitoring signs of distress and may become acidotic. Umbilical and uterine artery Doppler show increased impedance to flow in the smaller twin when the growth discordance has a placental origin.

Discordant growth because of genetic syndromes occurs in both monochorionic and dichorionic twins but is much more frequent in twins with monochorionic placentas. Usually the discordancy in growth can be detected by 16–20 weeks. Neural tube defects, cardiac abnormalities, and chromosomal defects are the most commonly found underlying problems. Ultrasound examination of these fetuses usually shows symmetric measurements without alterations in the head to abdomen and head to femur ratios. In most cases there is no significant difference in the Doppler studies between the twins. Similarly to twins that are small because of placental insufficiency, genetically abnormal twins may show signs of fetal distress in monitoring tracings.

The management of twin pregnancies with growth discordance differs depending on the cause of the problem. If the underlying reason is unequal placental mass, the well-being of the smaller twin should be assessed by means of frequent nonstress tests (NSTs), umbilical and cerebral Doppler studies, and amniotic fluid volume. Treatment with weekly injections of betamethasone is desirable in anticipation of a preterm delivery. Delivery of both babies is usually the best management when signs of fetal distress arise. Elective delivery should be seriously considered when the pregnancy reaches 34 weeks, and is indicated at 36 weeks. If the underlying problem causing the discordant growth is a genetic problem, the management will vary, depending on the nature of the defect, its prognosis, and the possibilities for corrective therapy. When the growth discordance is caused by a TTT syndrome, the best approach will depend on the gestational age and the severity of the syndrome.

The route of delivery of discordant twins is an area of controversy. Some authors recommend delivery of all of these babies by cesarean section, regardless of gestational age and fetal presentation. Others prefer a more selective approach to the problem and deliver vaginally if the cervix is ripe, the presentation is cephalic–cephalic, and the estimated weight of the discordant twin is 1500 g or more.

Twin–Twin Transfusion Syndrome

TTT affects 5–17% of monochorionic pregnancies and is responsible for 15% of the overall fetal mortality in twin pregnancies. The overall mortality, irrespective of gestational age, is approximately 60–70% and before 26 weeks is almost 100%. These figures reflect the severe effects of the parabiotic circulation for both the donor and the recipient. The recipient, as a consequence of the maximally increased intravascular volume, often develops cardiomegaly and congestive heart failure. Recipients frequently die in utero, and when born alive, may develop respiratory distress and congestive heart failure early in the neonatal period. They also frequently develop hyperbilirubinemia. The donor twin usually has retarded somatic growth, and will develop hydrops fetalis and high-output heart failure if the anemia is severe.

The donor twin in TTT usually shows poor growth, oliguria, anemia, and hyperproteinemia. The recipient twin produces increased amounts of natruretic peptide in an effort to control intravascular volume expansion and this results in excessive urine production and polyhydramnios. The recipient twin frequently develops biventricular cardiac hypertrophy and has diastolic dysfunction with tricuspid regurgitation and eventually develops congestive heart failure and dies. Fetal mortality before modern treatment was 80–100%. The fetal mortality is due to

BOX 12-1

Mechanisms of fetal death in twin–twin transfusion syndrome

- Placental insufficiency and severe anemia in the donor twin
- Congestive heart failure in the recipient twin
- Complications of prematurity
  - Preterm birth for fetal or maternal indications
  - Preterm birth secondary to preterm labor or to premature rupture of membranes
- Congenital abnormalities

several mechanisms (Box 12-1). The incidence of cerebral palsy and neurologic abnormalities is greater in twin pregnancies complicated by TTT.

Mechanism

TTT results from the presence of placental vascular communications between the infants that generate a hemodynamic imbalance resulting in anemia for one and polycythemia for the other twin. The vascular anastomoses in monochorionic placentation may be from artery to artery (A–A), artery to vein (A–V), and vein to vein (V–V). The anastomoses A–A and V–V are localized in the fetal surface of the chorionic plate. They have bidirectional blood flow and the net flow between the twins is usually balanced. In contrast, A-V anastomosis (Figure 12-3) is deep and has unidirectional flow. Another anatomic feature of the TTT syndrome is that in the majority of cases the placental mass of each twin is different such as it happens in Di–Di pregnancies with discordant growth. The combination of these two factors, vascular anastomoses and unequal placental mass, generates significant difficulties in the diagnosis of the condition and contributes significantly to the variation in therapeutic results. A recent study (Lopriore et al., 2007b) indicates that the unequal placental territory found in many cases of TTT syndrome is not a crucial factor for the development of this condition.

For the TTT syndrome to occur, it is necessary to have deep A–V vascular anastomosis. Compensation may occur if there is coexistent A–A anastomosis. Since there is a wide variation in the number and size of the vascular anastomoses, the degree of hemodynamic imbalance between the twins may also vary greatly. The existence of vascular anastomosis in dichorionic placentas is so rare that, for all practical purposes, the possibility of TTT should be disregarded when this type of placentation is present.

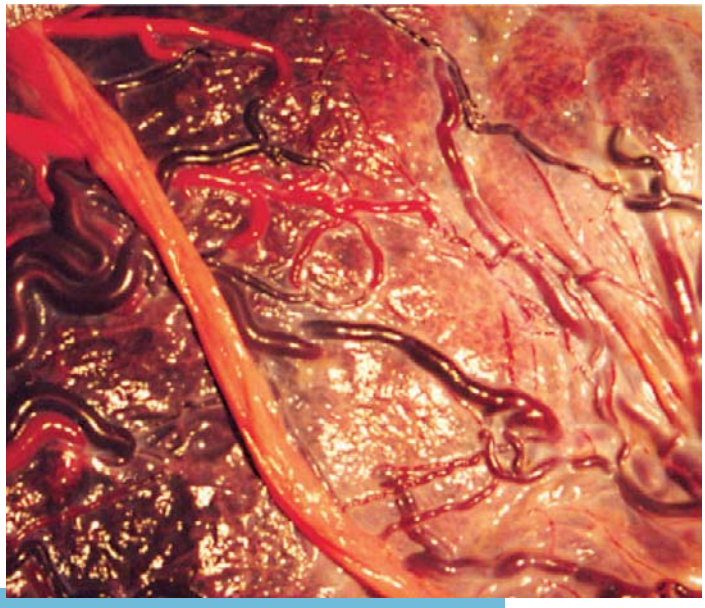

Figure 12-3. Deep arteriovenous anastomosis. An artery and a vein run in opposite direction on the surface of a placental cotyledon.

TTT may occur acutely during delivery of monochorionic twins (Uotila and Tammela, 1999). After delivery of the first twin the second monochorionic twin may lose blood rapidly into the first twin if the umbilical cord ligature is delayed, or more commonly lose blood into the placenta of the first twin if the interval between the delivery of the twins is prolonged. The possibility of an acute fetoplacental transfusion should be in the mind of the obstetrician during the vaginal delivery of monochorionic twins, and to avoid this problem the umbilical cord of the first born twin should be clamped promptly after delivery and the interval between the delivery of the twins should not be prolonged.

Diagnosis

The criteria most commonly used for the neonatal diagnosis of TTT syndrome are a difference in hemoglobin equal to or larger than 5 g/dl and a difference in birth weight greater than 20%. However, it has been shown that large differences in hemoglobin/hematocrit concentration may exist in the absence of TTT and that discordance in birth weight of 20% or more are as common in dichorionic as in monochorionic twins. In fact, most of the twins fulfilling the neonatal criteria for twin-to-twin transfusion are dichorionic.

The antenatal diagnosis of TTT is presumptive and requires that the conditions shown in Box 12-2 are present. The fundamental diagnostic criterion in TTT is the finding of a oligo/poly (oligohydramnios and polyhydramnios) sequence in the sonographic evaluation of a monochorionic twin pregnancy. TTT may be suspected but cannot be diagnosed in the absence of this finding. The criterion for the diagnosis of oligohydramnios is no fluid or a pocket of fluid < 2 cm in its largest diameter. The criterion for the diagnosis of polyhydramnios is a pocket of fluid 8 or more cm in its largest diameter. The "stuck" twin is a term used to describe the sonographic appearance of an extreme form

BOX 12-2

Criteria for the antenatal diagnosis of twin–twin transfusion

- Only one placenta is seen by ultrasound.
- The twins are of the same sex.
- There is a thin membrane between the twins (diamniotic placentation).
- There is a 20% or larger discordancy in estimated fetal weight between the twins.
- There is a significant discrepancy in the amniotic fluid volume surrounding each twin.
- Fetal hydrops is present in one or both twins.
- The umbilical cords are of different sizes.
- Gestational age is less than 28 weeks.

of TTT syndrome. In these cases the donor twin, markedly smaller in size and surrounded by little or no amniotic fluid, appears stuck against the uterine wall, in marked contrast with the large size and the polyhydramniotic sac of the recipient twin. The "stuck" twin mortality without treatment is approximately 80%.

The value of Doppler ultrasound in the diagnosis of TTT is questionable. Some investigators have reported discordant umbilical waveforms, while others have reported no significant differences or not consistent patterns. The latter finding seems more logical and it is possible that there is a wide range in the results of the umbilical artery Doppler analysis depending on the degree of anemia, the presence or absence of heart dysfunction, the coexistence of placental vascular changes, and the magnitude of the compensatory changes.

Classification

The next step following the diagnosis of TTT is an assessment of the severity of the condition using the Quintero's classification (Quintero et al., 1999) (Box 12-3). This classification is based on sonographic criteria and is of fundamental importance because it allows a more clear evaluation of the perinatal risk, helps to define which is the more adequate treatment, and permits comparison between the results obtained with different therapeutic modalities. The classification apparently cannot predict the outcome or the degree of progression of the condition (Luks et al., 2004).

Some have proposed to modify the Quintero's classification according to the presence of A–A anastomosis. In this system, stage III is subdivided into IIIa when A–A anastomosis are present and IIIb when they are absent. The presence of A–A anastomosis is advantageous for the fetus and the survival rate is 83% when they are present and 52% when they are not. In about 50% of the cases A–A anastomoses can be visualized after 18 weeks' gestation using power color Doppler.

BOX 12-3

Quintero's classification of the severity of twin–twin transfusion

- Stage 1. Oligo/poly sequence and bladder seen in the donor twin
- Stage 2. Oligo/poly sequence; donor bladder not seen; normal Doppler studies
- Stage 3. Oligo/poly sequence; donor bladder not seen; Doppler with at least one of the following alterations:
  - Absent or reversed diastolic flow in the umbilical artery of the donor twin
  - Reversed flow in the ductus venosus of the donor twin
  - Pulsatile flow in the umbilical vein of the recipient twin
- Stage 4. Fetal hydrops in any of the twins
- Stage 5. Death of one or both twins

Differential diagnosis

The differential diagnosis of TTT includes placental insufficiency, congenital abnormalities, umbilical cord abnormalities, fetal infection, and preterm rupture of the membranes selective for one of the fetus.

Treatment

Until recently, treatment of TTT was limited to bed rest and early delivery. The results of this therapeutic approach were poor. At present there are several therapeutic modalities for TTT that include serial amnioreduction, laser ablation of the vascular anastomosis between the twins, amniotic septostomy, and selective feticide.

Serial amnioreduction

Serial amnioreduction is the therapeutic modality most frequently used in cases of TTT. The removal of fluid decreases intra-amniotic pressure, improving placental perfusion. Amnioreduction is also useful to alleviate the maternal discomfort and respiratory difficulties caused by uterine overdistention. In TTT the placenta of both twins is compressed against the uterine wall due to the increased intra-amniotic pressure caused by excessive accumulation of amniotic fluid. Once the fluid is removed, it is possible to observe how the diameter of the placenta increases. This ultrasonographic observation may explain the beneficial effects of amnioreduction. The procedure may temporarily correct the blood volume overload of the recipient twin by switching a part of its intravascular volume to the placenta. However, the effects of this internal blood transfer between fetus and placenta are temporary and a new amnioreduction will be necessary a few days later. There is no experimental evidence supporting this hypothesis.

Amnioreduction is not difficult to perform. After adequate preparation, the needle insertion site is anesthetized with 1% lidocaine. Under ultrasound guidance, an 18-G amniocentesis needle is placed in the enlarged amniotic fluid sac and the fluid is drained manually with the use of three-way stopcock and a 50-ml syringe. Others drain the fluid by connecting the needle to a low-pressure suction equipment. The fluid should not be removed any faster than 1000 ml in 30 minutes and it is not recommended to drain more than 5000 ml in each session. In general, the amount of fluid to be removed is that necessary to reduce the largest pocket of fluid to a diameter of 5–8 cm. The frequency of amnioreductions is dictated by the rate of amniotic fluid reaccumulation. The rate of complications of amnioreduction is 3–5% per procedure. The main complications are rupture of the membranes, preterm labor, and chorioamnionitis. The risk of abruption, even with drainages > 2000 ml, is minimal.

With respect to the results of serial amnioreduction, the largest published series (Mari et al., 2001) included 223

twin pregnancies of less than 28 weeks' gestation. Seventy-eight percent of the twins (182 recipients and 164 donors) were born alive and 68% (144 recipients and 122 donors) were alive 4 weeks after birth. Survival of both twins occurred in 48% of the cases and survival of at least one of the twins occurred in 71% of the cases. Survival was better when the gestational age was advanced at the time of diagnosis, umbilical artery diastolic flow was present, hydrops fetalis was absent, and in those cases requiring a relatively small amount of fluid drained with each procedure.

Laser photocoagulation of placental vascular anastomoses

Laser photocoagulation of placental vascular anastomoses is a sophisticated but highly effective method for the treatment of TTT syndrome. The first, and most important, part of this technique is the endoscopic identification of the A–V anastomoses between the twins. These anastomoses are located in the vascular equator of the placenta which is the line that separates the vascular territory corresponding to each twin. Under normal conditions the vascular equator corresponds to the insertion of the intertwin membrane. In TTT the vascular equator does not correspond to the insertion of the intertwin membrane because the membrane has been separated from its original insertion due to the development of polyhydramnios in the recipient amniotic sac. Identification of the A–V anastomosis is crucial because this determines the outcome of the procedure. Once identified, the vascular anastomoses are photocoagulated with YAG laser using a microfiber of 400 μ which is inserted through the operative channel of a fetoscope. An amnioreduction is performed at the end of the procedure through the sleeve of the fetoscope.

A common complication of the laser surgery for TTT is premature rupture of the membranes which occurs in approximately 12% of the cases. A serious complication of the placental vascular surgery is a sudden reverse transfusion due to an incomplete separation of the placental circulations. Other complications include maternal death due to abruption placenta, maternal pulmonary edema, extensive separation of chorion and amnion, and fetal ischemic lesions.

The perinatal outcome of laser surgery in pregnancies less than 27 weeks is approximately 59.5% for two survivors and 83.5% for one survivor. Survival of both fetuses at stage I is 75.9%, at stage II 60.5%, at stage III 53.8%, and at stage IV 50%. Survival of one fetus at stage I is 93.1%, at stage II 82.7%, at stage III 82.5%, and at stage IV 70%. Donor survival is 70.5% and recipient survival is 72.5% (Huber et al., 2006). Neurologic lesions occur more frequently when a fetal death happens following laser coagulation, suggesting an incomplete coagulation of vascular anastomoses. Fetal survival requires at least an 18% of placental mass remaining available for the nutrition of the donor twin following the coagulation of vascular anastomoses (Quintero et al., 2005).

Laser photocoagulation is more effective than serial amnioreduction with respect to fetal survival and incidence of neurologic lesions. This was demonstrated in the Eurofetus Research Consortium TTTS study (Senat et al., 2004), which is the only randomized study comparing the two treatments. This study was interrupted following an interim analysis of the first 142 cases when it was found that treatment with laser photocoagulation had an overall survival rate of 57% versus 41% in the amnioreduction group. Neonatal survival at 28 days of at least one twin was 76% versus 56%, neonatal survival at 6 months of at least one twin was 76% versus 51%, mean birth weight was 1757 g versus 1359 g, incidence of periventricular leukomalacia was 6% versus 14%, and survival at 6 months without neurologic morbidity was 52% versus 31% in the laser and serial amnioreduction groups, respectively. However, a long-term study of survivors of fetoscopic laser surgery for TTT syndrome found neurodevelopmental impairment in 17% of the cases, caused by cerebral palsy, severe mental developmental delay, severe psychomotor developmental delay, and deafness, indicating the need for long-term follow-up of survivors to have a better assessment of the complications associated with this procedure (Lopriore et al., 2007a).

Laser photocoagulation of vascular anastomoses is not always the best therapy for all the cases of TTT. Pregnancies with stage I and II may be followed with serial sonographic observation. Placental surgery will be indicated when there is some degree of myocardial dysfunction or severe growth discordance or Doppler abnormalities (Quintero et al., 2003).

Septostomy

Septostomy is the intentional perforation of the intertwin amniotic membrane in an effort to equilibrate the amniotic fluid volume of the twins. A 22-G amniocentesis needle is used for the procedure. The size of the perforation should be small to avoid the formation of a monoamniotic pregnancy. It has been shown that iatrogenic "pseudomonoamniotic" pregnancies carry a perinatal mortality similar to that of true monoamniotic gestations, the main causes being entanglement of the umbilical cords and fetal and neonatal death (Gilbert et al., 1991) A randomized study comparing amniotomy with serial amnioreduction (Moise et al., 2005) demonstrated similar survival of at least one of the twins (80% versus 78%) and similar prolongation of pregnancy. In a significant number of cases, one extremity of one of the twins moved

to the opposite sac through the septostomy hole which was a complication that caused interruption of the trial.

Selective feticide

Selective termination of one of the twins is a method originally used for the reduction of dichorionic twins when one of them was affected by a chromosomal abnormality or a multifactorial defect. Selective termination is usually performed after 20 weeks of gestation and is associated with a worse perinatal prognosis than that with fetal reduction procedures which are usually carried out between 10 and 14 weeks (Lynch et al., 1996). The introduction of this technique followed the observation that in severe TTT syndrome with polyhydramnios not responsive to serial amnioreduction, death of one of the twins resulted in normalization of the fluid volume (Baldwin and Wittman, 1990). The most frequent indications for selective feticide are acardiac twins with reversed arterial perfusion, or TRAP, sequence, central nervous system and cardiac abnormalities, or fetal hydrops in TTT syndrome.

The presence of vascular anastomoses between the twins considerably limits the techniques that may be used for selective feticide because any substance injected in one of the twins will necessarily reach the other twin. The methods used more commonly are the ligature or the bipolar cauterization of the umbilical cord, under ultrasound or fetoscopic guidance. In bipolar coagulation the cord is coagulated in one or more sites using 20–50 W until the blood flow through the cord is interrupted. The survival rate of the other twin is between 70 and 85%. Complications occur in < 15% of the cases.

Preterm delivery is necessary in the overwhelming majority of TTT patients. Ideally, delivery should be effected after fetal lung maturation is documented by amniocentesis. However, this almost never occurs in practice, and in most cases it is necessary to deliver before lung maturity is achieved because of progressive, severe fetal deterioration. Because of the high probability of preterm delivery, glucocorticoids should be used to accelerate fetal lung maturity when the diagnosis of TTT is made. If amniocentesis is done to assess lung maturity, it should be noted that the smaller twin has a more advanced degree of lung maturation than the plethoric twin. Therefore, amniocentesis for fetal lung maturity should preferentially be performed in the sac of the large twin.

Monoamniotic Twins

Monoamniotic twin pregnancies are relatively rare, occurring approximately once out of every 12,500 births. They are of particular concern to the obstetricians because the associated perinatal mortality is approximately 50%, mostly due to umbilical cord entanglement. Two-thirds of the fetal deaths involve both fetuses and one-third one of them. TTT, congenital abnormalities, and preterm delivery are also significant contributors to the poor outcomes. Other frequent complications in monoamniotic pregnancies include low birth weight, birth weight discordance > 20%, preterm birth, and congenital abnormalities. The incidence of TTT syndrome is low possibly because of a large number of A–A anastomoses. Also, the diagnosis of TTT syndrome is difficult since the sequence poly/oligo cannot occur. One of the most common complications in monoamniotic twins is cord entanglement, which occurs between 42 and 60% of the cases (Figures 12-4 and 12-5). The majority of these cases can be detected antenatally, before 24 weeks of gestation. Once the diagnosis of cord entanglement is made, fetal surveillance with Doppler is important. The abnormalities suggesting cord compression include high velocity of blood flow in the umbilical vein and diastolic notching or absent diastolic flow in the umbilical artery. Also, FHR monitoring may show variable decelerations when cord entanglement is present.

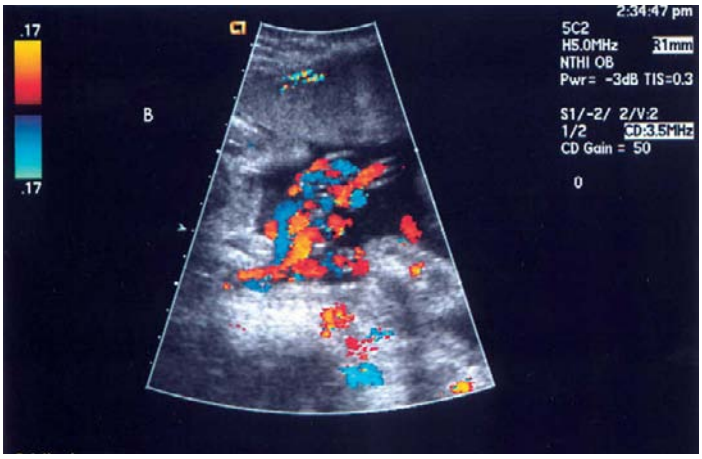

Figure 12-4. Color Doppler ultrasound image of entangled umbilical cords in monoamniotic twin pregnancy.

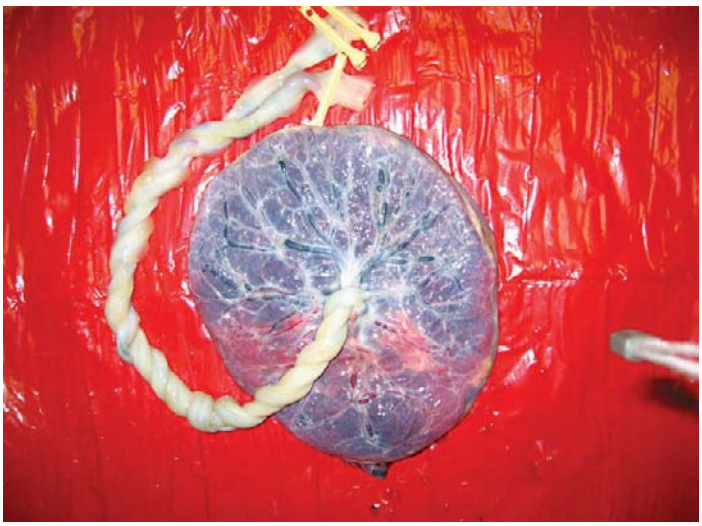

Figure 12-5. Severe entanglement of the umbilical cords in monoamniotic twin pregnancy.

Monoamniotic twins occur frequently following assisted reproductive techniques that involve manipulation of the zona pellucidum. The umbilical cords commonly have a central implantation and the separation of the insertion sites is usually less than 6 cm. One-third of the cases have velamentous insertion of one of the cords. There are vascular anastomoses between the twins but the TTT syndrome is less frequent than in Mo–Di type of placentation. Pseudomonoamniotic pregnancies occur in twin pregnancies when the intertwin membrane ruptured spontaneously or, more frequently, as a consequence of amniocentesis. The perinatal morbidity and mortality in these cases is similar to that of a true monoamniotic gestation, and the management of these pregnancies should be similar (Gilbert et al., 1991).

The prenatal diagnosis of monoamniotic placentation is made when it is not possible to visualize the amniotic membrane separating the twins in at least three different examinations. The membranes are visualized better before 14 weeks, ideally between 9 and 10 weeks. Before 8 weeks, visualization of one yolk sac and two fetal poles is diagnostic of monoamniotic placentation. When the membrane between the twins is not visualized in an initial examination, the positive predictive value of the finding for the diagnosis of monoamniotic pregnancy is only 25% and it is necessary to repeat the attempts to visualize the membranes until the diagnosis is certain. The observation, with color Doppler, of entanglement of the umbilical cords is diagnostic of monoamniotic pregnancy.

In difficult cases it is necessary to perform an amniography to confirm or rule out the presence of monoamniotic pregnancy. This technique has a 100% positive predictive value but is invasive and not free of complications. It consists in the injection of water-soluble contrast medium in the amniotic cavity and the performance of a flat plate of the abdomen 24 hours later. The x-ray film will show contrast medium around and in the digestive tract of both twins.

The management of these pregnancies is similar to other twin pregnancies with two exceptions. One is the need for more frequent fetal assessment and the second is the need for early pregnancy interruption. Monoamniotic pregnancies are usually terminated at 32 weeks by cesarean section, although there is no clear evidence of the benefits of this plan of management. Early delivery is predicated on the basis of a fetal mortality of 10% if the gestation continues beyond 32 weeks. With respect to antenatal fetal surveillance, there is no consensus about the best type, its frequency, and about the advantages of inpatient versus outpatient fetal assessment. However, a retrospective study (Heyborne et al., 2005) found no perinatal deaths when mothers were admitted to the hospital at 28 weeks' gestation and had FHR monitoring for a minimum of 2 hours per day in comparison with 13 fetal deaths (50%) for women managed as outpatients and monitored two to three times per week.

Pharmacologic reduction of the amniotic fluid volume with sulindac, 200 mg twice daily, has been used to limit the fetal movements and avoid cord entanglement in monoamniotic gestations (Peek et al., 1997). Similar to indomethacin, sulindac affects renal prostaglandin production, causing a decrease in fetal urine production. Sulindac also causes constriction and eventually closure of the fetal ductus arteriosus (Sawdy et al., 2003). However, the cardiovascular effects of sulindac do not seem to be of importance, and a recent report of 44 monoamniotic pregnancies treated with sulindac and delivered at 32 weeks with all the fetuses surviving concludes that the drug is useful in reducing the fluid volume, stabilizing the fetal lie, and preventing intrauterine death by diminishing the risk of constricting umbilical cords that are already entangled (Pasquini et al., 2006).

Care of monoamniotic twins should be in tertiary centers equipped to handle preterm babies. Fetal surveillance with ultrasound examinations performed at least every 2 weeks is necessary, once the diagnosis of monoamniotic twins is made.

Fetal Demise of One Twin

The death of one twin occurs in approximately 3–4% of all twin pregnancies and the incidence is higher in monochorionic than in dichorionic pregnancies (26.0% versus 2.4%). The most significant problem is that the mortality and morbidity of the surviving twin is significantly increased. In fact, morbidity may affect as many as 46.2% of survivors, and approximately 20% of them will have cerebral palsy (Pharoah and Adi, 2000).

The effect of the death of one twin upon the survivor varies depending on the gestational age at the time of death. A fetal demise before 14 weeks places no increased risk on the survivor. However, after 14 weeks death or severe morbidity in the remaining twin may ensue. When one of the twins dies, the lack of blood pressure in that part of the placental circulation causes an acute and massive transfusion of blood from the survivor to the dead twin with resulting severe anemia of the survivor which can be detected by Doppler assessment of the middle cerebral artery. There is a high risk, for the survivor twin, of renal, cardiac, and neurologic morbidity secondary to ischemic damage. The most feared sequela of the ischemic insult in the survivor twin is neurologic damage. Renal cortical necrosis may also occur as a result of the hypovolemic shock. In a review of this topic the acute ischemic insult to the survivor twin resulted in 38% probability of death and 46% probability of neurologic damage. The death of one twin may have potential morbid effects on the mother. The most serious maternal complication is disseminated intravascular coagulation. This complication is rare in the case of twins, usually occurs 3 or more weeks after the fetal demise, and may resolve spontaneously.

The traditional approach to the demise of a twin has been to deliver the survivor to avoid the complications described above. This is completely unnecessary. In dichorionic pregnancies the death of one of the fetuses will have no effect on the survivor. In monochorionic pregnancies it is impossible to know how many hours or days have passed since the death of one of the twins and the ischemic insult have already occurred. Severe bleeding from the survivor twin into the body and placenta of the dead twin may occur a few minutes after the fetal demise (Karsidag et al., 2005). A more logical approach is to measure the middle cerebral artery peak velocity of the survivor twin and if the value is in the zone of severe fetal anemia, proceed to intrauterine transfusion with the hope of limiting the ischemic damage. The family should be informed of the guarded prognosis for the survivor twin, the inability of cesarean delivery to prevent the outcome, and the added significant morbidity that early delivery will add to the survivor fetus. An MRI of the fetal brain 2–4 weeks after detection of the fetal demise may be extremely useful to detect ischemic lesions and redefine the fetal prognosis.

Congenital Abnormalities

Congenital malformations occur more often in twins than in singleton pregnancies. This has been consistent in all studies, but there is some variation in the figures reported by different investigators. Hendricks (1966) in a review of 438 multiple pregnancies found an incidence of congenital abnormalities of 10.6% for twins versus 3.3% for all births. Guttmacher and Kohl (1958) in their analysis of 1327 twin deliveries found 6.86% of twins and 3.98% of singletons to have abnormalities. A study of 1424 twin pairs found an incidence of malformations of 3.7 and 2.5% in monozygotic and dizygotic twins, respectively, with the highest risk of malformations (26%) in Mo–Mo twins (Cameron et al., 1983). The most frequent abnormalities were of the neural tube (33%), genitourinary system and abdominal wall (33%), cardiac (14%), VATER sequence (14%), and isolated limb abnormalities (8%). The presence of congenital abnormalities was associated with a perinatal mortality of 43%. Most congenital abnormalities in twins are multifactorial. The majority of twins with congenital abnormalities have a co-twin without abnormalities. Selective feticide of the twin with abnormalities improves the survival rate and decreases the morbidity of the one without abnormalities.

In the material collected for the Collaborative Perinatal Project, the malformation rate was 17.4 and 17.2%, respectively, in monochorionic and dichorionic twins. However, malformations among monochorionic twins were multiple or lethal, whereas those occurring in dichorionic infants were mostly minor. Congenital abnormalities occur more frequently in twins of the same sex and in monochorionic twins. The spectrum of abnormalities is wide, and they are not unique to multiple gestations. The abnormalities that are unique to multiple gestations are conjoined twins and fetal acardia. Neural tube defects and congenital heart disease are abnormalities occurring more frequently in twins.

There are conflicting opinions in the medical literature, concerning the frequency of chromosome abnormalities in twins. Several studies suggest that there is no increase in chromosome abnormalities, but other studies show the opposite. Since the majority of twins are dizygotic and each fetus has an independent risk of carrying a chromosomal abnormality, the likelihood that one will be affected is greater than one would expect for a singleton gestation. Some authors have used formulas to calculate that risk and have concluded that the risk of chromosomal abnormalities for a 33-year-old patient with twins is similar to that of a 35-year-old woman with a singleton pregnancy (Rodis et al., 1990).

Conjoined Twins

An interesting anomaly unique to multiple pregnancy is conjoined twins. This is a rare disorder affecting 1 out of every 200 monozygotic twin pregnancies, 1 out of every 900 twin pregnancies, and one out of every 25,000–100,000 births. Conjoined twins are mono-ovular and have the same sex and karyotype. The phenomenon occurs predominantly in females (female to male ratio 3:1), and the cause is unknown. However, most investigators believe that it results from an incomplete fission of the embryonic inner cell mass rather than a partial fusion of two separate centers of growth. In any case, the phenomenon happens early in gestation, probably before the 2nd week after fertilization.

Conjoined twins are classified according to the site of union that could be ventral or dorsal in 87 and 13% of the cases, respectively. Ventral unions include the following (Spencer, 1996):

1. Thoracopagus (19%), joined at the chest
2. Omphalopagus (18%), joined at the anterior abdominal wall
3. Ischiopagus (11%), joined at the ischium
4. Craniopagus (11%), joined at the head

The distribution of dorsal unions is as follows:

1. Craniopagus (5%), joined at the head
2. Pygopagus (6%), joined at the buttocks
3. Rachipagus (2%), joined at the spine

The antepartum diagnosis of conjoined twins is possible if an effort is made to rule out this condition in all monoamniotic twin gestations. In these cases, ultrasound examination of the twins should include a careful inspection of the thorax and abdomen of the infants, especially if they are in the same position. The following ultrasound

findings increase the probability that conjoined twins are present:

1. The twins face each other.
2. The heads are at the same level and plane.
3. The thoracic cages are in unusual proximity.
4. Both fetal heads are hyperextended.
5. There is no change in the relative position of the fetuses with movement, manipulation, or in repeat examination obtained hours or days later.

A comprehensive ultrasound examination between 18 and 22 weeks may be useful to determine the anatomy of the shared organs and to detect associated malformations. If the sonogram and fetogram are suggestive of conjoined twins, the diagnosis may be confirmed by introducing 40 ml radiopaque material into the amniotic cavity. The amniography makes it possible to demonstrate the existence and location of the union between the fetuses. Repeated 2D and 3D ultrasound examinations, CT, and MRI scanning are useful for antenatal determination of cardiac connections between the twins.

Termination of pregnancy is an option when the heart or the brain is shared because in these cases attempts to separate usually fail. Once the diagnosis is made, plans should be made for cesarean delivery unless there are special circumstances indicating the possibility of a safe vaginal delivery. If allowed to labor, the majority of these women will show abnormal patterns of cervical dilation and descent. The outcome of conjoined twins is poor: approximately 40% of them will be stillborn and another 35% will die within 1 day after delivery. The only hope of independent life is through surgical separation. The first successful surgical separation of conjoined twins was achieved in 1953. At present, with further advances in organ imaging, it is possible to obtain a better assessment of the characteristics of the union between conjoined twins and therefore determine more accurately the feasibility of separation. The absence of malformations, the lack of bone unions, and the existence of separate hearts are the most important indicators of the possibility of a successful surgical outcome.

Acardiac Twin

Acardia is another rare malformation that is unique to twin pregnancies. It is rare and occurs in 1 per 35,000 live births. In this situation, one twin has no cardiac structures or placental circulation and the blood supply comes from the healthy twin by means of an A–A anastomosis and the blood of the donor twin enters the acardiac twin via the umbilical artery and the iliac vessels. Thus, the arterial system of the acardiac twin is perfused in reverse with deoxygenated blood from the normal twin (twin reversed arterial perfusion, or TRAP). This results in better perfusion of the lower part of the acardiac body and poor perfusion of the upper body with lack of development of the heart, the head, and the upper extremities. Since the circulation for both infants is maintained by the healthy twin's heart, the circulatory load may be so large that the normal twin eventually succumbs to high-output heart failure. Mortality of the normal twin is approximately 50%.

There are four types of acardiac twins. In the acardiac-acephalus the thoracic organs and the fetal head are absent. In the acardiac-acormus only the fetal head develops. The acardiac-amorphous consists in a mass of tissue without recognizable human parts. Finally in the acardiac-myelacephalus the head and one or several extremities develop normally.

The diagnosis of acardiac twinning is not always simple. The most frequent confusion is with anencephaly or with fetal demise of one twin. It is easy to erroneously diagnose fetal death in these cases because of the absence of cardiac motion and movement in the acardiac twin.

Management of this disorder is complex. Potential treatments include administration of cardiotonics to the mother or the fetus, serial amniocenteses, selective removal of the acardiac twin, or insertion of a thrombogenic coil in the umbilical artery of the acardiac twin. Another method is the interruption of the A-A anastomosis between the donor and the acardiac twins. This can be achieved by endoscopic laser photocoagulation when the pregnancy is less than 24 weeks or by endoscopic or ultrasound guided ligature of the umbilical cord of the acardiac twin when the gestational age is more advanced. In one report the mortality rate of the donor or "pump" twin decreased to 13.6% following umbilical cord occlusion. Another alternative is expectant management. In a report (Sullivan et al., 2003) 9 of 10 healthy "pump" twins survived with expectant management. In 4 of these cases the blood flow to the acardiac twin stopped completely or decreased markedly during the expectancy period.

Umbilical Cord Problems

Umbilical cord problems are more frequent in twins than in singleton: a single umbilical artery occurs three to four times more frequently and velamentous insertion of the cord occurs six to nine times more frequently in twins than in singletons. Cord prolapse, vasa previa, and torsion of the umbilical cord at its abdominal wall insertion because of focal absence of Wharton's gelatin also happen more frequently in twins. Umbilical cord entanglement is a common problem in monoamniotic twins.

Cerebral Palsy

Neurologic morbidity is seven times higher in preterm monochorionic twins than in dichorionic infants (Adegbite et al., 2004). The main causes for this problem

are the intrauterine death of a co-twin, severely discordant twins, TTT syndrome, and asphyxiated, growth-restricted twins. Petterson et al. (1993) published a study showing an incidence of cerebral palsy of 1.6, 7.3, and 28.0 per 1000 survivors at 1 year of age for singleton, twins, and triplets, respectively. The risk increases when one of the twins die "in utero" (96 per 1000) than when both are born alive (12 per 1000). The neonatal death of one of the twins increases the risk of cerebral palsy in the survivor, particularly in monozygotic pregnancies.

The incidence of neurologic damage is significantly higher in monochorionic twins with selective fetal growth restriction (FGR), particularly if the umbilical artery Doppler shows absent or reversed diastolic flow. The incidence of fetal death (20.5% versus 0.0%) and parenchymal brain damage (20% versus 5%) is significantly greater in selective FGR fetuses with abnormal umbilical Doppler (Gratacos et al., 2004).

DIAGNOSIS

Early diagnosis is one of the most important factors in the successful outcome of a twin pregnancy. Studies demonstrate that perinatal losses are significantly larger when the diagnosis is made after 28 weeks. With earlier diagnosis close surveillance of mother and fetuses may be implemented as well as a planned approach to delivery. Fortunately, in most developed countries ultrasound examination has become a part of routine obstetrical practice and the delivery of undiagnosed twins is rare.

The most important clinical finding suggesting the possibility of a multifetal pregnancy is the presence of a uterine size disproportionately large for the patient's dates. Other findings suggestive of the possibility of a twin pregnancy include conception through the use of fertility agents, family history of twins, auscultation of two fetal hearts, and abdominal palpation of three fetal poles.

The sonographic diagnosis of twin pregnancy can be made as early as 6–7 postmenstrual weeks with the use of vaginal ultrasound. Early in pregnancy, it is difficult to see the thin membrane separating the amniotic sacs when the placentation is Mo–Di. However, when the placentation is Di–Di, it is easier to see the division.

The ultrasonic diagnosis of twin pregnancy should include an assessment of the placentation. This may require more than one examination and sometimes is impossible, particularly when the initial diagnosis of twins is made late in pregnancy. The first step is to determine whether the number of placentas is one or two and whether or not an intertwin membrane is present. If two placentas and a thick membrane are seen, the pregnancy is Di–Di. If only one placenta is seen, the next step is to identify the sex of the babies. If they are of different sexes, the placentation is Di–Di. If the babies are of identical sex or the gender cannot be determined, the next step is to study the thickness of the membranes. For this purpose, it is best to look between 16 and 24 weeks near the placental insertion of the membranes. The membranes should be examined using the largest magnification allowed by the ultrasound equipment. In monochorionic placentation the membranes are difficult to see and have a paper-thin or hair-like appearance. In dichorionic placentation, the membranes are readily seen and have a thickness similar to that of one wall of the umbilical cord. According to D'Alton and Dudley (1989) if only two layers are seen the placentation is monochorionic. If three or more layers are seen the placentation is dichorionic. The predictive accuracy of this method is 100% for dichorionic and 94.4% for monochorionic placentas. Better results can be obtained using high frequency, 7.5–10.0 MHz, transducers (Vayssiere et al., 1996). With this technique the predictive value for dichorionicity was 100% and almost 100% for monochorionicity. Other authors recommend measuring the thickness of the membrane and use a 2 mm cutoff for differentiating between monochorionic and dichorionic placentations. According to these investigators (Winn et al., 1989), the thickness of the membrane in monochorionic placentation is 1.4 ± 0.3 mm and in dichorionic placentation is 2.4 ± 0.7 mm. The accuracy of this method is 82% for monochorionic and 95% for dichorionic placentations.

Because it is difficult to visualize a thin membrane in the first trimester and because of the serious implications of a monoamniotic pregnancy, a repeat ultrasound between 20 and 26 weeks is necessary for confirmation of a single sac. Also, the umbilical cord of each twin can be seen with color Doppler. If the cords are entangled, the diagnosis of monoamniotic twin pregnancies can be made with confidence.

ANTEPARTUM MANAGEMENT

Once the diagnoses of twin gestation and the type of placentation are made, the efforts of the obstetrician must be directed toward prevention of preterm birth, evaluation of fetal growth, assessment of fetal well-being, and determination of the best mode of delivery. There are differences in the approach to these problems depending on the type of placentation.

Prevention of Preterm Birth

Preterm birth is the most important cause of mortality and morbidity in multiple gestations. The incidence of preterm birth is 57% before 37 weeks of gestation, 19% before 33 weeks, and 2% before 28 weeks. The mean gestational age at delivery for singleton, twins, and triplets is 39, 35, and 32 weeks, respectively. The measures most

commonly used for the prevention of preterm birth in twins are bed rest, administration of tocolytic agents, and uterine contraction monitoring. Another modality of treatment, the cervical cerclage, may be useful in certain cases but its generalized use does not improve the outcome of twin pregnancies and should be discouraged.

Bed rest

Bed rest is widely used for the prevention of preterm labor in twins. The rationale behind its use is that with bed rest in the lateral position, there is reduced pressure on the cervix and increase in uteroplacental blood flow. The increase in blood flow in turn has a quieting effect on myometrial contractility. Despite this apparently solid rationale, its use has been a highly controversial subject. Although well-conducted studies have shown that bed rest decreases perinatal mortality and morbidity in twins, a Cochrane review of the literature could not demonstrate a prolongation of pregnancy with bed rest in multiple gestations (Crowther, 2001).

It is clear that the worst morbidity and mortality caused by preterm delivery in twins occurs before 30 weeks of gestation. This point was clearly demonstrated in the study of Jeffrey et al. (1974) at the University of Colorado. These investigators demonstrated that if deliveries of twins occurring before 30 weeks of gestation are excluded from consideration, bed rest does not significantly change perinatal mortality or length of gestation. Another study by Powers and Miller (1979) in agreement with the Colorado data shows that twins are most vulnerable if born between 27 and 34 weeks. The conclusion is that bed rest should begin at approximately 24 weeks and finish at 34 weeks, when the chances of survival are almost 100%. These are general guidelines and there is room for variation depending on the particular situation of each individual patient.

Prophylactic tocolysis

The purpose of administering drugs that inhibit uterine activity is to avoid preterm labor and prevent cervical changes that facilitate ascending infection or preterm rupture of the membranes. The tocolytic agents most commonly used are betamimetic drugs and calcium channel blockers (see Chapter 8). Similar to bed rest, the usefulness of prophylactic tocolysis is controversial. In one study (TambyRaja et al., 1979), 42 patients with twin pregnancies were treated with salbutamol and their outcome was compared with an equal number of matched twin pregnancies who were treated with bed rest alone. The treated patients received an amount of salbutamol that kept the maternal pulse above 100 beats per minute during weekly checks. The authors found a significant increase in the length of gestation and in the birth weight in the medicated group. Only four of the salbutamol-treated babies weighed less than 2000 g and only one infant weighed less than 1500 g. It is not clear in this study, however, if there was a significant difference between the groups in gestational age at the time of initiation of therapy. The results of other studies are not as supportive of prophylaxis. One randomized study of 200 women with multiple pregnancies (Gummerus and Halonen, 1987) showed no difference with respect to duration of pregnancy and birth weight between treated and untreated patients. A Cochrane systematic review concluded that there is no benefit from tocolytic treatment in the prevention of preterm birth in asymptomatic women with multifetal pregnancies (Yamasmit et al., 2005). It should be noted that treatment with tocolytic agents is not without risks. Women with twin pregnancies have a large expansion of intravascular volume and a low plasma oncotic pressure—factors that place them at high risk for developing pulmonary edema following the administration of beta-adrenergic agents.

Home uterine activity monitoring

Another subject of controversy in the management of twin pregnancies is that of home uterine monitoring. The patient at her home uses a tocodynamometer to monitor the frequency of her uterine contractions. The activity registered by the dynamometer is transmitted through a telephone line to a central station, and the obstetrician, and the patient, is notified if the number of contractions per hour exceeds a certain threshold, usually four to six contractions per hour. The proponents of this system believe that because approximately 35% of all patients with multiple pregnancies are not aware of their uterine contractions, detection of those contractions is important to institute adequate therapy and to avoid preterm delivery. Other investigators question the accuracy of a monitoring system that frequently identifies simple uterine irritability as contractions, and they point out its high cost. Most studies have shown beneficial effects of home monitoring for patients with multifetal pregnancies. However, since there are no adequate means to prevent or treat preterm labor, early detection of increased uterine activity does not result in improvements in the perinatal outcome (ACOG, 2004).

Infection surveillance

The data from the Collaborative Perinatal Project indicate that infection of the amniotic membranes, with or without ruptured membranes, is the most common pathologic finding underlying prematurity in twin gestations. Romero et al. (1990) found positive amniotic fluid cultures in one or both sacs in 10.8% of a series of twin pregnancies admitted in preterm labor. The presenting sac was involved in all of their infected patients, a fact that supports the theory of ascending infection.

The increasing amount of information suggesting that a significant number of twin patients in preterm labor and with ruptured membranes are infected, possibly through a mechanism of ascending infection, should be incorporated into the management of twin pregnancies. All patients with multifetal gestations and preterm labor or with premature rupture of the membranes should be considered infected until their clinical evolution and laboratory tests demonstrate that this is not the case.

Progesterone

Two recent randomized clinical trials have shown a beneficial effect of progesterone in the prevention of preterm birth (da Fonseca et al., 2003; Meis et al., 2003). However, a recent randomized study of the effects of progesterone in twin pregnancies shows that the medication was not useful (Caritis and Rouse, 2006).

Fetal fibronectin

Fetal fibronectin (FFN) has been shown to be an excellent marker of risk for preterm labor and preterm delivery in singleton and twin pregnancies. The test is more useful for its negative predictive value and a negative FFN (<50 ng/ml) in the cervicovaginal secretions of a symptomatic patient indicates that the probability of preterm birth in the 2 or 3 weeks following the test is less than 3%. In the study of Goldenberg et al. (1996) 30% of women at less than 28 weeks with a positive FFN had preterm birth as compared with 4% when the test was negative. When the test was performed at 30 weeks the incidence of preterm birth before 32 weeks for a positive test was 38% and 1% for a negative test.

Cervical length

Similarly to FFN, measurement of the cervical length is an important index to assess the risk of preterm birth in symptomatic women with singleton pregnancies. In a comparative study of the predictive value of several known factors for preterm birth, it was found that in asymptomatic twin pregnancies a cervical length of ≤ 25 mm at 24 weeks of gestation was the best predictor for preterm birth at < 32, < 35, and < 37 weeks (Goldenberg et al., 1996). Another study revealed that a cervical length ≥ 35 mm at 24–26 weeks identifies women at low risk for preterm delivery before 34 weeks (Imseis et al., 1997). A French prospective multicenter study (Vayssiere et al., 2002) demonstrated that cervical length and funneling are good predictors of preterm birth in twins when obtained at 22 weeks. In symptomatic women the finding of a cervical length > 25 mm is reassuring because the probability of preterm delivery in the following 7 days is low (Fuchs et al., 2004). Unfortunately, there is no evidence that the use of cervical length in multifetal pregnancies leads to effective interventions to prevent preterm birth.

Cervical cerclage

Several randomized clinical trials have investigated the role of cervical cerclage in the prevention of preterm birth in twin pregnancies with negative results (Newman et al., 2002).

Fetal Growth

Alterations in fetal growth occur frequently in twin gestations and in many instances they are the initial indication of fetal and neonatal distress and death. The fetuses of a twin pregnancy may grow normally, may have abnormal growth, or may have discordant growth, and monitoring of fetal growth is an essential component of the antenatal management of twin pregnancies. The most frequent abnormality is FGR that is defined similarly as for singleton pregnancies, EFW below the 10th percentile for the gestational age. In twin pregnancies the diagnosis of FGR may be apparent as early as 20–22 weeks.

During the first and second trimesters of pregnancy twin growth is similar to that of singletons. However, in the third trimester the growth of twins is slower than that of singletons (Alexander et al., 1998). The growth of twins and singletons is similar between 24 and 35 weeks but at 36, 37, and 38 weeks the mean difference in weight is 365, 327, and 362 g, respectively. At 39 weeks, the mean difference is 791 g and at 40 weeks it is 757 g. The slow growth rate in the third trimester has been attributed to placental insufficiency secondary to the increased metabolic demands of two fetuses and the limitations of an abnormal placentation. Another common association of abnormal growth is with umbilical cord abnormalities, particularly velamentous insertion of the cord. Investigators have developed growth curves specific for twin pregnancies, but they have limited usefulness because they are derived from small populations and have not been differentiated by chorionicity. Some investigators believe that the growth curves to evaluate singleton pregnancies are the best tool to determine the presence or absence of growth abnormalities in twin pregnancies (Hamilton et al., 1998).

Discordant growth

A frequent problem in the prenatal care of twin gestations is the occurrence of discordant growth, a condition that affects 15–29% of these pregnancies. Discordant growth is expressed as a percentage of the weight of the larger twin. It is calculated by dividing the difference in EFW among the twins by the EFW of the larger twin. The majority of investigators consider 20% or more to be a

significant difference. Approximately 15% of twins have a discordance of ³ 20% (Demissie et al., 2002). The importance of discordance is that perinatal mortality in the smaller twin increases with the severity of discordance. Perinatal mortality was 3.8 per 1000, 5.6 per 1000, 18.4 per 1000, and 43.4 per 1000 in twins without discordance, with 15–19, 20–24, 25–30, and ≥ 30% discordance, respectively (Branum and Schoendorf, 2003). The number of complications is greater and the prognosis is worse when the smaller discordant twin is second in order.

There are several potential causes of growth discordance. The most common is a difference in placental mass between the twins. The twin with smaller placental mass will have selective growth restriction while the twin with the largest placenta will grow normally. Other etiologies are genetic abnormalities, chromosomal or multifactorial, of one of the twins. A third cause is TTT syndrome. The differential diagnosis between these causes is usually not difficult.

The critical part of the management of twin discordance is the need to balance the risk of continuation of pregnancy for the smaller twin against that of prematurity complications. In the most frequent case, when the discordance is due to unequal placental mass, fetal surveillance with NST, Doppler ultrasound, and assessment of fluid volume are essential for the management. Usually the NST is performed twice every week and the amniotic fluid volume, umbilical and cerebral Doppler assessment every week. Steroid treatment should be given in anticipation of preterm delivery. Once the fetal surveillance tests show signs of hemodynamic decompensation, the pregnancy should be interrupted, usually by cesarean. Otherwise, pregnancy should be interrupted when it reaches 34–36 weeks.

When the etiology of the growth discordance is a genetic problem, the management will vary depending on the nature of the defect, its prognosis, and the possibilities of corrective treatment. When the origin of discordance is TTT syndrome, treatment will depend on the severity classification and the gestational age, the best option being endoscopic laser photocoagulation of vascular anastomoses.

There are conflicting opinions with respect to the route of delivery of discordant twins. Some recommend universal cesarean delivery independent of gestational age and presentation. Others use cesarean more selectively and will try vaginal delivery if the cervix is ripe, presentation is cephalic–cephalic, and the EFW of the smaller twin is ≥ 1500 g.

Screening for Chromosomal Abnormalities

Each fetus of a multiple gestation has the same risk of aneuploidy as has a singleton fetus from the same couple at similar maternal age and gestational age. Therefore, the risk of aneuploidy for a twin pregnancy is higher than that for a singleton pregnancy because there is more than one fetus at risk. Also, the incidence of aneuploidy is increased in twin pregnancy, most probably as a result of the increased frequency of twins in women with advanced maternal age.

Maternal age has been used to estimate the risk of aneuploidy in twins. It has been calculated that the risk for trisomy 21 for a singleton pregnancy at a maternal age of 35 years is equal to the risk of a 32-year-old mother carrying dizygotic twins (Meyers et al., 1997; ACOG, 2007). However, the sensitivity rate of screening by maternal age is less than 30% and the false positive rate is quite high.

Another method for genetic screening of twin pregnancy is second trimester screening with triple or quad tests. These methods have a sensitivity of 60–70% and a false positive rate of 5%. Wald and Rish (2005) described a formula to calculate the "pseudorisk" risk for trisomy 21 in twin pregnancies that is based on zygocity, maternal age, gestational age, nuchal translucency (NT), and biochemical analytes. The sensitivity of this calculation is about 73%. However, the use of mathematical models has been criticized because they assume an equal contribution from each fetus to the serum levels of analytes and because they do not take into consideration racial differences. Also, IVF affects the biochemical analytes and this information should be taken into consideration in calculating the risk of aneuploidy in twins resulting from IVF.

First trimester screening using NT and biochemical analytes has been used in twin pregnancies. Using serum markers alone the detection rate for Down syndrome is 52% and when combined with NT increases to 80%. Other investigators have reported 75% sensitivity and 9% false positive rate (Spencer and Nicolaides, 2003). Using NT alone makes possible to calculate the specific risk for Down syndrome for each twin. Sebire et al. (1996) reported a detection rate of 88% and Spencer (2000) a detection rate of 75% using NT alone. The advantage of using NT alone for aneuploidy screening in multifetal pregnancies is that it is possible to know the specific risk of each twin and target the diagnostic and therapeutic intervention to a specific twin. Also, an increased NT thickness is a predictor of TTT syndrome (Sebire et al., 1997) and an independent risk factor for congenital heart disease and other multifactorial conditions.

Abnormal first trimester screening results require further investigation with chorionic villus sampling (CVS) or amniocentesis. However, to avoid the fetal loss associated with these procedures it has been suggested to use sequential screening and modify the results of the first trimester by a second trimester screening with the quad test. Using this "integrated" test (holding the results of the first

trimester screening until the second trimester test is obtained) the rate of detection is 93% for monochorionic twins, 78% for dichorionic twins, and 95% for singleton pregnancies. Using the "combined" test (first trimester screening is not held) the rates of detection are 84, 70, and 85%, respectively.

Both CVS and amniocentesis are used for definite diagnosis in multifetal pregnancies at high risk for aneuploidy. CVS is as effective as amniocentesis in providing accurate diagnosis but does not provide confirmation that individual samples are retrieved unless the placentas are separated. In a comparative study (Wapner et al., 1993) the total fetal loss rate following CVS (3.9%) was significantly less than that (9.3%) following amniocentesis. The risk of pregnancy loss following invasive prenatal diagnosis is inversely proportional to the experience of the operator, and CVS and amniocentesis in multiple pregnancies should ideally be performed by specialists in maternal–fetal medicine.

Fetal Surveillance

The use of tests to evaluate fetal well-being in uncomplicated dichorionic twin pregnancies has not been shown to be beneficial. Fetal well-being testing is indicated in high-risk situations such as selective or universal FGR, abnormal amniotic fluid distribution, monoamniotic twins, preeclampsia, diabetes, and chronic hypertension. Fetal monitoring is also indicated in Mo–Di pregnancies because of the increased risk of fetal death.

The NST, modified BPP, and BPP are used for the monitoring of fetal well–being, and there is no evidence supporting the preferential use of one of them over the others. Determination of the amniotic fluid volume can be made by several methods including subjective evaluation, measurement of the largest diameter of the largest pocket of fluid around each twin, and amniotic fluid index. The second method measures the largest pocket in each uterine quadrant without consideration to the amount of fluid around each of the twins and is not recommended. The subjective evaluation of the amniotic fluid distribution in each sac is as precise as the quantitative evaluation of the largest pocket around each twin.

Fetal Lung Maturation

Evaluation of fetal lung maturation is often required in the management of twin pregnancies, especially in cases of discordant fetal growth, and the question arises about the need for amniotic fluid studies in each sac. The evidence collected to date indicates that lung maturation in normal twins occurs simultaneously and that results of biochemical analysis of one amniotic sac may be applied to the other. However, this general rule does not apply to twins with discordance. In these cases, the growth-retarded fetus usually has a more advanced degree of lung maturity than the other. Therefore, the timing of premature delivery of discordant twins should be based on the testing of the amniotic fluid surrounding the larger twin.

Since amniocentesis for fetal lung maturity is a relatively frequent procedure in twin pregnancies, the question arises about the need to sample one or both of the amniotic sacs. Evidence indicates that fetal pulmonary maturity in twin pregnancy occurs simultaneously and therefore the result of pulmonary maturity tests in one of the sacs can be applied to the other. However, this rule does not apply to discordant twins in which case the time of delivery should be based on the results of amniocentesis in the larger twin.

Is a common belief that fetuses from twin pregnancies have faster pulmonary maturation than fetuses from singleton pregnancies. However, most studies on this topic show that this is not true. When the delivery of twin pregnancies occurs before 37 weeks, the rate of respiratory complications may be three times higher than when delivery occurs after 37 weeks (Lewis et al., 2002).

Summary of Antepartum Management

In summary, once twins are diagnosed, the following rules should be observed:

1. The patient should be scheduled for office visits every 2 weeks, or more frequently if she develops complications. Attention should focus during those visits on evaluation of blood pressure, proteinuria, uterine fundus growth, and fetal movements.
2. The patient should be scheduled for an ultrasound examination every 3–4 weeks to evaluate fetal growth. It may be necessary to perform examinations at closer intervals if complications appear.
3. Vaginal and bladder infections should be recognized and treated promptly.
4. All patients with twins should stop working and rest in the lateral decubitus position for a minimum of 2 hours each morning and afternoon. They should sleep at least 10 hours each night, starting at 22 weeks of gestation. Bed rest may be necessary before 22 weeks in patients who develop polyhydramnios, an early increase in uterine activity, or early discordant growth.
5. Assessment of the cervix by means of vaginal ultrasound should start at 18 weeks of gestation. The purpose is to detect, as early as possible, cervical changes indicative of a high risk for preterm delivery. Unfortunately, in many cases, women with twin pregnancies show shortening and funneling of the cervix as early as 18 weeks. The overwhelming majority of these cases are early preterm labor secondary to intrauterine infection. These women will

not benefit from cerclage, bed rest, or antibiotics and the only hope is that the process will be slow and they could reach > 26 or > 28 weeks when the possibilities of fetal survival without sequelae start to increase. Another important cervical length measurement is at 24 weeks of gestation because the finding of a short cervix at this time places the woman at risk for preterm labor and preterm delivery. A determination of FFN in these cases is extremely useful to assess more precisely the likelihood of delivery in 1 week, 2 weeks, and before 32 weeks (Gomez et al., 2005).

6. Administration of betamethasone 12 mg IM daily for 2 consecutive days at 28 weeks of gestation should be a part of the management of twin gestations for which preterm birth is a strong possibility. This includes patients showing discordant growth patterns, cervical changes, or poor compliance with bed rest and medications.
7. If discordant fetal growth is observed an attempt should be made to find the underlying cause. A search for congenital abnormalities, for the type discordancy (symmetric or asymmetric), and for the presence of indicators of TTT is necessary. Genetic studies, cordocentesis, serial amniocentesis, and fetal surveillance may be required depending on the circumstances. Consultation with or referral to a maternal–fetal medicine specialist is advisable.
8. Women with multifetal gestations need to increase their total daily caloric intake 300 kilocalories more than if they carried a singleton pregnancy or 600 kilocalories more than if they were not pregnant. The optimal weight gain for a twin pregnancy has not been determined precisely but most investigators agree that it should not be greater than 35–45 lbs (Institute of Medicine, 1990). The increase in body weight should be about 1.75 lbs/week after 20 weeks for thin women and 1.5 lbs/week for women with normal weight. The meal plan should include an adequate amount of iron (60 mg/day) and folic acid (1 mg/day).

MANAGEMENT OF LABOR AND DELIVERY

Timing of Delivery

Twin pregnancies are at increased risk of intrapartum complications and is important to determine the optimal moment for parturition. About 50% of twin pregnancies end in spontaneous or indicated preterm birth. In the other 50%, amnionicity becomes the most important variable to determine the optimum time for delivery. Epidemiologic studies (Kahn et al., 2003) have demonstrated that the lowest perinatal mortality in twin pregnancy occurs when delivery is between 37 and 38 weeks of gestation. Furthermore, after 38 weeks the risk of fetal death is greater than the risk of neonatal death. In a study that included 60,000 twin pregnancies (Soucie et al., 2006) it was found that the risk of neonatal death increased dramatically at gestational age of 40 weeks or more as compared with 37 weeks. Another population study (Sairam et al., 2002) showed that the risk of stillbirth in multiple gestation increases from 1:3333 at 28 weeks to 1:69 at 39 or more weeks and the stillbirth risk in multiple pregnancy at 39 weeks is greater than that of postterm pregnancy (1:526). The conclusion from a review of the literature is that in the absence of maternal or fetal indications for delivery, Di–Di pregnancies should not be interrupted before 38 weeks (Chasen et al., 1999). If there are complications increasing the risk of perinatal morbidity or mortality such as oligohydramnios, abnormal fetal growth, or maternal hypertension, delivery may be effected before 38 weeks and it is not necessary to perform tests to evaluate fetal pulmonary maturity.

Uncomplicated Mo–Di pregnancies are at increased risk for fetal death late in the third trimester and it is reasonable to deliver them at 36 weeks. Patients should be adequately counseled about the relatively slight neonatal risks of delivery at 36 weeks and the risk of preeclampsia and fetal demise with cystic encephalopathy in the surviving twin if the pregnancy is allowed to continue.

In Mo–Mo pregnancies interruption of gestation should occur early in the third trimester. There are insufficient data to determine the best time to end the pregnancy but the majority of investigators suggest 32 weeks. Mortality in Mo–Mo pregnancies that continue beyond 32 weeks is 10% while the neonatal death rate at this gestational age is less than 1%.

Fetal Presentations

The fetal presentation at the time of labor is one of the most important determinants of the route of delivery, vaginal versus cesarean, in twin pregnancy. Ideally, this decision should be made before labor or when the patient is in the early stages of labor. The best way to assess the fetal presentation is by ultrasound examination. Even if the patient had a recent ultrasound examination, a sonogram should be obtained in all twins at the beginning of labor to avoid mistakes. Some investigators have suggested that the perinatal outcome will improve with a policy of cesarean delivery for all multifetal pregnancies. This is based in concerns about the increased mortality and morbidity risk for the second twin. However, others argue that with adequate intrapartum surveillance the second twin's morbidity and mortality is not excessive and therefore, the route of delivery should be based on the presentation and amnionicity of the twins and the presence or absence of additional obstetrical factors.

There is a high incidence of malpresentation at the time of delivery in twin gestations. In the review by Farooqui et al. (1973) the frequency of different fetal presentations was as follows:

Cephalic–cephalic	39.6%
Cephalic–breech	27.7%
Cephalic–transverse	7.2%
Breech–breech	9.0%
Breech–cephalic	6.9%
Breech–transverse	3.6%
Other combinations	6.9%

When both twins are in cephalic presentation, there is consensus about the safety of a trial of labor at any gestational age. In cephalic–noncephalic presentations, many allow the vaginal birth of the first twin followed by external version and vaginal birth or by vaginal breech delivery of the second twin. The rationale is that after the birth of the first twin there is a possibility of spontaneous conversion of the second twin to a cephalic presentation, and if this does not occur it is relatively easy to perform an external version at this time or have a breech delivery. When this approach is followed, 71.2% of noncephalic second twins can be delivered vaginally without problems. In almost 30% of the cases the second baby does not convert to cephalic presentation and is necessary to perform a cesarean for the second twin.

In order to perform an external version after the delivery of the first twin, the exact fetal position should be determined by ultrasound. The obstetrician, with the help of the ultrasound transducer, gently attempts first a forward rotation, with frequent monitoring of the FHR. If there are no signs of fetal distress and the fetus does not move forward easily, a backward flip may be attempted. If the backward rotation fails, a decision should be made to deliver the breech vaginally or to perform a cesarean section for the second twin. Fetal bradycardia requiring emergency cesarean delivery may occur in up to 15% of these cases. External version after delivery of the first twin is successful in 40–50% of the cases and vaginal breech delivery can be performed in 96% of the cases.

To be delivered vaginally, a breech second twin should have an estimated weight, by ultrasound, between 2000 and 3000 g, have the head flexed, and should be of the same or smaller size than the first vaginally delivered twin. These weight limits are based on the fact that with an ultrasonic estimated weight of 2000 g the actual weight will rarely be less than 1500 g and with an EFW of 3000 g the true weight will rarely be greater than 3500 g.

The main problem with breech presentation of a second twin is the high chance of cord prolapse. Singleton babies in frank breech presentation fill the low uterine segment and the vagina with the buttocks, usually preventing cord prolapse, but second twin breech infants are high within a uterus that remains large and flaccid after the birth of the first twin. They do not occlude the birth canal, and if the membranes rupture or if the gestation is monoamniotic, the probability of a cord prolapse is high (overall incidence of 4.2% in twins). For that reason, it is important not to rupture the sac of the second twin until the baby has descended and the breech is well engaged. Another problem with second twin vaginal breech delivery is the use of manual and instrumental maneuvers by the obstetrician to shorten the delivery interval. Rayburn et al. (1984) has demonstrated that with FHR monitoring, the interval between delivery of twins is not a critical factor. As long as there are no signs of fetal distress, the obstetrician should wait for the presenting part to descend.

A rare malpresentation occurring one time per every 1000 twins and per every 50,000 births is the "interlocking of twins." The perinatal mortality of this complication is high (62–84%), probably because most cases are not recognized until late in the expulsive phase of labor. A typical case is a primipara with generous pelvic measurements and a breech–vertex presentation that is allowed to deliver vaginally. The labor proceeds smoothly until twin A is partially delivered and there is difficulty in delivering the infant head, which remains high in the pelvis. Manual examination at this time reveals the head of twin B interposed between the body and the head of twin A. In most cases, attempts to elevate twin B using various pelvic and abdominal maneuvers fail, and it is necessary to proceed with an emergency cesarean section. Death for twin A is an almost certain outcome. To avoid this disastrous sequence of events, one must rule out interlocking twins in every case of breech–cephalic presentation delivering vaginally. Interlocking of various body parts may also rarely happen in cephalic–cephalic, cephalic–transverse, and breech–breech presentations. Perhaps the first indication of interlocking is an abnormal labor pattern, usually an arrest disorder. In these cases, obviously, it is best to perform a cesarean section. Some investigators suggest obtaining anteroposterior and lateral x-ray films of the twins and repeating the films after 2 hours of active labor. If the head of twin B is descending below the level of the head of twin A, suggesting collision of the twins, a cesarean-section is the best method of delivery.

A situation requiring cesarean delivery in twin pregnancies is a monoamniotic placentation. The fetal mortality in these pregnancies is greater than 50%, and the overwhelming cause is cord accidents such as cord prolapse or entanglement. Therefore, if a membrane separating the twins is not visualized by ultrasound, it must be assumed that a single sac is present, and the pregnancy delivered by cesarean section.

In the past, it was thought that cesarean section was better than vaginal delivery if the birth weight of twins was less than 1500 g. This theory has been refuted by the work of Morales et al. (1989) who found no advantage to

cesarean versus vaginal delivery in nondiscordant twins of less than 1500 g.

There are insufficient data about the safety of labor and vaginal delivery in women with twins and a history of cesarean in prior pregnancy. Some of the data do not show differences in the incidence of uterine rupture or increase in maternal and perinatal morbidity and mortality in comparison with singleton pregnancies (Miller et al., 1996).

The different possibilities for the delivery of twins should be discussed with the patient early in the antepartum care. In offering alternatives it is important to have into consideration the expertise of the obstetrician in performing external version and vaginal breech delivery. If that expertise does not exist it is better to offer to the patient cesarean in presentations other than cephalic– cephalic.

Vaginal Delivery

In the majority of cases, when patients have been carefully selected for vaginal delivery, delivery of the first twin usually proceeds smoothly. The first stage of labor is usually rapid and the second stage and the delivery itself are uncomplicated. Oxytocin can be used in twins if it is necessary for abnormal patterns of labor. Ideally, pain relief should be by epidural anesthesia. Electronic monitoring should include both twins, which can be done by coupling the intrauterine pressure transducer to two fetal heart monitoring instruments. Also, modern fetal monitoring equipment allows simultaneous recording of FHR of one fetus by fetal scalp electrode and of the other by transabdominal Doppler. Once the first twin is delivered, ultrasound examination and electronic monitoring of the second twin are necessary to evaluate fetal presentation and to detect signs of fetal distress. Twins should be delivered in the operating room. Otherwise, the delivery room must be prepared for emergency cesarean section, and the necessary personnel must be on standby until the second twin is delivered. The necessary precautions to be taken in the vaginal delivery of twins are shown in Box 12-4.

Most problems with vaginal delivery of twins occur after delivery of the first fetus. After delivery of the first twin, augmentation with oxytocin may begin if the monitor tracing of the second twin is normal and contractions have not resumed in 10 minutes. Once the second presenting part is engaged, the membranes are ruptured and a scalp electrode for direct FHR monitoring is applied. As long as the monitor tracing remains normal, there is no reason to expedite delivery with the exception of monochorionic twins where it is prudent not to prolong the delivery interval more than 15–20 minutes. If vaginal bleeding occurs suggesting abruptio placentae, or a sinusoidal rhythm indicating fetal anemia, or a pattern of late decelerations with loss of variability indicating fetal distress is detected, delivery should be immediate by forceps, cesarean section, or breech extraction. For this reason delivery of twins should take place in or immediately adjacent to the operating room with full, immediate access to anesthesia and surgical personnel and equipment.

BOX 12-4

Measures for the vaginal delivery of twins

- Good intravenous access should be established immediately after admission and kept during labor and delivery.
- A bedside ultrasound examination should be done after admission to verify the position of the twins.
- Blood should be obtained for typing and screening so that blood is available at any time.
- Both fetuses should be continuously monitored using external or internal devices.
- Placement of an epidural catheter early in labor is ideal. This way anesthesia could be activated later when the mother is in active labor and in need of pain relief or after the delivery of the first twin if cesarean is necessary for the delivery of the second twin.
- Placement of an epidural catheter is mandatory in monochorionic pregnancies and in pregnancies with fetal presentations other than cephalic–cephalic, because of the high risk for cesarean of the second twin.
- Delivery should be in the operating room or in a delivery room equipped to perform an emergency cesarean section.
- An ultrasound machine should be available in the delivery room to determine the presentation and position of the second twin after the delivery of the first fetus.
- An anesthesiologist/anesthetist should be present in the delivery room during the vaginal delivery of twins.
- A pediatrician or neonatologist or neonatal nurse practitioner should be present during delivery.

The management of second twins in a noncephalic presentation is effected by several variables. The most important is the success of external cephalic version. To perform an external version the ultrasound transducer is used to apply gentle pressure on the back and neck of the fetus and attempt to change the presentation to vertex or breech. No intrauterine manipulations should be carried out in order to influence or determine a change in presentation. If the infant converts to a breech or a vertex spontaneously or with the help of external manipulation, the possibilities for a safe vaginal delivery are excellent. If the external version is not successful the next consideration is the EFW of the second twin. If the EFW is < 1500 g is better to avoid a breech delivery and cesarean is the best option. If the EFW is > 1500 g and the fetus is in frank breech position the best option is to let labor resume and have a spontaneous or assisted vaginal breech delivery. If the fetus is presenting as a footling breech or is in transverse lie the obstetrician needs to decide between a breech extraction and vaginal delivery or a cesarean section. Some obstetricians perform total breech extractions in cases of transverse lie or breech presentations. The expertise of the obstetrician in intrauterine manipulation is the most important factor in

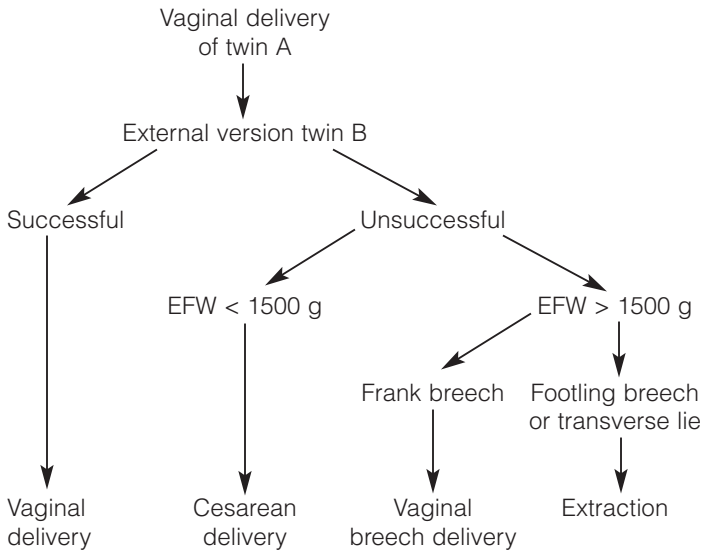

Figure 12-6. Sequence of steps in the vaginal delivery of the noncephalic second twin.

this decision. If that expertise does not exist, the safe management is a cesarean section. Cesarean for the delivery of the second twin occurs in approximately 9.5% of vaginal twin deliveries (Wen et al., 2004) but may be as high as 26.8%. The most important risk factors for cesarean delivery of the second twin are breech or other malpresentations, fetal distress, cephalopelvic disproportion, and cord prolapse. A diagram of this process is in Figure 12-6.

After delivery of the second twin and the placenta, the attention of the obstetrician should be directed to the prevention of postpartum hemorrhage. The uterus should be massaged continuously, and intravenous oxytocin (50 units in 1000 ml of lactated Ringer's solution) should be administered simultaneously. Many obstetricians prefer to administer prostaglandins ("Hemabate" 250 mg IM or misoprostol 1 g rectally) immediately after delivery of the placenta.

Delayed delivery of the second twin

There are several case series in the obstetrical literature (Rydhstrom and Ingemarsson, 1990; Arias, 1994; Farkouh et al., 2000) about delayed delivery of the second twin in situations where the first twin is delivered prematurely, before 24 weeks of gestation. The perinatal survival of the twin that remains "in utero" is between 42 and 50%. The mean prolongation of pregnancy is 35 days and delays of up to 143 days have been reported. In some series cervical cerclage has been used following the delivery of the first twin but others have been successful without the cerclage. The main problem with this approach to the early delivery of one twin is the high incidence of infection that is present in all the unsuccessful cases. However, it is a management that should be considered when a first unviable fetus is delivered within a clinical picture consistent with the diagnosis of incompetent cervix. Exclusion criteria for delayed delivery of the second twin include gestational age ≥ 26 weeks, any sign or suspicion of intrauterine infection, monochorionic twins, severe preeclampsia, abruption placenta, or any other maternal or obstetrical indications for the delivery of both twins.

The first and most important variable when considering delay delivery of the second twin is to rule out the presence of intrauterine infection. Patients with elevated white blood cell count and elevated C-reactive protein (CRP) are not adequate candidates. Transabdominal amniocentesis may be performed for Gram stain, cell count, glucose, LDH (lactate dehydrogenase), and CRP. After the birth of the first twin the umbilical cord is ligated as high as possible inside the uterus and the placenta is left "in situ." Tocolysis with IV terbutaline (250 µg) or IV nitroglycerin (200 µg) and oral nifedipine (30 mg initial dose and then 20 mg every 4–6 hours) is initiated. Triple IV antibiotic therapy is initiated using ampicillin, clindamycin, and gentamycin for at least 3 days to be followed by cephalosporin and metronidazole orally for 4–7 more days. A cervical cerclage using the McDonald or Espinosa-Flores methods is carried out or the cervix may be left intact. The patient should remain in the hospital for at least 1 week and if stable followed as outpatient with weekly visits and frequent ultrasound assessments of the cervix.

Cesarean Delivery

The ideal anesthesia for the cesarean delivery of twins is an epidural because it allows a systematic, unhurried approach to the delivery of the infants without the fetal hypoxia or depression caused by the transplacental passage of general anesthetics. Ideally, epidural anesthesia should be administered by an obstetric anesthesiologist aware of the peculiarities of twin pregnancy and able to prevent or treat the hemodynamic changes caused by the anesthetic blockade.

The best abdominal incision for the delivery of twins is a transverse. Although the vertical incision can be made quickly, has less blood loss, and allows more room for manipulation of abnormal presentations, it has a higher incidence of dehiscence and a less acceptable aesthetic result than with transverse incision. Also, most intrauterine manipulations can be performed through a transverse abdominal incision. Most patients with twin pregnancies have a well-developed low uterine segment that favors transverse uterine incisions. Any vertical uterine incision predisposes to future uterine rupture and necessitates a repeated cesarean section in subsequent pregnancies. In contrast, the patient who receives a low transverse uterine incision and is allowed to labor in a subsequent normal pregnancy has a high chance of a vaginal delivery. Vertical incisions on the uterus are rarely needed if the twins are near term, if the precise fetal lies are known.

MANAGEMENT OF GESTATIONS WITH HIGH FETAL NUMBER

Everything that has been said about twin pregnancies applies to gestations with greater fetal numbers. Multifetal pregnancies are becoming more frequent as a result of the use of ovulation-inducing drugs in the management of infertility (Russell, 2003). In patients treated with gonadotropins, the occurrence of multiple pregnancies is 20%, of which 75% are twins and 25% are triplets or gestations of higher number. In patients treated with clomiphene, the occurrence of multiple pregnancy is 10%.

Triplets occur once in every 6000–9000 deliveries in USA and quintuplets once in every 41 million births. The number of triplets have increased dramatically in USA in the last decade and this increase has been associated with a decrease in stillbirths and neonatal mortality (Getahun et al., 2006). The majority of spontaneously conceived triplet pregnancies are trichorionic-triamniotic but 44% are dichorionic-triamniotic (Adegbite et al., 2005). Dichorionic triplet pregnancies have a higher risk of delivery before 32 weeks and birth weight less than 1000 g than trichorionic pregnancies. They also have a 5.5-fold increase in adverse perinatal outcome mainly because of TTT and premature rupture of membranes. Uncomplicated triplet pregnancies should be delivered at 36 weeks because at that gestational age the prospective risk of fetal death is equal to the neonatal death rate (Kahn et al., 2003).

Fetal and neonatal morbidity and mortality is high in patients with high fetal numbers. Preterm delivery affects more than 85% of them and the neonatal death rate is approximately 20%. Similar to twins, preterm delivery is the most important hazard for patients with high fetal numbers. The mean gestational age at delivery for triplets is 32–33 weeks, and for quadruplets it is 30–32 weeks. The incidence of fetal growth retardation is greater than 15%.Other frequent problems are antepartum anemia, postpartum bleeding, and preeclampsia. Cesarean section is common, mainly because of the difficulties in ensuring adequate monitoring of all babies during labor. The fetal mortality and morbidity is high and closely related to fetal weight, birth order, and fetal position. Small babies, those born last or close to last, and those in breech or transverse presentation have the worst outcomes. The complexity of the antepartum, intrapartum, and neonatal care of multiple pregnancies of high fetal number necessitates referral to tertiary care perinatal centers. With modern perinatal management more than 80% of triplets, quadruplets, and quintuplets will survive, and 90% of survivors will not have major handicaps.

REDUCTION OF MULTIFETAL PREGNANCIES

In the last few years, reduction of higher order multifetal pregnancies has developed as an alternative to the large mortality and morbidity figures associated with this condition (Berkowitz et al., 1988; Evans et al., 1988). The main problem with multifetal reduction is the risk of losing the whole pregnancy. The overall postprocedure loss rate is 11.7% and the incidence of early preterm delivery, between 25 and 28 weeks, is 4.5%. More recent studies indicate that the unintended loss rate associated with multifetal reduction decreases with increased number of procedures and increased operator experience and stabilizes at 5.4% (Stone et al., 2002). The possibilities of losing the whole pregnancy are directly related to the starting number of fetuses. Another problem with multifetal reduction is the increased frequency of FGR in the remaining fetuses. One study found 36% FGR in twins reduced from triplets and 42% in twins reduced from quadruplets compared with 19% in nonreduced twins (Depp et al., 1996).

Patients undergoing this procedure usually have four or more fetuses but reductions of triplets to one or two fetuses are common. More rare are maternal petitions for reductions of twins to one. Between 9 and 12 weeks, under ultrasound guidance, the chosen fetuses receive intracardiac injection of potassium chloride. Any fetus smaller that the others and monochorionic twins are selected for termination. Otherwise fetal selection for termination is random and usually those fetuses that can be accessed easily by the operator are terminated first. The procedure is not completely free of complications. Technical failure, such as the development of uterine contractions and amnionitis, may also occur. The likelihood of losing all of the fetuses may be as high as 30%.

INDIAN EXPERIENCE OF MULTIFETAL GESTATION

The incidence of multifetal pregnancies has registered an increase globally. This is partly due to the widespread use of ovulation induction drugs in the treatment of infertility and also due to delaying childbearing to a later age by many women because of career constraints. The diagnosis of multifetal pregnancy is important as it is often associated with an adverse outcome, such as prematurity, birth asphyxia, birth injuries, infections, malpresentations, and congenital anomalies (Kant, 2000). In patients with multifetal pregnancy, particularly of high order (3 or more), embryo reduction or multifetal pregnancy reduction helps to reduce later obstetric risks. However, the ethical dilemmas facing the patient and the clinician need to be resolved during counseling sessions prior to undertaking

these procedures. Pregnancy loss has been reported in 10–25% of all attempted multifetal pregnancy reductions. The advantages accruing from the procedure are most apparent in quadruple and higher order births. The methods used for fetal reduction in India include fetal intracardiac injection of cardiotoxic drugs like KCl under ultrasonographic control (Desai et al., 2001; Sekhar et al., 2002; Mittal et al., 2004). Other methods include direct puncture of the fetal heart, aspiration of the amniotic fluid from the sac and suction evacuation of the dependent gestation sac (Sekhar, 2002); however, the former method is generally preferred.

The incidence of preterm labor following cervical incompetence is quoted to be higher in multifetal pregnancies. Prophylactic cervical os tightening has been advocated by several workers in the West, but most practitioners in India undertake the procedure only when there is sonographic evidence to suggest an incompetent cervix. The incidence of IUGR (intrauterine growth restriction) is more than double in twin pregnancies (12–47%) as compared to singleton births (5–7%). Twin-to-twin transfusion and dysmorphic twins are associated with higher perinatal morbidity and mortality. These are being diagnosed more often because of the routine practice of using sonography to monitor pregnancy growth and fetal well-being.

Death of one fetus in a twin gestation occurs in 2–6% of cases. Its occurrence taxes obstetric judgment greatly as the clinician is called upon to decide upon whether to permit continuation of pregnancy or terminate it. In an interesting case of a dichorionic gestation from Mumbai (Nayak et al., 2003), the authors reported that one fetus died in utero at 22 weeks, but the pregnancy was conserved and closely monitored, resulting in a live birth of the other fetus at 36 weeks. The later in pregnancy that a fetal death occurs, the higher are the obstetric risks to the surviving fetus and the mother.

Conjoint twins (Jiwane and Shah, 2002; Kulkarni and Joshi, 2002; Manchanda et al., 2002; Wahal and Sarin, 2002) are a complication of twin gestation. Such cases have been reported in Indian literature. If these are detected antenatally on sonography, the wiser course is to deliver them by cesarean section. However, vaginal delivery of conjoint twins has been reported. Locked twins are another rare complication of twin delivery. It is reported to occur in 1:817 twin deliveries. Patil and Rita (2002) from Hubli and Misra and Tripathy (2002) from Cuttack reported this complication in Indian literature.

Decisions regarding the route of delivery depend upon the gestational maturity, fetal lie and presentations, and the experience of the clinician. The commonest combination of fetal presentations is vertex–vertex. It is customary to anticipate a vaginal delivery; cesarean section is resorted to for indications that apply to singleton deliveries. About 80% vaginal delivery rate is expected. On occasions, the second of the twin that was initially in cephalic presentation may assume an abnormal presentation and call for a fresh approach to delivery. In 5% cases, cesarean section may be called for emerging indications like cord prolapse, fetal distress, abnormal presentation, failure to progress, or for cephalopelvic disproportion the second of twins. In case the combination of twins is vertex–nonvertex, as observed in 40% cases, conflicting views exist. If the gestational maturity and the estimated size of the fetuses appear to be satisfactory, then most clinicians prefer to deliver these women by cesarean section. In India, successful vaginal delivery of the second of twins by breech extraction or following conversion of breech–transverse lie to cephalic presentation through external has been reported. Whenever the combination of fetal presentations is nonvertex–any other presentation, the preferred mode of delivery is by a cesarean section. The interval between the births of the twins is not considered critical. It is important to closely monitor the FHR of the second of twins. In practice, after the birth of the first twin, it is customary to wait for half an hour, thereafter inducing pains with amniotomy for the second of twins, followed by oxytocin stimulation of uterine activity.

Perinatal mortality is 5–10-fold higher in twin gestation as compared to singleton births. It is higher in monozygotic pregnancies, premature births, IUGR pregnancies, and because of higher risks of fetal distress, hypoxia, metabolic disturbances, fetal malformations, and birth injuries. Studies from India reported higher perinatal mortality in twin gestations as compared to singleton births. From Jaipur, Agarwal et al. (2000) reported the perinatal mortality of 291/1000 births in twin pregnancy as compared to 90.5/1000 singleton births. Shinde and Pati (Ambejogai; 2000) reported a perinatal mortality of 105/1000 in twins as against 82.9 in singleton births. Pandole et al. (Mumbai; 2003) reported that 63.3% of these neonates weighed < 2.0 kg. In her study the perinatal mortality for the birth of second of twins (276/1000) was decidedly higher than in the first twin (138.5/1000 births).

Triplet pregnancies are uncommon. However, their numbers have increased following assisted reproductive technology. Many obstetricians are of the opinion that fetal reduction should not be advised to women with triplets. Kore et al. (2002) from Mumbai reported an incidence of triplets in 1:2660 pregnancies. The incidence of cesarean section was 80%, and the total perinatal loss was 33%. Pathania et al. (2001) from Shimla reported an unusual case of triplets in which there was a combination of conjoint twins and a single baby—a very rare occurrence indeed.

IMPORTANT POINTS

1. Approximately two-thirds of all twin pregnancies are dizygotic and one-third are monozygotic. All dizygotic gestations are Di–Di. In about 30% of monozygotic twins the zygotic division occurs within 72 hours of fertilization and the placenta will also be Di–Di. In approximately 65% of monochorionic twins the placenta will be Mo–Di and in approximately 5% will be Mo–Mo.
2. The diagnosis of chorionicity and amnionicity is one important objective of ultrasound examination of twin pregnancies. In monochorionic placentation the thickness of the amniotic membrane is less than 2 mm and they show only two layers. In dichorionic placentation thickness of the membranes is more than 2 mm and three or more layers are seen. A peak or lambda sign is usually seen in the intertwin membrane insertion in dichorionic twins.
3. The main causes of maternal morbidity in multifetal pregnancies are preeclampsia, sepsis, and postpartum bleeding.
4. The main causes of perinatal mortality in multifetal pregnancies are prematurity, TTT syndrome, congenital defects, placental insufficiency, and traumatic delivery.
5. The main causes of discordant twin growth are unequal placental mass, genetic syndromes, and TTT syndrome.
6. The neonatal criteria most commonly accepted for the diagnosis of TTT are a difference in hematocrit of 20% or more or hemoglobin of 5 g/dl or more, a difference in birth weight of 20% or more, and signs of fetal hydrops in one or both twins.
7. After the death of a monochorionic twin, mortality of the other twin occurs in almost 50% of the cases and when the second twin survives that is affected by neurologic morbidity in 30% of the cases. The typical neurologic lesion is multicystic encephalomalacia.
8. Congenital malformations occur in approximately 17% of twins. Malformations among monochorionic twins are frequently multiple or lethal while those occurring in dichorionic twins are mostly minor.
9. Several studies indicate that there is a difference in birth weight between twins and singletons of the same gestational age after 36 weeks.
10. Frequent office visits, ultrasound examinations every 3–4 weeks, frequent vaginal examinations after 20 weeks for cervical assessment, and fetal surveillance with NST and fluid volume after 36 weeks are important components of the antepartum care of patients with twins.
11. If the first twin is in breech presentation or transverse lie it is better to deliver by cesarean section. Cephalic–noncephalic presentations may be managed by cesarean section or by vaginal delivery of the first twin followed by external version or vaginal breech delivery of the second twin.
12. As long as FHR monitoring remains normal, there is no reason to shorten the delivery interval between twins.
13. Fetal and neonatal morbidity and mortality are high in patients with more than two fetuses. Preterm delivery affects more than 85% and the neonatal death rate is approximately 20%.

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13

Bleeding During Pregnancy

CHAPTER OUTLINE

Vaginal bleeding at any stage of pregnancy is an alarming event that generates significant concerns in both patient and doctor. Vaginal bleeding may be categorized by the gestational age—at the time of its occurrence—into first, second, and third trimester and postpartum bleeding. Although there is some overlap between the different causes of bleeding in each trimester of pregnancy, the classification is useful in practice. The main causes of vaginal bleeding in the first trimester of pregnancy are spontaneous abortion of anembryonic pregnancies, subchorionic bleeding, and embryonic or fetal death. In the second trimester the most common causes are embryonic or fetal deaths, subchorionic bleeding, and intrauterine infection presenting as incompetent cervix. In the third trimester the most common causes are abruptio placentae, placenta previa, and marginal placental separation. The main causes of postpartum bleeding are uterine atony and retention of products of conception. This chapter analyzes these frequent causes of bleeding during pregnancy.

FIRST TRIMESTER BLEEDING

The most common reason for vaginal bleeding during the first trimester of pregnancy is spontaneous abortion secondary to embryonic or fetal death or anembryonic pregnancy. A spontaneous abortion, also called miscarriage, is defined as the unintentional termination of pregnancy before 20 weeks of gestation or when the birth weight is less than 500 g. This means that spontaneous abortion may occur in both the first and the second trimesters of pregnancy. This definition is different from the legal definition used for intentional abortion which is the interruption of pregnancy before viability (the time when the fetus is sufficiently developed to survive outside of the uterus) with the purpose of achieving fetal death. The gestational age when fetal viability has been reached is legally defined as 24 weeks. This means that when a pregnancy is terminated intentionally between 20 and 24 weeks it is an abortion. However, if a pregnancy is spontaneously lost between 20 and 24 weeks it is not an abortion, it is a preterm delivery.

The introduction of ultrasound into obstetrical practice has been extremely useful in providing a better understanding of the etiology of first trimester spontaneous abortion and a basis for its clinical classification and management. Ultrasound allows the differentiation between spontaneous abortions secondary to a severe developmental abnormality, the so-called "blighted ovum" or "anembryonic pregnancies" and spontaneous abortions secondary to embryonic or fetal death. In a recent study of 652 women with first trimester abortions, 58% had embryonic or fetal death and 36% anembryonic pregnancies (Zhang et al., 2005). These are two different situations with different etiologies and requiring different approaches to their diagnosis and prevention. Therefore, according to the clinical and ultrasound findings it is possible to separate first trimester spontaneous abortions into two groups:

1. *Anembryonic pregnancies or blighted ova,* which are abortions usually occurring before 12 weeks in which fetal development is not observed by ultrasound examination and fetal tissue is not present or has only rudimentary development.
2. *Spontaneous abortions secondary to embryonic or fetal death,* which is the most common presentation of spontaneous abortions occurring after 12 weeks. In these cases, normal fetal/embryonic development is or has been observed by ultrasound examination and a fetus/embryo is found on examination of the products of conception.

The differentiation between these two types of abortions is important. The lack of development of fetal structures defines a subset of abortions of genetic origin. In contrast, the early spontaneous loss of a fetus that is alive or was alive is a complex phenomenon with multiple etiologies. Therefore, anembryonic pregnancies do not require extensive work-up while women aborting cytogenetically normal fetuses need an extensive search for nongenetic factors responsible for the pregnancy loss.

Gestational age is a useful but not a definite parameter to differentiate between these two types of spontaneous abortions. The definite differentiation between these two types of abortion is by ultrasound examination or by examination of the products of conception. It is exceptional that a blighted ovum does not present symptoms before 12 weeks and when this happens there is usually an error in the estimation of the gestational age of the pregnancy. The opposite is not true, and occasionally an abortion with an adequately developed fetus/embryo—a characteristic feature of second trimester abortions—occurs before 12 weeks. With the understanding that there is an overlap in the gestational age when they occur, we have chosen to describe spontaneous abortion secondary to anembryonic pregnancy under first trimester bleeding and spontaneous abortion secondary to embryonic or fetal death under second trimester bleeding.

First Trimester Spontaneous Abortion

Approximately 80% of all spontaneous abortions occurring during the first 12 weeks of gestation are the result of early developmental abnormalities, causing lack of or limited embryonic development. This situation has been recognized for many years as "blighted ovum" but more recently the term "anembryonic pregnancy" has become more commonly used. Characteristically, women with anembryonic pregnancies present to the emergency room with vaginal bleeding during the first trimester of pregnancy. In other occasions, the discovery of the blighted ovum is made in asymptomatic women in the course of an early ultrasound examination.

Etiology

Between 60 and 80% of blighted ova will reveal an abnormal chromosome complement. In the other 20–40% there is not usually a recognizable cause for the severe developmental defect. The chromosomal abnormalities most frequently found in abortions (Eiben et al., 1990) are as follows:

1. *Autosomal trisomy.* This nondisjunctional defect is found in approximately 60% of blighted ova with abnormal karyotypes. The trisomy predominantly affects chromosomes 16, 21, and 22, although it may affect any other of the autosomes. Trisomy 16 is most frequently found in abortus material and in these cases the sac is completely empty.
2 *Triploidy.* This defect, which results in a mean chromosomal count of 69, occurs in 15–20% of all abortions with abnormal chromosomes. In many cases the sac is empty, but if a fetus is present, it has obvious abnormalities (omphalocele, syndactyly, cleft lip and palate, etc.). In about 50% of the cases, hydropic degeneration of the placenta is present. In humans, the most common reason for triploidy is double fertilization of a single ovum. In triploidy without molar degeneration, the extra chromosomal set is probably maternal.
3 *Monosomy X.* About 25% of all abortions with chromosomal abnormalities have a karyotype 45,X. About 1 out of every 15 fetuses with 45,X karyotype will not be aborted and will be identified at birth as Turner's syndrome. Some of the abortion specimens with 45,X karyotypes are sacs containing a small umbilical cord that inserts into an amorphous mass of embryonic tissue. Monosomy X may be the result of the loss of an X chromosome at the time of fertilization or it may be the result of nondisjunction during either male or female meiosis.
4 *Tetraploidy.* This anomaly, resulting in a mean chromosomal count of 92, is found in 3–6% of blighted

ova with abnormal chromosomes. In these cases, abortions usually occur very early in pregnancy and the embryo cannot be recognized in the specimen. This condition probably results from a failure of cytoplasmic division following a chromosome division in the germinal cells.

5. *Structural rearrangement of the chromosomes*. This subset consists of unbalanced translocations and inversions, and accounts for 3–5% of abortions with abnormal chromosomes. Couples that have abortions with structural rearrangements of the chromosomes should have karyotype analysis because 5% will be carriers of the rearranged chromosome. Couples having abortions with numerical abnormalities of the chromosomes (1–4 above) usually have normal karyotypes.

Clinical and laboratory findings

The most common symptom of women with anembryonic pregnancies is vaginal bleeding in the first trimester of pregnancy. There are other conditions that cause first trimester vaginal bleeding but the obstetrician should always assume that a threatened abortion is present and carefully assess all patients with this complaint. In most patients, there is an interval of several days between the onset of vaginal bleeding and the actual miscarriage. In some, the symptoms progress rapidly and there is little time for diagnostic procedures. Because it is impossible to know in advance if there is sufficient time for testing, the obstetrician should examine patients with first trimester bleeding within a reasonable time period.

Important information to be obtained during the initial assessment is the gestational age of the pregnancy. A bimanual examination of the uterus is useful to determine if the uterine size is consistent with the clinical dating. Unfortunately, assessment of the uterine size is not a reliable indicator of gestational age. The presence of a tender adnexal mass should raise the suspicion of an ectopic pregnancy. A speculum examination is mandatory to rule out cervical or vaginal lesions that occasionally are the cause of the vaginal bleeding. Also, the speculum examination may show that the external cervical os is open and there are products of conception in the cervical opening indicating that the abortion is unavoidable.

Determination of serum (human chorionic gonadotropin) HCG and progesterone concentration is particularly useful in patients with vaginal bleeding at less than 6 weeks. It is possible to see a gestational sac inside of the uterus using transvaginal ultrasound when the quantitative HCG concentration is 1000 mIU/ml or more. To visualize an intrauterine gestational sac using transabdominal ultrasound the serum HCG concentration must be approximately 3000 mIU/ml. Patients with first trimester bleeding and serum HCG values below these critical values should have another quantitative HCG evaluation 3 days after the initial one. If there is a doubling of the HCG concentration, the pregnancy is likely intrauterine and there is a high probability of a normal outcome. If the HCG concentration does not double and the initial progesterone concentration is less than 15 ng/ml, the pregnancy is abnormal, either a blighted ovum or an ectopic gestation. The predictive accuracy of low values for HCG and progesterone is 90–95% and most patients exhibiting this combination have spontaneous abortions or tubal pregnancies. The prediction of a normal outcome based on normal hormone concentrations early in gestation is accurate in approximately 80% of the cases.

Ultrasound assessment

Vaginal ultrasound examination may produce varied findings in women with blighted ova. The most common are the following:

1. There are no identifiable products of conception inside the uterus. The possibilities in this case are ectopic pregnancy, complete abortion, or bleeding before 4 weeks of gestation. Intelligent use of clinical information, repeated ultrasound examination, histopathology of endometrial sample, and serum levels of HCG and progesterone will permit differentiating between these diagnostic possibilities.
2. There is a gestational sac, usually larger than expected for the gestational age, without detectable embryo. The yolk sac may or may not be present and when it is present usually is abnormally large. These findings are characteristic of blighted ovum.
3. There is a gestational sac, yolk sac, and a fetal pole but no detectable fetal heart activity. This is also characteristic of blighted ova, and the presence of the fetal pole should not deviate the clinician from this diagnosis. In blighted ova the embryonic development may be interrupted at different stages, resulting in varied degrees of fetal disorganization. In these cases the ultrasound examinations show a fetal pole without heart activity.

Management

Patients with first trimester vaginal bleeding and reassuring ultrasound and hormonal findings should be told that the possibility of spontaneous abortion is small (2.5–3.2%) and that most likely the outcome of the pregnancy will be normal. Bed rest is indicated as long as bleeding persists and progesterone supplementation may be indicated if the serum value is less than 15 ng/ml.

Women with blighted ova need evacuation of the uterus. Traditionally, this was accomplished by suction curettage of the uterus under paracervical block or under general anesthesia. In the last few years medical evacuation of the uterus with misoprostol is being used increasingly and is rapidly replacing the surgical approach (Zhang et al., 2005). Misoprostol may be used orally or intravaginally. For incomplete abortions the oral dose is 400 µg every 4 hours for three doses or misoprostol vaginally, 800 µg in a single dose. Both treatments are > 80% successful within 48 hours. For women with missed abortions the vaginal dose may be repeated in 24–48 hours, if necessary. Approximately 1–5% of women undergoing a medical abortion will experience vaginal bleeding large enough to require intervention with D&C.

It is advisable to have genetic studies of the products of conception in women with blighted ova. This information is important because when the karyotype of the blighted ovum reveals an autosomic trisomy, the patient will be at higher than usual risk for another trisomic pregnancy and genetic screening should be performed in the following pregnancies. When the karyotype of the blighted ovum reveals structural rearrangement of the chromosomes, the mother and the father should have chromosome analysis to rule out the possibility that one or both of them are carriers of a translocation or inversion.

With respect to future pregnancies the risk of a recurrent blighted ovum does not increase above the background frequency following one abortion. After two consecutive first trimester anembryonic abortions the risk increases to about 20%. After three abortions the risk of a similar event in the following pregnancy increases to 35%. There is a strong tendency to have the same type of abortion in subsequent pregnancies. If a previous spontaneous abortion was a blighted ovum, a subsequent abortion has a 70% chance of being another blighted ovum. If an apparently normal fetus was seen in the products of conception, the probability that the following abortion will be similar is 85% (Warburton et al., 1987).

SECOND TRIMESTER BLEEDING

Under this denomination we include all patients presenting with vaginal bleeding after 12 weeks of gestation. Uterine contractions are also a frequent presenting symptom. In addition to the obvious difference in gestational age, these patients are different from those with first trimester bleeding in that ultrasound examination shows an embryo or fetus with or without heart activity. Many women presenting with bleeding and a fetal demise had an alive embryo/fetus documented by a previous ultrasound examination or by auscultation of fetal heart sounds using Doppler devices. A large number of these cases will end with the expulsion of the products of conception and therefore the terms "second trimester abortion" and "second trimester bleeding" are used in this chapter to denominate the same clinical entity.

Etiology

The most common causes of spontaneous abortion in the second trimester are genetic abnormalities, antiphospholipid antibody syndrome, maternal thrombophilia, subchorionic bleeding, and incompetent cervix secondary to intrauterine infection (Box 13-1). In addition, there is abundant literature regarding the association of second trimester abortions with anatomic abnormalities of the uterus, infections, endocrine disorders, immunological and environmental factors but, as we will see later, there is not a well-established cause–effect relationship for several of these associations.

BOX 13-1

Causes of second trimester abortion

- Genetic abnormalities
- Antiphospholipid antibodies
- Maternal thrombophilias
- Subchorionic bleeding
- Incompetent cervix
- Intrauterine infection
- Uterine synechia
- Mullerian abnormalities
- Abnormal placentation
- Autoimmune antibodies
- Alloimmune antibodies
- Progesterone deficiency
- Thyroid deficiency
- Maternal diabetes
- Polycystic ovarian syndrome

Genetic abnormalities

Chromosomal abnormalities are found in approximately 5–10% of second trimester abortions. In this case autosomal trisomies predominate but fetuses with triploidy and monosomy X are occasionally recognized.

In a significant number of second trimester abortions, extensive investigations, including karyotype, produce negative results. In these cases, it is suspected that a lethal mutation undetectable with the presently available methods of analysis is responsible for the problem. It is possible that lethal mutations similar to those found in experimental models may be present in man. Animal experiments using insertion and integration within the genome of a DNA fragment which causes disruption of the function of one or several genes have provided evidence indicating that inactivation of the genes containing the information for collagen synthesis causes an arrest in development and embryonic death. Fetal death may also be secondary to

mutations affecting genes that control the expression of other genes at the transcriptional level (homeobox genes) or to mutations that cause excessive concentration of products toxic to the embryonic cells.

Antiphospholipid antibody syndrome

The possibility of an immunologic rejection of the conceptus is frequently used as an explanation for recurrent second trimester abortions. However, few patients fulfill rigorous criteria indicating that their pregnancy losses are the result of an immunologic process. The best known immunologic cause of second trimester losses is the antiphospholipid antibody syndrome. Typically, women with anticardiolipin antibodies have a history of alive fetus documented by ultrasound or by Doppler before demise or abortion occurs. The majority of the pregnancy losses occur between 12 and 18 weeks. As many as 28% of these patients have a history of one or more episodes of venous or arterial thrombosis.

In 1957 Laurell and Nilsson described a patient with five prior intrauterine deaths who had a biologically false positive syphilis test (FPST) and an anticoagulant antibody. Later it was found that the circulating anticoagulant and the molecule responsible for the false positive syphilis serology were antiphospholipid antibodies. In the last 25 years numerous investigators have further described the association between antibodies that bind phospholipid molecules and repetitive pregnancy losses. Antiphospholipid antibodies account for 3–5% of patients with second trimester repetitive pregnancy losses. The frequency of fetal death and recurrent abortion in untreated patients with antiphospholipid antibodies is greater than 90%.

The diagnosis of antiphospholipid antibody syndrome has two components. The first is an obstetrical history with poor outcomes and the second is laboratory criteria. With respect to pregnancy outcomes it is necessary to have a history of one or more unexplained pregnancy losses after 10 weeks of gestation or a history of preterm birth at less than 34 weeks due to preeclampsia or uteroplacental insufficiency. The laboratory criteria are the presence of anticardiolipin IgG or IgM in medium or high titers obtained twice, at least 6 weeks apart or a positive lupus anticoagulant (LAC) obtained twice, at least 6 weeks apart.

There are several antiphospholipid antibodies. The most relevant to the obstetrician are the LAC, the ACA (anticardiolipin antibody), and the antibody that causes FPST. The significance of antibodies against phosphatidyl-serine, phosphatidyl-ethanolamine, and phosphatidyl-inositol is unknown at this time.

The name lupus anticoagulant was adopted because this antibody was found first in patients with lupus erythematosus and acted as an anticoagulant by prolonging the laboratory determination of the partial thromboplastin time (PTT). This name was a poor choice because LAC is present in many patients who do not have lupus and because the antibody is responsible for thrombosis rather than anticoagulation. Typically, patients with LAC have a prolonged PTT. When this occurs, most laboratories repeat the test after mixing the patient plasma with an equal volume of normal plasma. If the normal plasma does not correct the PTT within 4 seconds of the control value an antiphospholipid antibody is likely present. Unfortunately, a normal PTT does not exclude the possibility of LAC, and if the clinical suspicion is strong and the PTT is normal a diluted Russell viper venom time test should be performed.

The ACA is the antiphospholipid antibody most commonly found in patients with repetitive second trimester pregnancy losses. The ACA is found in 90% of patients with LAC, but the majority of patients with positive ACA do not have LAC. ACA is measured in the laboratory by means of an ELISA test that measures the concentration of IgG, IgM, and IgA ACA antibodies. The clinical significance of the IgA antibodies is unknown. A serum IgG or IgM antibody titer greater than 20 units is significant.

The less common antiphospholipid antibody is that which causes a false positive syphilis serology. FPST and ACA are antibodies against cardiolipin, but they are not the same antibody. Some patients with FPST do not have ACA and most patients with positive ACA have nonreactive syphilis serology.

The presence of any or several of the three antiphospholipid antibodies is associated with recurrent early pregnancy losses, episodes of venous and arterial thrombosis, severe preeclampsia of early onset, severe IUGR (intrauterine growth restriction), and chorea gravidarum. Other associations are a history of ischemic stroke, transient ischemic episodes, and migraine headaches. Patients with antiphospholipid antibodies may develop catastrophic antiphospholipid syndrome, which is a life-threatening situation characterized by rapid development of multiple organ failure and histologic evidence of multiple small vessel occlusion. Pulmonary infiltrates, fever, and cardiac symptoms may appear following delivery and have life-threatening severity. Pulmonary complications rarely occur before delivery.

The antiphospholipid antibody syndrome is the best known acquired cause of thrombophilia. Fetal death in these patients is caused by extensive thrombosis of the placental vessels and the placenta is usually smaller than expected for the gestational age. On microscopic examination, the spiral arteries show absence of physiologic adaptative changes and contain thrombi, many of which are recanalized indicating a chronic process. The placenta show infarcts, frequently extensive, and accelerated maturity of the chorionic villi. Most of the effects of antiphospholipid

antibodies are explained by their interaction with beta-2 glycoprotein—a natural anticoagulant which inhibits the conversion of prothrombin to thrombin—platelet aggregation, and contact activation of the coagulation cascade. The antiphospholipid antibody combines with beta-2 glycoprotein, causing platelet aggregation and activation of the coagulation cascade with formation of thrombi in the utero-placental and fetoplacental circulations (Gharavi et al., 2001).

Treatment of antiphospholipid antibody syndrome consists of prophylactic heparinization and low-dose aspirin. Exceptionally it is necessary to use therapeutic heparinization, steroids, or immunosuppressant agents. For unfractionated heparin the initial dose is 5000 units subcutaneously twice daily. This dose may be increased to 7500 units twice a day in the second trimester and 10,000 units twice a day in the third trimester of pregnancy. This dose of heparin does not affect the PTT and does not require monitoring of the level of anticoagulation. Another choice is low molecular weight heparin, 40 mg subcutaneously twice daily. The usual dose of aspirin is 81 mg orally daily.

Maternal thrombophilia

Congenital abnormalities of the hemostatic system are frequently implicated as a cause of spontaneous abortion, and several studies have indicated a higher risk for pregnancy loss in affected individuals in the second rather than in the first trimester. Evidence suggestive of this etiology exists for women heterozygous or homozygous for the factor V Leiden (FVL) mutation, increased activated protein C (APC) resistance, prothrombin promoter mutation, hyperhomocysteinemia, and protein S deficiency. The possible role of other hemostatic abnormalities in the etiology of early pregnancy loss is weak or nonexistent. The interested reader will find an excellent review of this subject in the article by Kujovich (2004).

The FVL is an autosomal dominant point mutation in the factor V gene, resulting in a single amino acid change in factor V that alters a binding–cleavage site for APC which is a natural inhibitor of factor V. This results in impaired inactivation of factor V that causes increased thrombin generation and a prothrombotic state. The heterozygous mutation is found in 5–8% of the Caucasian population of USA and is associated with a four- to eightfold increase in the risk of thrombotic events. The risk of thrombosis is much higher, 80-fold increased, in homozygous individuals.

The presence of FVL mutation is associated with increased risk of unexplained recurrent pregnancy loss. Several case-control studies, some retrospective cohort studies, and a meta-analysis of 3000 cases (Rey et al., 2003) found an association between FVL mutation and both early first trimester (OR 2.1) and late (OR 7.8) recurrent pregnancy loss.

The FVL mutation is not the only cause of APC resistance. There are other cleavage points in the amino acid structure of factor V that may be rendered nonfunctional by other mutations or by specific inhibitors. The evidence suggests that APC resistance caused by mutations different from FVL is also associated with second trimester pregnancy loss, and a meta-analysis found a three- to fourfold increase in first trimester abortion frequency in women with increased resistance to APC (Rey et al., 2003).

A recent prospective study contradicts the evidence suggesting an association between FVL and adverse pregnancy outcome (Dizon-Townson et al., 2005). These investigators recruited 4485 pregnant women before 14 weeks of gestation and tested them, as well as the resultant conceptus, for FVL mutation and the frequency of adverse outcomes were compared between FVL carriers and noncarriers. No thromboembolic events occurred among 134 FVL mutation carriers and the presence of this mutation was not associated with increased pregnancy loss, preeclampsia, placental abruption, or small for gestational age infants. Their conclusion was that screening pregnant women for FVL and other thrombophilias in the absence of a prior episode of thromboembolism and prophylactic anticoagulation treatment of carriers is not justified. We believe that the conclusions of this study are not supported by the data. The absence of thromboembolic events and poor pregnancy outcome in 134 carriers of FVL mutation is not conclusive due to the small sample size. This study found an incidence of thromboembolic disease of 0.84 per 1000 in noncarriers, and therefore more than 77,000 women would need to be studied to evaluate a potential fourfold increased risk in carriers of FVL.

A thrombophilic mutation which has been associated with recurrent early pregnancy loss is the single nucleotide substitution of guanine for adenosine in position 20210 of the gene coding for prothrombin. This mutation occurs in the promoter region of the gene and results in increased production of prothrombin and a two- to fourfold increase in the risk of venous thrombosis. Studies have shown a frequency of the abnormal gene in 4–9% of women with recurrent pregnancy loss as compared with a frequency of 1–2% in the overall population. Other studies have shown no association of the abnormal gene with pregnancy loss. A meta-analysis that included more than 2000 women found a two- to threefold increase in recurrent pregnancy losses early in the first trimester and in the second trimester (Rey et al., 2003). The same meta-analysis found a 15-fold increase in overall risk of pregnancy loss in women with protein S deficiency.

A frequently found thrombophilic mutation is the C677T in the gene coding for the enzyme methylene

tetrahydrofolate reductase (MTHFR). The resulting amino acid substitution in the enzyme produces a thermolabile variant that is not effective in the remethylation of homocysteine to methionine. The consequence is an increased concentration of homocysteine, which is an independent risk factor for thromboembolic disease and pregnancy loss (Nelen et al., 2000; Kumar et al., 2003). Individuals heterozygous for the C677T MTHFR mutation usually have normal or mildly elevated serum homocysteine. Therefore, the heterozygous state, which occurs in 40% of the population, is not associated with arterial or venous thrombosis or adverse pregnancy outcomes. Similarly, the majority of studies, including meta-analysis, have found no association between homozygosity for the C677T MTHFR mutation and increased risk of pregnancy loss or placental vasculopathy.

Subchorionic bleeding

A relatively frequent cause of first and second trimester vaginal bleeding is subchorionic bleeding. Patients with this condition present with first and second trimester vaginal bleeding of varying severity. The bleeding occurs between the chorion and the decidua, and in many cases is detectable by ultrasound examination. Usually patients have minimal or no cramping. Ultrasound shows a normal, active fetus and a hypoechoic area between the chorion and the uterine wall. The membrane separating the amniotic cavity from the hematoma is relatively thick and has limited mobility.

In the majority of these patients, bleeding decreases dramatically after the initial episode and stops spontaneously a few days after its onset. However, some patients continue bleeding in small amounts for several weeks and a few abort or become infected. Some of these patients show discoloration with blood pigments of the amniotic fluid when they have genetic amniocentesis in the second trimester. Many of them are asymptomatic and the subchorionic hematoma is an incidental finding in the course of an ultrasound examination.

Subchorionic bleeding has a guarded prognosis that is worse when it occurs before 9 weeks (Johns et al., 2003; Maso et al., 2005). The main complications are spontaneous abortion, premature rupture of the membranes, premature labor, placental abruption, and fetal growth restriction (Ball et al., 1996; Nagy et al., 2003). There are no well-defined indicators of the prognosis for the pregnancy, but persistent and recurrent bleeding is a poor sign. The size of the hematoma and the severity of the initial bleeding episode have little prognostic value. Maternal serum alpha-fetoprotein may increase as a consequence of the transfer of fetal red cells in the maternal circulation, causing a false increase in the risk for open neural tube defects as determined by the triple or quad screening.

The treatment of subchorionic bleeding is expectancy. There are no therapeutic modalities found to have a beneficial effect in these cases.

Incompetent cervix

Incompetent cervix is a well-known cause of second trimester spontaneous abortion. The main clinical feature of this condition is painless cervical dilatation. Typically, the main complaint of these patients is a sensation of vaginal pressure. Speculum examination reveals bulging membranes, as well as various degrees of cervical dilatation. Most patients also notice the onset of or an increase in mucous vaginal discharge for a few days before the acute onset of symptoms. Cervical incompetence may be caused by an intrinsic or primary defect in the anatomy of quality of the cervix such as it happens in women with extensive conization or LEEP (loop electrosurgical excision procedure) or in women with Marfan syndrome. However, the majority of women with a clinical picture of incompetent cervix have intrauterine infection, causing early premature labor. A cervical cerclage operation will only benefit women with intrinsic or primary cervical conditions. The interested reader will find more information about this subject in Chapter 10 of this book.

Infection

Overt intrauterine infection is not a frequent cause of second trimester abortion. Most commonly the infection is subclinical and presents with the clinical picture of incompetent cervix. Intrauterine infections are usually ascending from the vagina. In a minority of patients the infection is hematogenous and varicella, parvovirus, rubella, toxoplasmosis, herpes simplex, syphilis, and listeria are an unexpected finding on fetal autopsy or in histologic or bacteriologic examination of the aborted tissues.

Patients with ascending infection usually develop temperature elevation and uterine cramps after 14 weeks. This is followed rather quickly by the onset of uterine contractions or by rupture of the membranes. At the time of arrival to the hospital, the cervix is usually dilated 3 cm or more and the bag of waters is protruding through the cervix. The erroneous diagnosis of cervical incompetence is frequently made in these cases. Histologic examination of the placenta shows severe chorioamnionitis. The bacteria isolated from the placenta are a mixture of anaerobic and aerobic organisms with predominance of group B streptococci and *Escherichia coli*. Ascending infections frequently recur in subsequent pregnancies, suggesting the presence of a maternal immunologic deficiency or genetic predisposition.

Mycoplasma hominis and *Ureaplasma urealyticum* are frequently found in cultures of aborted products of

conception. Also, there are uncontrolled studies suggesting that diagnosis and treatment of mycoplasma infection before pregnancy prevents recurrent abortion. Despite these observations, the evidence linking mycoplasma infection to early pregnancy loss is unconvincing. Even more tenuous is the possibility of a causal relationship between early pregnancy loss and chlamydia infection.

Uterine synechia

The association between uterine synechiae and early pregnancy loss has been known since the original work of Asherman in 1947. Uterine synechiae are band-like structures between the walls of the uterus, causing minimal to almost complete obliteration of the uterine cavity. Histologically these bands are made of fibrous tissue, myometrium, and endometrium. The endometrium around these adhesions is usually atrophic, with distorted gland openings.

In the majority of cases synechiae are the result of intrauterine infection combined with surgical trauma following the retention of products of conception after abortion or delivery. Schenker and Margalioth (1982) found that intrauterine adhesions were associated with postabortal and postpartum curettage in 66 and 22% of 1856 cases, respectively. In the same study, it was noticed that 14% of patients with synechiae presented with a history of multiple pregnancy losses.

The diagnosis of uterine synechiae is usually made by hysterosalpingogram or by direct observation with the hysteroscope. Treatment requires surgical division of the fibrous bands, placement of an intrauterine device to avoid contact between the sectioned ends of the adhesions, and treatment with estrogen to stimulate endometrial growth.

There are no randomized, controlled studies comparing the efficacy of hysteroscopic-guided division or blind ablation of the uterine bands in preventing abortion. However, most studies using historical controls suggest that there is a substantial reduction in the number of spontaneous abortions following treatment.

Mullerian abnormalities

Anatomic abnormalities of the uterus are associated with approximately 10–15% of second trimester abortions with adequate fetal development. Septate uterus and bicornuate uterus are examples of Mullerian fusion abnormalities associated with early pregnancy loss. Some other abnormalities such as double uterus and unicornuate uterus are more commonly manifested as preterm labor, characteristically occurring later with each successive pregnancy. It has been suggested that septate and bicornuate uteri are associated with early pregnancy losses because of inadequate blood supply to the conceptus when the pregnancy is implanted in the relatively avascular septum. Another mechanism of pregnancy loss in these patients is incompetent cervix, an abnormality which is frequently present in patients with abnormal uterine anatomy.

Abnormal placentation

During normal placentation the spiral arteries undergo adaptative changes characterized by loss of the normal musculoelastic arterial wall and replacement by fibrinoid material containing trophoblastic cells. These changes transform the narrow, thick-walled arteries into widely open, tortuous vascular channels that provide the necessary blood flow for the developing conceptus. The lack of these changes has been named abnormal placentation and is a feature shared by patients with preeclampsia, severe growth restriction, preterm labor, and also by some patients with early fetal deaths. Abnormal placentation may occur in fetuses with normal or abnormal chromosomes. Patients with recurrent abortions due to abnormal placentation who are able to prolong a pregnancy beyond the second trimester remain at high risk for preeclampsia, preterm labor, and fetal growth restriction.

There is evidence (Leible et al., 1998; Nakatsuka et al., 2003) suggesting that transvaginal Doppler velocimetry may be useful in identifying impaired uteroplacental perfusion which may result in pregnancy loss. The vascular impedance to flow is greater in women affected with thrombophilic conditions or in those who are destined to have early pregnancy loss. Unfortunately, the overlap between women with normal outcomes and those with abnormal placentation is significant, making it difficult to use the test in practice.

Autoimmune antibodies

Investigators have reported a significantly greater prevalence of low-titer antinuclear antibodies (ANA) in patients with unexplained fetal losses before viability than in normal controls. This high frequency of positive ANA titers also occurs in patients with fetal losses due to nonimmunologic factors such as uterine anatomic malformations and luteal phase defect. These findings are not universally accepted and there are studies showing no differences in the prevalence of ANA and anti-DNA antibodies in habitual aborters versus normal control subjects. In these patients the ANA titer is between 1:20 and 1:160 and the fluorescent pattern is usually speckled or homogeneous. Other than the abnormal serology and the history of prior pregnancy losses, these women have no signs or symptoms and do not fulfill established criteria for the diagnosis of lupus.

A positive ANA titer in a patient with prior early pregnancy losses indicates the need for further investigation of

autoimmune factors as well as a search for LAC, ACA, FPST, and anti-DNA antibodies. If there is conclusive serologic evidence of autoimmunity, adequate treatment may be instituted in an effort to prevent further losses. Therapeutic interventions to modulate the immunologic system are not justified in the absence of clear evidence that autoimmunity is present.

Progesterone deficiency

Progesterone deficiency has been an obvious candidate as an etiologic factor of early pregnancy loss because of its well-known effect in maintaining uterine quiescence. Unfortunately, progesterone deficiency is overdiagnosed and progesterone supplementation is overused.

Most of the evidence incriminating progesterone deficiency in early pregnancy loss comes from studies demonstrating that luteal phase deficiency occurs more frequently in patients with recurrent abortions than in controls. A rigorous diagnosis of corpus luteum defect requires histologic confirmation of an endometrium out of phase by 2 or more days during the secretory period of the menstrual cycle. Because endometrial biopsies are not obtained during pregnancy the only possible documentation of a corpus luteum deficiency during gestation is by measuring the serum progesterone concentration. However, progesterone production by the corpus luteum is pulsatile and characterized by marked fluctuations in serum levels. As a result, many studies have shown a poor correlation between serum progesterone levels and endometrial biopsy findings.

Another problem with the use of serum progesterone levels for the diagnosis of progesterone deficiency in patients with first trimester bleeding or with a history of multiple pregnancy losses is that patients with blighted ova have a low serum progesterone concentration. In these patients, low serum progesterone concentration is the result rather than the cause of the abortion. Because blighted ova are so frequent, patients with low progesterone concentrations in early pregnancy must be examined for blighted ova rather than being treated for corpus luteum deficiency.

Thyroid deficiency

Measurements of TSH (thyroid-stimulating hormone) and free thyroxine are almost routine in patients with a history of repeated pregnancy losses. However, it is rare that a deficiency or an excess of thyroid hormone is the etiology of early pregnancy loss. Patients with thyroid dysfunction are rather affected by preterm labor, usually occurring after 24 weeks.

Diabetes

A large multicenter, controlled study found that diabetics with both an elevated blood glucose and hemoglobin A1C in the first trimester have a significantly increased risk of spontaneous abortion while those with good metabolic control had a risk similar to that of controls. The frequency of fetal congenital abnormalities is larger in diabetics, but most of these abnormalities do not cause early fetal losses.

Polycystic ovary syndrome

Spontaneous abortions occur more frequently in patients with polycystic ovary syndrome than in normal controls. It seems that the elevated serum luteinizing hormone (LH) concentration that characterizes this syndrome has a deleterious effect on the corpus luteum. Pituitary suppression with gonadotropin-releasing agonists followed by HCG administration has been found to be useful in the prevention of this type of miscarriage.

Alloimmune antibodies

The possibility that some abortions result from maternal immunologic rejection of the fetal allograft is intellectually attractive. Unfortunately, it is difficult to define this mechanism of abortion in terms of its clinical and laboratory characteristics and, as a consequence, many patients are submitted to potentially dangerous, unproven, and expensive forms of therapy to modify their immune response.

One of the immunologic theories of abortion is that there are allotypic antigens in the trophoblast that may be characterized because they elicit the production of antibodies that are cytotoxic to peripheral blood leukocytes. Therefore these trophoblast antigens have been called trophoblast lymphocyte cross-reactive antigens, or TLX. In theory, if the embryo inherits from the father TLX antigens that do not exist in the mother, the mother's immune system will not recognize those antigens and will mount a protective response that will result in abortion. If the TLX antigens of the father and the mother are similar, the embryo will inherit paternal TLX antigens that will not stimulate the maternal immune system to produce the protective response and the pregnancy will not be aborted.

This theory further proposes that the similarity in TLX antigens between the parents can be demonstrated in some patients because they share several HLA antigens. However, HLA sharing is not a condition for TLX sharing. This theory is highly controversial and there is evidence indicating that HLA antigen sharing is no more common in patients with increased pregnancy losses than in normal controls. Also, there is not a clear definition of the nature of the embryonic protective factors that are produced during normal pregnancy and allegedly absent in couples sharing HLA antigens.

Another variation of the same theory is that the mother produces anti-paternal blocking antibodies that have complement-dependent or antibody-dependent lymphocytotoxicity. These antibodies would have a protective effect and avoid pregnancy rejection. Blocking antibodies can be detected by mixing lymphocytes of the mother and the father (MLC assay). Under normal circumstances the lymphocytes will recognize each other as foreign and this will lead to cell proliferation and increased uptake of radioactive DNA precursors by the nuclei of the dividing cells. This reaction will be absent or minimal in primary aborters who have never carried a pregnancy to term. Secondary aborters, those patients who have had one or more children before they began to have spontaneous abortions, have a high concentration of antipaternal blocking antibodies. These findings have been interpreted to indicate that the primary aborter does not mount a protective immunologic reaction to the pregnancy while the secondary aborter mounts an exaggerated response that is cytotoxic to the trophoblast. There are multiple problems with this theory. First, the MLC test is not reproducible and the results have wide variation. Second, the molecular mechanism of action of these anti-paternal blocking antibodies has not been elucidated. Finally, there is evidence that pregnancy and abortion may occur irrespective of the presence or absence of blocking antibodies.

Despite the lack of scientific and clinical data supporting the alloimmune theory of spontaneous abortion, immunotherapy with paternal or donor pool leukocytes is being promoted as a solution for this emotionally charged disorder. Most of the immunotherapy studies are affected by imprecise definition of the patients being studied, absence of histologic and genetic data to define the nature of prior pregnancy losses, and lack of randomized double blind trials. At this time, immunotherapy with leukocyte transfusion for repeated pregnancy losses is purely experimental, and potentially dangerous. Rigorous research in this area is urgently needed to clarify some of the conflicting information.

Clinical and Laboratory Assessment

The physical examination of women with second trimester vaginal bleeding may show a uterine size in agreement with the gestational age but it may be smaller than expected if a fetal demise happened several days before the examination or when early fetal growth restriction is present. Routine laboratory examinations are usually within normal limits unless bleeding has been severe. Speculum examination may reveal cervical changes consistent with advanced labor or with incompetent cervix. In a few cases the medical history and physical examination will help to focus on a few etiologic possibilities, but in many occasions the history and the physical examination are unrevealing and it is necessary to make extensive use of laboratory testing.

Histologic and microbiologic examination of the placenta is a fundamental part of the evaluation of these patients. The placenta will show extensive acute inflammatory changes in patients with ascending infection and typical lesions in patients with chronic villitis caused by cytomegalic virus infection. Examination of the decidual tissue attached to the placenta will reveal physiologic changes in the spiral arteries. Thrombosis of fetal and maternal vessels will be apparent in patients with thrombophilia, particularly antiphospholipid antibodies and FVL mutation. The placenta may also show changes suggestive of fetal chromosome abnormalities.

A carefully performed fetal autopsy, preferably by someone interested in fetal pathology, may also provide valuable information about the etiology of the late abortion. Anatomic abnormalities suggestive of a genetic syndrome or histologic changes suggestive of an infectious process may be discovered. Fetal blood should be obtained by cardiac puncture and used for karyotyping the fetus as well as for bacteriologic cultures if infection is suspected. A radiologic examination of the fetus may reveal skeletal abnormalities secondary to genetic syndromes.

A mother having a second trimester fetal demise or abortion should have a Kleihauer-Betke test to rule out the possibility of extensive fetal–maternal hemorrhage. The search for connective tissue disorders includes an ANA titer, ACA, and LAC. If any of these tests is positive, further laboratory analysis will be necessary. A TORCH titer may reveal unexpected elevation of CMV, herpes, or toxoplasma IgG antibodies, suggesting an intrauterine infection with one of these organisms.

Unless there is an obvious cause for the problem, all women having a second trimester abortion, particularly those with ascending infection and incompetent cervix, should have a hysterosalpingogram a few weeks after their miscarriage to rule out a uterine anatomic abnormality.

Ultrasound Assessment

After the physical, speculum, and laboratory examinations, the patient should have an ultrasound examination using abdominal and endovaginal transducers. The examination will be useful to document the presence of a fetus or embryo and may reveal or not the presence of anatomical abnormalities of the fetus, suggestive of a genetic etiology for the problem. Occasionally, a septated or bicornual uterus will be detected by the ultrasound examination. Vaginal ultrasound is also useful to assess cervical ripening and predict the length of the induction of labor.

Treatment

The treatment of second trimester abortions is evacuation of the uterus. The method of evacuation is important because examination of the products of conception in search for a cause of the second trimester pregnancy loss is of the greatest importance. The two methods of uterine evacuation are dilatation and evacuation (D&E) and mechanical cervical ripening with laminaria tents followed by intravaginal misoprostol. In the hands of an expert operator the D&E will provide an intact fetus and placenta that may be analyzed by the pathologist, the geneticist, and the microbiologist. When the experience of the operator in second trimester abortions is not extensive, the procedure will end with fragmented products of conception that preclude diagnosis of fetal anatomic abnormalities. In this situation it is preferable to dilate the cervix with laminaria and induce labor with a combination of vaginal and oral misoprostol. Two or more laminaria tents are inserted in the endocervical canal the day before induction of labor. The following day the laminaria tents are removed and 800 μg of misoprostol is placed in the posterior vaginal fornix and followed with 400 μg of oral misoprostol every 4 hours for three or four doses. Abortion usually occurs 6–8 hours after the initial dose.

THIRD TRIMESTER BLEEDING

Placenta Previa

Definition and classification

Traditionally, four types of placenta previa are recognized:

1. Total placenta previa, in which the internal cervical os is completely covered by the placenta
2. Partial placenta previa, in which the internal cervical os is partially covered by the placenta
3. Marginal placenta previa, in which the edge of the placenta does not cover but it is close to the internal cervical os
4. Low-lying placenta, in which the placental edge is not near the internal cervical os but it may be palpated by an examining finger introduced through the cervix

This definition of different types of placenta previa is based on the findings during vaginal examinations performed at the time of delivery. However, prenatal and intrapartum diagnosis and differentiation between partial, marginal, and low-lying placenta previa using digital examination is imprecise and obsolete. Today, with the use of endovaginal ultrasound, it is possible to precisely define the relation of the low border of the placenta to the internal cervical os. When endovaginal or abdominal ultrasound demonstrates that the placenta completely covers the internal cervical os and extends over both lips of the cervix the placenta is a total previa. When the placenta does not cover the internal os but its lower border is within 2.0 cm of the internal cervical os the placenta is a partial previa. When the placental border is more than 2.0 cm from the internal os the placenta is classified as low-lying. Studies have demonstrated that the cesarean section rate is 90% when the placental edge–internal os distance is less than 2.0 cm and 37% when it is over 2.0 cm (Bhide et al., 2003).

Incidence

The incidence of placenta previa varies greatly from one series to another, ranging from 1 out of 167 to 1 out of 327 pregnancies beyond 24 weeks of gestation. The frequencies of different types are, approximately, the following:

Total	23.0–31.3%
Partial	20.6–33.0%
Low-lying	37.0–54.9%

Etiology

No specific etiology has been found for placenta previa. However, a history of prior cesarean section and that of uterine curettage unrelated to pregnancy or following a spontaneous abortion are events significantly more frequent in patients with placenta previa than in normal controls. This suggests that damage to the endometrium or myometrium may be the initial event causing the necessary conditions for abnormal placental implantation.

Abnormal fetal presentations and congenital malformations are strongly associated with placenta previa. Breech, shoulder, and compound presentations may be found in up to 30% of the cases. In addition, when patients with placenta previa have fetuses in vertex presentation they are in persistent occiput posterior or transverse positions in as many as 15% of the cases. However, malpresentations are the result rather than the cause of low placental implantations.

Other associations include increasing maternal age, increasing parity, multiple gestations, smoking, cocaine use, male fetuses, anemia, short interpregnancy intervals, tumors distorting the contour of the uterus, and history of endometritis (Faiz and Ananth, 2003). Also, the patients who have placenta previa have 12 times the usual risk of having a placenta previa in a subsequent pregnancy.

The association of placenta previa with prior cesarean section is of particular importance in view of the increasing number of patients being delivered by cesarean. The probability of placenta previa is four times greater in

patients with prior cesareans than in patients without uterine scars (Nielsen et al., 1989). The probability of placenta accreta and the need for cesarean hysterectomy are also greater in patients with prior cesareans and placenta previa than in patients with placenta previa and no uterine scars (Clark et al., 1985). Most of these problems occur when the placenta is implanted in the anterior aspect of the uterus, over the cesarean section scar.

Clinical presentation

The most common symptom associated with placenta previa is painless vaginal bleeding in the third trimester of pregnancy. However, the initial bleeding episode may occur, and frequently occurs, during the second trimester. According to Crenshaw et al. (1973), approximately one-third of patients with placenta previa have their first bleeding episode before 30 weeks, a third from 30 to 35 weeks, and a third after 36 or more weeks. The mean gestational age at the first bleeding episode is 29.6 weeks. Although dramatic in nature, the initial bleeding episode is not usually associated with maternal mortality and completely stops a few hours after its onset.

The earlier in pregnancy the first bleeding occurs, the worse is the outcome of the pregnancy. In fact, the incidence of preterm delivery and the number of bleeding episodes, the severity of the bleeding, and the number of units of blood required for transfusion are higher for patients who begin bleeding before 28 weeks (McShane et al., 1985). The worst prognosis is for those patients with placenta previa who have had prior cesarean sections.

The severity of the bleeding and the need for blood transfusion usually increase with each bleeding episode. Fetal distress is unusual unless the hemorrhage is severe enough to cause maternal hypovolemic shock. Uterine contractions commonly occur in association with episodes of bleeding and may aggravate the bleeding tendency.

Major long-term complications of placenta previa are related to hemorrhagic shock and prolonged hypotension. Naturally, all complications inherent to cesarean section and emergency surgery pertain. Postpartum uterine atony and bleeding from the placenta implantation site are common events. Disseminated intravascular coagulation (DIC) rarely occurs in connection with placenta previa.

Diagnosis

The antepartum diagnosis of placenta previa is made by transabdominal and endovaginal ultrasound examination of the patient with vaginal bleeding. The diagnosis may be confirmed by direct visual observation at the time of operative delivery. The diagnosis of placenta previa should not be made by digital vaginal examination. In fact, there is no justification for digital vaginal examination in patients with painless vaginal bleeding. The prohibition of vaginal examinations in these patients may appear, particularly to an inexperienced resident, to be an unjustified holdover from less sophisticated days. However, even when the pelvic examination is cautious and gentle, 1 out of every 16 examinations produces a major hemorrhage and 1 out of every 25 examinations results in hypovolemic shock. Also, the accuracy of digital pelvic examination in the diagnosis of placenta previa is only 69%. A gentle speculum examination may be carried out, although the diagnostic yield is low. Speculum examination is not associated with increased risk of hemorrhage.

As mentioned before, placental localization with ultrasound has superseded all other methods for the diagnosis of placenta previa. The accuracy of transabdominal ultrasound in the diagnosis of placenta previa is excellent, with false positive and false negative rates of 7% and 8%, respectively. This accuracy is even higher when a vaginal probe is used for evaluation of the patient with vaginal bleeding during pregnancy (Farine et al., 1988). Endovaginal ultrasound (Figure 13-1) has a positive predictive value of 93.3% and a negative predictive value of 97.6% for the diagnosis of placenta previa. Both transabdominal and endovaginal ultrasound examinations are safe techniques with minimal or no risks for mother and fetus.

An understanding of the evolution of uterine anatomy throughout pregnancy is necessary for an appropriate interpretation of ultrasound findings with respect to the placental localization. At 20 weeks of gestation the length of the lower uterine segment is less than 1 cm. With progressive enlargement of the uterus the lower uterine segment enlarges and measures more than 5 cm at the end of the pregnancy. Thus, in many patients, early in pregnancy the placenta appears to cover the internal cervical os, but

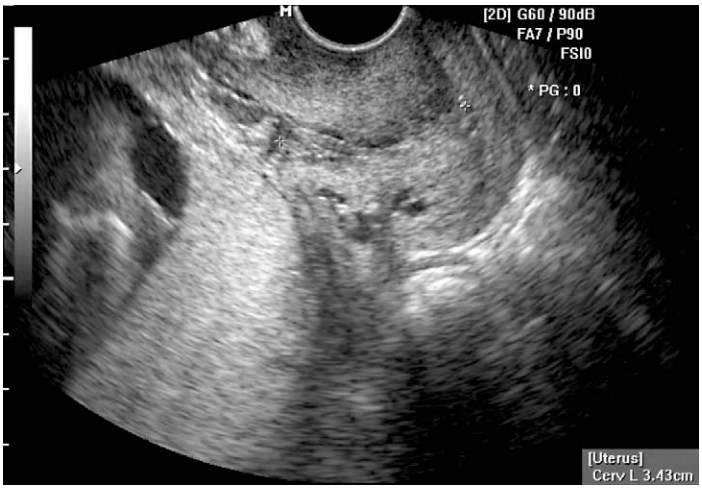

Figure 13-1. Endovaginal ultrasound of a patient with a total placenta previa: the placenta is posterior and its low border covers completely the internal cervical os.

as the lower uterine segment develops, a placental hedge inserted in the lower uterine segment appears to move cephalad, away from the internal os. This movement is incorrectly referred to as "placental migration." Therefore, before 24 weeks of gestation, only a cautionary significance should be attributed to the finding of a placental position close to the internal cervical os, particularly in asymptomatic patients. In more than 90% of these patients, the placenta will move away from the cervical os by term. Therefore, all diagnoses of placenta previa in asymptomatic patients based on ultrasonic examinations performed during the first and second trimesters of pregnancy must be confirmed during the third trimester. When both the transabdominal and endovaginal examinations show that the bulk of the placenta is centered over the internal os after 24 weeks of gestation, it is much less likely for the placenta to be away from the cervix at term.

In most patients with placenta previa, the bleeding is maternal in origin. However, a fetal component could be significant if some disruption of the villi occurs. Certainly, if a portion of the vaginal blood is fetal, the pregnancy is at higher risk for fetal and neonatal mortality and morbidity than if the blood is exclusively maternal. The possibility of fetal blood loss may be suspected with the occurrence of fetal tachycardia, decreased variability, sinusoidal rhythm, or episodes of bradycardia in the fetal heart rate (FHR) monitor tracing.

There are several tests available to determine the presence of fetal blood, but they are unreliable or difficult to perform in an emergency situation. A simple test to distinguish fetal from maternal blood consists of placing 5 ml of tap water into each of two small test tubes and adding six drops of 10% KOH. To one of the tubes add three drops of vaginal blood and to the other three drops of maternal blood. The tube with maternal blood will turn green yellowish brown after 2 minutes. If the vaginal blood contains fetal red cells the KOH solution will be pink in color (Loendersloot, 1979).

Outcome

A placenta previa is destined to bleed unless the pregnancy is interrupted by cesarean section. The amount of blood loss usually correlates with the type of previa. With total, partial, and marginal placenta previa, the numbers of units of blood replaced per patient were, respectively, 4.7, 3.6, and 2.5 in the study of Crenshaw et al. (1973).

There is a significant correlation between the gestational age at which the first bleeding episode occurs and preterm delivery. Perinatal mortality is high when the first bleeding episode occurs before 28 weeks of gestation but there is a progressive decline in mortality with advancing gestational age. The number of bleeding episodes does not correlate with total amount of blood loss or with perinatal mortality.

All types of placenta previa, irrespective of the gestational age at the first bleeding episode or the amount of bleeding, are associated with high perinatal mortality. However, the perinatal mortality is higher with earlier bleeding, greater amount of bleeding, and greater extent of placenta previa. The main reason behind the perinatal mortality in placenta previa is preterm birth. When Crenshaw et al.'s (1973) data are broken down according to gestational age and fetal weight, the predominance of preterm fetuses is evident. Most authors suggest that if preterm delivery could be avoided, the perinatal mortality problem would disappear. However, there are other factors in addition to preterm birth that compromise the infants of mothers with placenta previa. In fact, for babies born after 28 weeks of gestation there is a greater neonatal mortality associated with placenta previa than is for babies born at a similar gestational age because of other reasons. This is also evident if the data are broken down by fetal weights. For fetal weights more than 1000 g and under 3 g there is a greater neonatal mortality if the pregnancy is affected by placenta previa. Fetal and neonatal hypovolemia and fetal asphyxia are the logical explanations for these findings.

Beyond hemorrhage, the single most common cause for preterm delivery in patients with placenta previa is preterm labor, which occurs in approximately 30% of these patients. Many patients who have increased bleeding also have spontaneous uterine contractions, which may contribute to the excessive bleeding. Another reason for preterm delivery is preterm rupture of the membranes, which may occur even in patients with total previa.

The risk of fetal congenital malformations is increased two to four times in patients with placenta previa. It is a sobering experience to expectantly manage a patient with previa and to maintain her pregnancy for several weeks only to deliver an infant with no capacity for extrauterine life. There are no abnormalities specifically associated with placenta previa.

Management

Three fundamental areas of concern must be evaluated quickly and efficiently when dealing with a patient who is bleeding as a consequence of placenta previa: (a) the mother's condition as primarily evidenced by the degree of obstetric hemorrhage; (b) the fetal condition, including particularly gestational age estimation; and (c) the ability of the neonatal unit to handle an infant of that gestational age.

A massive hemorrhage threatening maternal life requires termination of the pregnancy without consideration to the maturity of the fetus. A mild to moderate bleeding episode in a patient at term should be managed

similarly as by operative delivery. However, if the patient is preterm and the bleeding is not an immediate threat to the mother's life, a more conservative approach is appropriate.

With respect to the fetus, no single issue is as important in the management of placenta previa as gestational dating. In fact, the risk of neonatal mortality and morbidity if the pregnancy is interrupted is closely related to the gestational age and should be balanced against the risk of increased maternal morbidity if the pregnancy is allowed to continue.

Finally, the ability of pediatricians to handle preterm infants must also be strongly considered. Intervention on behalf of a fetus at 26 weeks is inappropriate when a neonate at 30 weeks of gestation has a great deal of difficulty surviving in the same hospital. If neonatal facilities are limited, the mother should be transported to a perinatal center where obstetric interventions on behalf of 26-week fetuses are relatively common and produce a high proportion of normal outcomes. Postdelivery transport of these high-risk preterm infants to a tertiary center does not produce the same good outcome as when these infants are delivered at tertiary care centers.

Evaluation of severity of bleeding

The average blood volume of a pregnant woman increases during pregnancy and is about 8–9% of the total body weight, 6–7 L for a 70-kg person. Severe bleeding in persons who are not receiving intravenous fluids will cause a decrease in intravascular blood volume with no changes in hemoglobin concentration. The delivery of oxygen to the tissues will be adequate until the blood volume drops approximately 50% at which point the oxygen delivery drops rapidly, resulting in a depressed cardiac output. The number of open capillaries increases with the onset of hypoxia in an effort to maintain the flow of oxygen to the tissues but this counter-regulatory mechanism is rapidly overwhelmed if bleeding continues and the mitochondria cannot sustain aerobic metabolism. The decreased aerobic plus the anaerobic ATP production eventually reach a point where they are incapable of maintaining cellular functions, and membrane depolarization occurs with severe changes in the ion-transport systems, characterized by entry of calcium and sodium and extrusion of potassium from the cells, cellular swelling and acidosis, irreversible tissue damage, and death.

Aggressive intravascular volume expansion with electrolyte solutions in patients actively bleeding results in isovolemic anemia. In these cases the intravascular volume is preserved but the hemoglobin concentration and oxygen-carrying capacity are affected. The mechanisms of compensation are increased cardiac output and decreased peripheral vascular resistance. In these cases a deficit in oxygen supply to the tissues is reached when the hemoglobin concentration drops to about 4 g/dl or the hematocrit to 8%. Once the critical level in hemoglobin concentration necessary to maintain oxygen supply to the cells is reached, anaerobic metabolism starts and a sequence of events at the cellular level similar to those described for hypovolemic shock take place.

Evaluation of the severity of the bleeding is the initial and important step in the management of patients with placenta previa. However, making an adequate evaluation of the severity of a bleeding episode is sometimes difficult. Visual inspection of the patient and her blood-stained clothes is notoriously inaccurate. Blood pressure and pulse may remain within normal ranges despite considerable blood loss because of the unusual tolerance for bleeding of the hypervolemic pregnant woman. Hematocrit and hemoglobin during or shortly after a bleeding episode in individuals not receiving fluid replacement are within normal limits. Measurements of blood volume are usually inaccurate during bleeding and may be normal in spite of significant blood loss. Finally, the absolute amount of bleeding should always be evaluated in relation to the clinical status before the bleeding episode: an anemic patient may lose 1 unit of blood and show signs of profound hypovolemia, whereas a normal patient may handle a similar loss without significant change in vital signs. Classification of the severity of bleeding into four groups (Table 13-1) may be useful clinically to guide volume

Table 13-1. Severity of bleeding

	I	II	III	IV
Blood loss	<750 ml <15%	750–1500 ml 15–30%	1500–2000 ml 30–40%	>2000 ml >40%
Pulse rate (bpm)	<100	100–120	120–140	>140
Blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (per minute)	14–20	20–30	30–40	>40
Urine output (ml/hour)	>30	20–30	5–15	Negligible
CNS symptoms	Normal	Anxious	Confused	Lethargic

From Gutierrez G, Reines HD, Wulf-Gutierrez ME, et al. Clinical review: hemorrhagic shock. Crit Care 2004; 8: 373–81.

replacement (Gutierrez et al., 2004). Individuals with class I or mild bleeding have lost less than 15% of their intravascular volume (<750 ml) and show no change in vital signs, postural hypotension, or urinary output. Individuals with class II or moderate bleeding have lost between 15 and 30% of their blood volume (750–1500 ml) and exhibit baseline tachycardia and postural changes in pulse rate (increase of 10–20 bpm when changing from the supine to the upright position) and in diastolic blood pressure (drop of 10 mmHg or more). They also show evidence of inadequate circulatory volume (dyspnea, thirst, pallor, tachycardia, clammy extremities). Mental status changes may also be present (apathy or agitation). In severe bleeding (class III and IV) the patient has lost 30 to > 40% of her blood volume. She is in shock with decreased or unobtainable blood pressure and the fetus may be dead or showing signs of distress. Oliguria or anuria is present.

Management of patients with severe bleeding

For patients with severe bleeding it should be assumed that a catastrophic event is present and that the patient could develop hypovolemic shock and die in a matter of minutes. In these situations an efficient management plan including life-support measures and immediate operative intervention is the only way to avoid a maternal death. Management includes constant observation and monitoring, administration of intravenous fluids, transfusion therapy, assessment of renal function and intravascular status, assessing the fetus, and delivery.

Intensive observation and monitoring. Pregnant patients with severe bleeding should never be left alone. Frequent monitoring of vital signs, precise measurement of the fluid input and the urinary output, recording the amount of vaginal bleeding, and keeping complete records of what has transpired is essential for a positive outcome. Retrospective reconstruction of what went on in an emergency is, at best, inadequate. One health professional must be in charge of directly executing the physician's orders without leaving the room.

When the intravenous lines are being established, samples of blood should be obtained for CBC (complete blood count), type and crossmatch of at least 4 units, electrolytes, glucose, creatinine or blood urea nitrogen, and DIC profile. Although the hemoglobin and hematocrit values have been the basis for evaluation of blood loss for decades, acute and dramatic changes can often remain hidden, only to be fully revealed a few days later after complete vascular equilibration. On the other hand, rapid fluid infusion can expand the intravascular space and produce a decrease in the hematocrit level that a few days later will also re-equilibrate, only at a higher value. The electrolyte, glucose, and creatinine levels are baseline, primarily in preparation for anesthesia, and also serve as a crude screen for major problems. The DIC profile is essential for identifying the rare patient with previa who develops DIC and requires more sophisticated management.

Intravenous fluids. One or two large-bore cannulas, at least 18-G, should be inserted for the administration of a balanced electrolyte solution such as lactated Ringer's (LR). If the patient is in shock, two intravenous administration lines should be started. One liter of crystalloid solution results in approximately 250 ml of intravascular volume expansion. The patient's response to the initial fluid administration provides a rough index of the severity of the bleeding. In fact, if the blood pressure becomes normal and the pulse rate decreases with less than 3 L of IV fluids, the blood volume loss is probably less than 50%.

Transfusion therapy. Most patients receiving blood transfusions will receive packed red blood cells (packed red cells, or PRC). Transfusion of whole blood is unnecessary in most cases and is a waste of useful products. A similar comment can be made about transfusion of "fresh blood" when a patient is bleeding and in need of clotting factors. These factors can be replaced more adequately by transfusion of specific blood components. PRC transfusion is an essential component in the treatment of obstetrical hemorrhage and the support of a good blood bank is vital to any obstetrical service. PRC transfusions, however, are not without danger. Transfusion reactions, transmission of infection, and volume overload are some of the complications associated with transfusion therapy.

The frequency of complications following transfusion of PRC is low (0.1–2.3 per 1000). The most common complication is acute hemolytic reaction due to ABO incompatibility and, in women with reproductive potential, the development of Rh alloantibodies that may cause hemolytic disease of the newborn. Acute intravascular hemolysis occurs with a frequency of 1 out of every 6000 units transfused, and usually results from incorrect identification of the donor or the recipient. Most severe transfusion reactions are the consequence of clerical errors. To avoid these errors it is necessary to carefully identify the patient and the blood product that is going to be administered before the transfusion starts.

One of the dangers of transfusion therapy is the possibility of infecting the recipient with some microorganism present in the donor's blood. Hepatitis C and B, HIV (human immunodeficiency virus), and CMV are some of the microorganisms that may be transmitted with the administration of blood products. Fortunately, the probability of infection with transfusion therapy is small (Brecher and Hay, 2005). Infectious complications are rare since the institution of nucleic acid amplification testing for donated blood. This technology has reduced the time between infection and when antibodies or antigens

become detectable for HIV from 22 to 10 days and for hepatitis C from 70 to 20 days. Only three cases of HIV transmission have been reported since nucleic acid amplification testing was started in 1999 and none since 2002. Despite this small risk, the fear of acquiring HIV infection has caused a considerable increase in request for autologous blood transfusions. Currently, donated blood is screened for HIV-1 and HIV-2, hepatitis B and C virus, human T-cell lymphotropic virus, West Nile virus, and syphilis.

Bacterial contamination is the second most common cause of transfusion-related mortality and morbidity, and it occurs more frequently following platelet rather than red cell transfusion. The predominant bacteria are *Staphylococcus* and *Streptococcus* but Gram-negative infections also happen frequently. To prevent bacterial infections the blood bank community has adopted strict criteria for cleaning of the skin before blood collection. Also, all platelet units undergo bacterial cultures before administration.

Autologous blood donation during pregnancy is safe but is limited by the mother's hemoglobin concentration and by the potential effects on the fetus and on uterine activity of sudden changes in intravascular volume. Autologous blood donation for routine vaginal delivery or routine cesarean section should be discouraged. The likelihood of requiring transfusion during these procedures is low, and it is difficult to predict which patients will require transfusion. Only 0.3–1.6% of patients receive transfusion after vaginal delivery and 4.6–7.3% after cesarean section. Also, special arrangements and procedures are necessary for the collection of the blood and this places a burden on the obstetrician and the blood bank.

In the majority of situations, before the initiation of transfusion therapy, it is necessary to know the recipient's blood type and whether or not irregular antibodies are present. This is accomplished by means of a procedure named "type and screen." With this information the blood bank can rapidly select units of donor red blood cells that are most compatible with the recipient. With this system a given unit of PRC may be compatible and selected for potential use by several recipients. Because all the anticipated transfusions do not actually result in patients being transfused, the "type and screen" procedure allows a more efficient use of resources and a more rapid response of the blood bank. Also, the typing and screening procedure is more likely to detect significant antibodies than the crossmatch test.

Another method to select blood for a potential transfusion is to order a "type and crossmatch." In this procedure the patient's *serum* is tested for antibodies against the donor's RBCs, and if no antibodies are detected, one or more units of blood are set aside for eventual use in that particular patient only. It is obvious that the "type and crossmatch" procedure limits the use of the blood bank's resources and should not be used to select blood when the transfusion is only probable. A "type and crossmatch" usually requires 45–60 minutes if no major antibodies are found, a time that is not consistent with the needs in the case of severe obstetrical bleeding. In the majority of cases the units of stored blood that are determined to be compatible with the recipient's RBCs by means of the "typing and screening" procedure will be crossmatched only when the transfusion becomes necessary. However, the probabilities of finding an unrecognized significant antigen in the crossmatch are less than 0.05% if the recipient's antibody screening was negative and the ABO typing was adequate.

In most cases of severe obstetrical bleeding, the blood bank can "type and screen" the patient's blood while she is receiving crystalloid solutions. This procedure requires 15–30 minutes. In a severe emergency the obstetrician may order transfusion of type-specific blood that has not been screened for antibodies and can be made available in a few minutes. The administration of type-specific blood requires physician's release and is justified only in situations of extreme emergency. Military experience has demonstrated the safety of administering type-specific blood in severe emergencies. In rare circumstances there is no time available to wait for type-specific blood and the patient should be given type O Rh-negative PRC. Type O Rh-positive PRC can be used if type O Rh-negative blood is not available. The potential problem with type O Rh-positive blood is the possibility of Rh alloimmunization if the patient is Rh-negative. However, this consideration should not be an obstacle to transfusing the patient with massive obstetrical hemorrhage.

As blood is used for patients with severe obstetrical hemorrhage, more units need to be crossmatched so as to constantly have 4 units available. The need for massive blood transfusion (10 units or more within 24 hours) occurs occasionally in obstetrics, mostly in patients with placenta previa and accreta, abruptio placentae, and severe postpartum bleeding. There are multiple problems associated with massive transfusions, but the most common is platelet depletion secondary to replacement with platelet-poor blood. After transfusion of 4 units of PRC, the clotting mechanism should be evaluated, particularly the platelet count and platelets should be given when the count is less than 50,000/mm^3. The best approach to platelet transfusion is to administer 1 unit of platelets obtained from a single donor. This will increase the platelet count by approximately 50,000 and has the advantage of minimizing exposure to the multiple platelet antigens present in pooled units. If platelets from a single donor are not available, pooled platelets, 6–10 units, will accomplish the same task but antigenic exposure will be greater. If the patient

becomes deficient in clotting factors as demonstrated by alterations in PT (prothrombin time) or PTT, 1 unit of fresh frozen plasma should be administered for every 4 units of PRC. The routine use of fresh blood or whole blood with the purpose of avoiding coagulopathy is a waste of resources. Since it may take up to 60 minutes to prepare blood components for use, the blood bank should be notified periodically of the clinical condition of the patient and the probability that blood components will be required.

Assessment of renal function. Most long-term complications from severe hemorrhage are related to shock. Particularly, acute tubular and cortical necrosis are associated with anuria or oliguria resulting from hypovolemic shock. Thus, urine output observation is critical for appropriate management. A patient with severe hemorrhage needs a Foley catheter and aggressive therapy for decreased urine output. The initial treatment should consist of expansion of the intravascular volume. Maintenance of a urine output of 30 ml/hour should protect the kidney from permanent damage. Furosemide in an intravenous bolus of 20–40 mg is usually sufficient to re-establish urinary output, once adequate hydration and blood replacement have been obtained.

Central venous pressure. A patient in critical condition needs accurate monitoring of her intravascular status. Hemoglobin, pulse, and blood pressure can all be misleading, particularly in the presence of a decreased urine output. A peripherally inserted central venous pressure line especially if there is coagulopathy, or a more centrally inserted line, internal jugular, will provide the necessary information for safe and rapid expansion of the intravascular space. A femoral arterial line may be necessary in patients with shock or when noninvasive monitoring of the patient's blood pressure is inadequate.

Fetal evaluation. Initially, the objectives of the treatment are to restore the maternal intravascular volume, to improve her oxygen-carrying capacity, and to prepare for delivery. During these critical minutes, no time is usually available for an in-depth fetal evaluation. However, FHR monitoring should begin shortly after the patient is admitted to the hospital. Also, as soon as it is feasible, an ultrasound examination should be performed to determine fetal number, fetal position, and estimated fetal weight. The ultrasound will also be useful for determining the placenta localization and, in patients with abruption, the examination occasionally reveals the presence of a retroplacental hematoma.

Speculum examination. In the acutely bleeding patient, there is no indication for a digital vaginal examination. However, once the patient's vital signs become stable following the infusion of PRC and crystalloids, and after preparations are complete for operative delivery, a speculum examination may be performed. Visual inspection of the vagina and the cervix will confirm the intrauterine origin of the hemorrhage and rule out the rare vaginal or cervical causes of bleeding.

Delivery. Patients with placenta previa and severe bleeding should be delivered by cesarean section irrespective of the type of placenta previa. The anesthesia of choice for the patient who is hemorrhaging or who may hemorrhage (i.e., patient with previa and prior cesarean section scar) is general anesthesia with endotracheal intubation. Systemic maternal disease must be quickly evaluated in preparation for surgery. A history of hypertension, diabetes, renal disease, etc., may alter management and the choice of anesthesia. Diabetic patients should receive less glucose and those with renal disease should have strict electrolyte and fluid management.

The uterus customarily is entered through a low transverse incision, regardless of the placental location or fetal lie. However, effective delivery of a transverse lie or a preterm infant through a low transverse incision may be difficult. This type of incision is appropriate if the presenting part is easily accessible and the lower uterine segment has developed enough to allow a generous incision. Otherwise, a vertical incision provides greater flexibility in the approach to delivery and less trauma to the fetus. If the placenta previa is anterior, it is necessary to cut through the placenta to access the fetus, a maneuver that occasionally produces varied degrees of fetal anemia.

Management of patients with moderate bleeding

In a patient with moderate bleeding, knowledge of the gestational age and evaluation of fetal pulmonary maturity dictate the plan of management. Delivery by cesarean section should be performed if the pregnancy is 36 weeks or more. If the pregnancy is between 32 and 36 weeks it is necessary to evaluate the fetal pulmonary maturity as soon as the acute bleeding episode subsides and the patient's condition is stabilized.

In the majority of patients under 36 weeks of gestation, the rapid tests for fetal pulmonary maturity, FLM (fetal lung maturity) test and phosphatidyl glycerol, show fetal immaturity. Therefore, the management of patients with moderate bleeding who are between 32 and 36 weeks should be based on the result of the L/S (lecithin to sphingomyelin) ratio. If the L/S ratio is mature, greater than 2.0 in most laboratories, the fetus should be delivered. Delivery should not be delayed in patients with mature L/S ratios and immature PG or FLM determinations. Under these circumstances, the probability that neonatal RDS (respiratory distress syndrome) will occur is less than 5%, and if it occurs, it will

be mild. Obviously, the dangers of continuation of pregnancy are greater than the dangers of delivery.

If the fetal lungs are immature, the patient with placenta previa and moderate bleeding should remain under intensive monitoring in the labor and delivery unit for 24–48 hours. A hemoglobin level of roughly 11 g/dl should be maintained by transfusion. The uterus should be kept quiescent with the use of calcium channel blockers or beta-adrenergic agents. Steroids should be administered to induce lung maturation at a dose of 12 mg betamethasone IM, to be repeated in 24 hours. If the patient's condition remains unstable, with steady blood loss in moderate amounts, and she requires 2 or more units of blood daily for several days to compensate for losses, she should be delivered despite the early gestational age or lack of fetal lung maturation. The pediatrician should be alerted to the imminent delivery of a baby at risk for developing RDS. If the patient's condition becomes stable and remains stable for 24–48 hours, she becomes a candidate for expectant management, as will be described later.

Most patients with placenta previa and moderate bleeding stop bleeding and return to a stable condition shortly after admission, thereby becoming candidates for expectant management. In some cases the presence of complicating factors such as premature rupture of the membranes, maternal medical conditions, or fetal distress may make continuation of the pregnancy inappropriate.

Attempts have been made to identify patients at high risk for life-threatening hemorrhage so as to preclude their being included in an expectant management protocol. For example, if the initial bleeding episode results in a blood loss of more than 600 ml or if the placenta previa is total, immediate interruption of the pregnancy has been recommended. However, objective evaluation of published series on placenta previa does not substantiate these caveats. If the patient is stable, conservative management is the plan of choice since even a few days of delay in delivery may radically improve the neonatal outcome.

Management of patients with mild bleeding

As with moderate bleeding, fetal pulmonary maturity dictates the management of patients with mild bleeding. Immediate delivery of mature fetuses is the appropriate course, regardless of the minor degree of bleeding. Each published series on placenta previa recounts term infants dying while awaiting cesarean section. If the fetal lungs are immature or gestational age is less than 36 weeks, the patient with mild bleeding and placenta previa becomes a candidate for expectant management.

The objective of expectant management of placenta previa is to reduce the high fetal mortality associated with early delivery. Before 1920, when the risk of abdominal delivery was high due to the lack of availability of blood transfusion, maternal mortality was approximately 10% and fetal mortality as high as 70%. When cesarean section became safe and practical, it was common to deliver patients with placenta previa immediately after a bleeding episode, regardless of the fetal age. With this aggressive approach, maternal mortality was drastically reduced, but perinatal mortality, mostly due to prematurity, remained high. Approximately 25 years later, a re-evaluation of the aggressive surgical approach was initiated because it was thought that maintenance of the pregnancy under close supervision might decrease perinatal mortality. However, not all patients with placenta previa are eligible for expectant management. Noneligible patients include those at term, with excessive bleeding, with ruptured membranes, etc. In individual cases, one must assess the risk of pregnancy maintenance in terms of the chance that massive hemorrhage will result in fetal demise against the chance of complications of preterm delivery. In modern obstetrics, however, a delay of delivery for even a few days may significantly alter the neonatal outcome.

The following discussion outlines some characteristics of the expectant management regimen.

Patient selection. The importance of proper selection of patients cannot be overemphasized. Only hemodynamically stable patients between 32 and 36 weeks of pregnancy and with proven fetal pulmonary immaturity or those with less than 32 weeks' pregnancy should be managed expectantly. Patients with unstable vital signs or bleeding in moderate amounts should remain in intensive care until bleeding stops and vital signs become stable.

Hospitalization. Because of the multiple inconveniences associated with a prolonged hospital admission, attempts have been made to identify a "safe" group of patients who could be managed at home with constant supervision. Some selection criteria for outpatient management of patients with placenta previa are shown in Box 13-2.

BOX 13-2

Criteria for outpatient management of patients with placenta previa

1. Seventy-two hours of inpatient observation without vaginal bleeding
2. Stable serial hematocrit ≥ 35%
3. Reactive nonstress test at the time of discharge
4. Transportation between home and hospital available, 24 hours daily
5. Compliance with bed rest at home
6. Patient's and family's comprehension of potential complications
7. Weekly clinical follow-up until delivery including serial hemoglobin levels and repeat sonography

From Silver R, Depp R, Saggagha RE, et al. Placenta previa: aggressive expectant management. Am J Obstet Gynecol 1984; 150: 15–22.

However, the implications of prolonged hospital stay are important, and continued hospitalization is the best management plan that can be offered to these patients.

Prevention of labor. Uterine contractions are common in patients with placenta previa admitted to the hospital because of vaginal bleeding. Since uterine contractions have the potential to disrupt the placental attachment and aggravate the bleeding, most obstetricians favor the use of tocolytic agents in the expectant management of patients with placenta previa. A large retrospective review of women with placenta previa suggests that tocolysis in women with symptomatic placenta previa is associated with significant prolongation of pregnancy and increased birth weight (Besinger et al., 1995). Therefore, once the patient's condition is stabilized, the use of nifedipine, 10–20 mg orally every 4–6 hours, is recommended. In patients with placenta previa, terbutaline and ritodrine are not the drugs of choice because they cause tachycardia and make the assessment of the patient's pulse rate unreliable. Indocin, another powerful tocolytic agent, is not the first choice drug for uterine activity inhibition in patients with placenta previa because it causes inhibition of the platelet cyclooxygenase system and prolongs the bleeding time. If terbutaline or ritodrine is used, the patient should not be actively bleeding and her vital signs should be in the normal range. Indocin use should be limited to stable patients who have significant uterine activity not controlled by nifedipine. The patients should continue on tocolytic agents until they deliver. However, the evidence suggesting that administration of tocolytic agents results in better pregnancy outcomes is not conclusive.

Acceleration of fetal lung maturation. The objective of expectant management in the patient with placenta previa is to reach 36 weeks of gestation because neonatal morbidity is minimal at this gestational age. Neonatal morbidity increases when the gestational age is less than 36 weeks, and if delivery is planned before this gestational age it is necessary to determine if FLM is adequate, by means of amniocentesis. The most important test is the L/S ratio. The obstetrician should have no trepidation in interrupting the pregnancy, once a mature L/S ratio is obtained even if the FLM is negative and the PG is absent. The risk of significant neonatal RDS after a mature L/S ratio is significantly smaller than that of an obstetrical catastrophe if pregnancy is not interrupted. Determination of FLM is not necessary when delivery is required at less than 36 weeks because of maternal or fetal reasons.

Multiple studies have shown about a 50% reduction in the incidence of hyaline membrane disease (HMD) in preterm infants born after the mother received glucocorticoids. The time necessary for this effect can be as little as 24 hours or as much as 72 hours. In the clinical situation of placenta previa and preterm gestation, glucocorticoids may be lifesaving for the baby and under 34 weeks of gestation, it should be assumed that the fetal lungs are immature, and the medication should be given.

The reduction in HMD found in the original study by Liggins and Howie (1972) was restricted to preterm babies delivered 1–7 days after maternal glucocorticoid treatment. After 7 days, they found no difference between glucocorticoid and placebo groups, and there was a rebound effect in the treated group that was not statistically significant. Thus, it is possible that if pulmonary maturation is obtained with glucocorticoids at an early gestation, it may not persist if more than 1 week intervenes before delivery. Hence, glucocorticoids were given weekly in the past as long as the patient remained undelivered or until 36 weeks of gestation were reached. However, studies have demonstrated that repeated administration of steroids for several weeks has undesirable side effects, and this practice is no longer recommended.

Other measures. Bed rest is an essential component of expectant management. Limited bathroom privileges are usually allowed after the patient has been asymptomatic for a number of days. Although the clinician is acutely aware of the danger of vaginal manipulation, the patient may not appreciate the significance of the problem. Intercourse, douching, and vaginal suppositories are contraindicated. In addition, stool softeners are appropriate to avoid straining at defecation. The antenatal use of vitamin K and phenobarbital for the prevention of intraventricular bleeding in the neonate is controversial.

Cervical cerclage. In 1959, Lovset presented evidence obtained through uncontrolled observations of the beneficial effect of cervical cerclage for patients with placenta previa. This observation was further extended by Von Friesen (1964, 1972). Another cohort study (Sadauskas et al., 1982) of 75 cases treated with cerclage demonstrated a significantly greater prolongation of pregnancy (38.4 days) in women treated with cerclage than in women managed conservatively (12.8 days). The rationale behind this temporizing approach is that a cervical cerclage limits the development of the low uterine segment brought about by advancing gestation and the effect of uterine contractions. This, in turn, avoids the partial detachment of the placenta from the lower uterine segment, which most probably is the cause of bleeding.

The first randomized study on the use of cerclage in placenta previa included only 13 women assigned to cerclage and 12 assigned to expectant management (Arias, 1988). Cerclage patients had significantly better outcomes as indicated by more advanced gestational age at delivery, greater birth weight, less neonatal complications, and decreased

cost of hospitalization. However, a second randomized trial of 19 women receiving cerclage and 20 women treated with expectant management did not show significant differences in gestational age at delivery, prolongation of pregnancy, units of blood transfused, hospital costs, and admission to the NICU (Cobo et al., 1998). A recent Cochrane systematic review looked at the available information (Neilson, 2003) and found that cervical cerclage may reduce the risk of delivery before 34 weeks (RR 0.45, CI 0.23–0.87) and that of the birth of a baby weighing less than 2 kg (RR 0.34, CI 0.14–0.83) or having a low 5-minute Apgar score (RR 0.19, CI 0.04–1.00). The conclusion of the systematic review is that the available data should encourage further work to address the possible value of insertion of a cervical suture in women with placenta previa.

When to deliver. There are no advantages in pregnancy prolongation, once the gestational age reaches 36 weeks. The danger of catastrophic bleeding clearly overrides considerations about fetal pulmonary maturity. Only a small number of babies delivered at 36 weeks will have significant respiratory distress, and the need for assisted ventilation is unusual at this gestational age. Before 36 weeks, delivery should be accomplished for fetal or maternal reasons, the most common reason being maternal bleeding.

The following is a summary of the main points in the expectant management of patients with placenta previa.

1. *Selection criteria:* Only patients in stable conditions and remote from term should be managed expectantly. Patients actively bleeding or with unstable vital signs should remain in labor and delivery and should be monitored frequently.
2. *Duration of hospitalization:* The patient should stay in the hospital for the duration of her pregnancy unless she has a cervical cerclage or meets the criteria shown in Box 13-2.
3. *Medications:*
   (a) Nifedipine, 10–20 mg orally every 4–6 hours
   (b) Betamethasone, 12 mg IM every 24 hours, for two doses
   (c) $FeSO_4$, 325 mg orally three times daily
   (d) Stool softeners, high-residue diet
4. *Laboratory tests:* These include weekly blood count, and hemoglobin level should be maintained above 11 g/dl using blood transfusion if necessary.
5. *Criteria for delivery:*
   (a) Before 36 weeks, indications for delivery are mostly maternal, especially continuous or recurrent bleeding.
   (b) After 36 weeks, pregnancy needs to be interrupted.

A flow chart for the management of patients with placenta previa is shown in Figure 13-2.

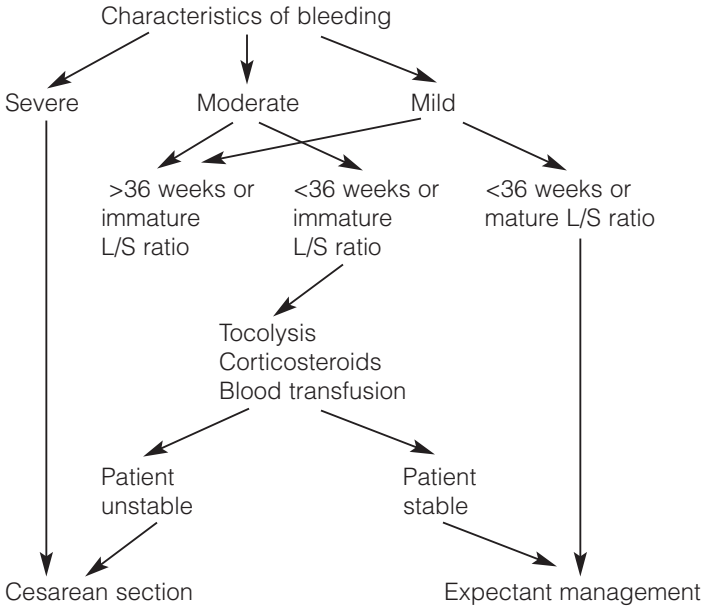

Figure 13-2. Management of placenta previa.

Placental Abruption

Definition and incidence

Placental abruption is the separation of the placenta from its implantation site before the birth of the fetus. The initial event in abruption is bleeding into the decidua basalis. The hematoma formed separates the placenta from the maternal vascular system, causing impairment in fetal oxygenation and nutrition.

Abruptio placentae occurs in approximately 1% of all deliveries. Abruption, severe enough to cause fetal death, occurs in approximately 1 in 100 deliveries, with a range of 0.52–1.29%. This wide range probably reflects differences in the incidence of abruption between different socioeconomic groups. The incidence of abruptio placentae increases with gestational age and more than 90% of the fetuses involved weighed more than 1500 g at birth.

The most serious maternal complications in abruptio placentae are the consequence of hypovolemia. One of the complications is acute renal failure, a topic that is extensively treated in Chapter 14. Another complication is coagulopathy which can aggravate bleeding and is a significant risk factor if operative treatment is necessary. Postpartum uterine atony and Couvelaire uterus can occur with abruptio placentae. Amniotic fluid embolization is a catastrophic complication associated with abruption that cannot be anticipated. Also, it should be noted that the Rh-negative mother with abruptio placentae may have had massive fetal–maternal transfusion, requiring a larger than usual RhoGAM dosage in order to avoid alloimmunization.

With respect to the fetus, the majority of complications result from prematurity and hypoxia (Ananth and Wilcox, 2001). Hypovolemic shock of the newborn is rare but may be associated with any maternal antepartum hemorrhage (APH). A fetal and neonatal coagulopathy has been suggested in connection with abruption but is very infrequent.

Etiology

Hypertension during pregnancy is associated with severe abruption. Pritchard et al. (1970) found that 45% of their patients with abruption severe enough to kill the fetus had elevated blood pressures. External trauma, cocaine abuse, acute decompression of polyhydramnios, preterm rupture of the fetal membranes, intrauterine infection, and oligohydramnios are also associated with abruptio placentae (Ananth et al., 2004). Naeye (1977) found a strong association between abruption and poor weight gain during pregnancy. He also demonstrated that maternal smoking is a significant contributory factor to the development of placental infarcts and abruption. Several studies have shown an association between high parity and abruption but the strongest association of abruption is with a previous history of abruption. The risk of recurrence is approximately 17% for patients with one abruption and as high as 25% for patients who have had more than one episode. Advanced maternal age, short umbilical cord, uterine anomalies, and inferior vena cava occlusion do not appear to be significant etiologic factors. Abruption is more frequent in twins and triplets—a fact that is important in view of the increased frequency of multiple gestations in the last few years in USA (Salihu et al., 2005).

Inherited thrombophilias are associated with placental abruption (Facchinetti et al., 2003; Prochazca et al., 2003). The strongest associations are with the FVL mutation, prothrombin promoter mutation, and hyperhomocysteinemia. The risk is significantly higher in women with more than one thrombophilia. The association of hyperhomocysteinemia with abruption is interesting. In a large number of cases hyperhomocysteinemia results from a homozygous mutation in the gene coding for the enzyme MTHFR and the elevated levels of homocysteine can be normalized with the ingestion of folic acid. This may explain why in an old study (Whalley et al., 1968) folic acid supplementation was associated with a decreased incidence of abruption.

Clinical presentation

The predominant sign of placental abruption is vaginal bleeding, present in 78% of the patients. Uterine tenderness and back pain are present in 66% of the patients. Uterine hypertonicity and frequent contractions are exhibited by approximately 17% of the patients. Fetal demise occurs before admission to the hospital in 25–35% of the patients. The classical clinical presentation involving all of these signs—vaginal bleeding, uterine tenderness, hypertonic uterus, fetal demise—does not occur frequently. The majority of patients with abruption have at least one of these signs, but occasionally none of them will be present. Indeed, no vaginal bleeding will be observed in 25–35% of patients. These patients with concealed bleeding usually exhibit severe forms of the disease. DIC occurs in approximately 13% of patients with concealed bleeding and it is usually limited to patients with abruption severe enough to cause fetal demise.

A common presentation of abruptio placentae is with mild vaginal bleeding, no uterine tenderness, and no coagulopathy, usually occurring in the last 4 weeks of gestation. The cause of this is a peripheral placental separation or "marginal sinus rupture" of the old literature. This topic will be reviewed more extensively later on in this chapter.

The natural history of abruptio placentae is controversial. Some investigators believe that the magnitude of the placental separation is determined at its onset and no further enlargement occurs. Others believe that abruption causes progressive placental separation. At present there are no adequate means to measure the dimensions of the initial separation and the frequency and severity of further separations if they occur.

Ultrasound examination is useful in the diagnosis of women with concealed bleeding. In these cases the most important finding is a globular placenta with a diameter of at least 6 cm. In a few cases it is possible to visualize the retroplacental clot but in the majority of cases the most important finding is the presence of thickened, globular placenta (Figure 13-3). Ultrasound is also useful to assess fetal presentation, estimated weight, and fetal well-being.

Classification

Sher (1978) in an excellent review of clinical material from the Groote Schur Hospital in Cape Town, South Africa, proposed a clinical grading system for placental abruption:

Grade I corresponds to cases in which the diagnosis of abruptio placentae is made retrospectively. Most of these patients have a retroplacental clot volume of approximately 150 ml, and none had more than 500 ml. With this small degree of abruption, fetuses are usually not at risk and a favorable perinatal outcome occurs frequently.

Grade II are those cases in which APH is accompanied by the classic features of abruptio placentae and

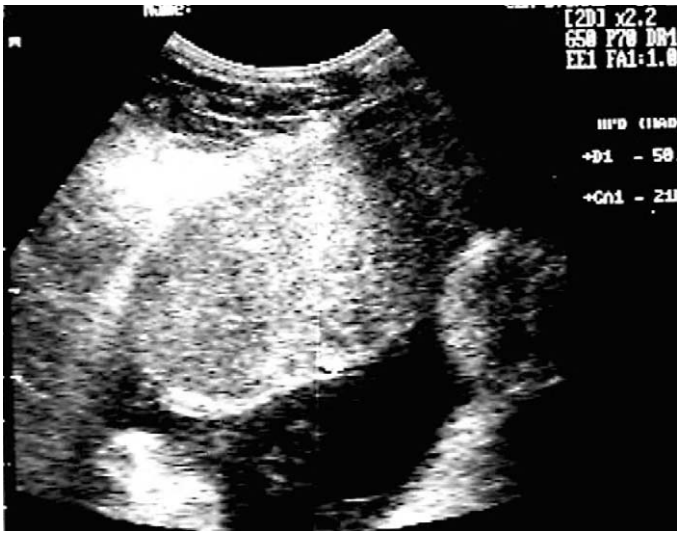

Figure 13-3. Globular, thick placenta in woman with placental abruptio.

the fetus is alive. The retroplacental clot volume in these patients is usually 150–500 ml, with approximately 27% of them having a clot larger than 500 ml. Ninety-two percent of patients in this category have abnormal fetal heart patterns and perinatal mortality is high especially when patients are delivered vaginally. It appears that the presence of a palpable rigid uterus represents a significant high-risk situation for the fetus.

Grade III incorporates the features of grade II but fetal demise is confirmed. It is further subdivided based on the presence (A) or absence (B) of coagulopathy. Virtually all maternal mortalities in association with abruptio placentae occur in grade III patients. Meticulous attention to the cardiovascular and renal status of these patients is necessary to ensure a good maternal outcome.

Management of severe abruption causing fetal demise

The question of fetal viability in abruptio placentae is particularly important because it provides an index for evaluating the severity of the disease, the size of the retroplacental clot, and the probability of coagulopathy and acute renal failure. With fetal demise, the placental detachment is usually greater than 50%, approximately 30% of the patients will show evidence of coagulopathy, and as many as 10% may develop acute renal failure. Therefore, any case of abruption with fetal death should be classified as severe.

The management of such patients should focus on decreasing maternal morbidity and mortality. To achieve this objective, delivery is necessary. However, it is necessary to carefully evaluate the mother before delivery to obtain information useful for the successful management of this obstetrical catastrophe.

Evaluation and replacement of blood loss

Pritchard and Brekken (1967) demonstrated that when abruptio placentae is severe enough to kill the fetus, the average intrapartum blood loss, mostly retroplacental, is about 2500 ml. Therefore, all patients with severe abruptio placentae have significant blood loss and require aggressive measures to avoid progressive impairment in organ perfusion. Immediate transfusion of at least 2 units of PRC should be instituted regardless of the initial vital signs and the initial hemoglobin/hematocrit. Transfusion should not be withheld as the patient exhibits a normal blood pressure, because if the patient was previously hypertensive the blood pressure may be normal. The pulse may also be normal until appropriate hydration produces tachycardia. In patients with concealed hemorrhage, a vast underestimation of blood loss frequently occurs, and when the vital signs deteriorate, hypovolemia is so severe that adequate replacement is difficult. Caution should also be used in the interpretation of hemoglobin and hematocrit values in patients with severe abruption. Very frequently blood counts are within the normal range as a consequence of intense reactive vasoconstriction. Therefore, patients with abruptio placentae severe enough to cause fetal demise should be transfused despite normal hematocrit/hemoglobin values and normal vital signs.

Immediately after admission while the initial assessment is performed, the intravascular volume should be expanded using LR solution. Expansion of volume with crystalloids is inefficient since only 250 ml of each 1000 ml injected IV will remain in the intravascular compartment. Also, in cases of severe bleeding in addition to volume expansion it is critical to improve oxygen-carrying capacity. Transfusion of PRC should therefore be started as soon as possible. More information regarding blood transfusion will be found in the section of this chapter about treatment of women with severe bleeding due to placenta previa.

The guidelines for the administration of red blood cells and intravenous fluids to women with severe abruption are to keep a hematocrit of at least 30% and a urinary output of at least 30 ml/hour. These two criteria are of fundamental importance. By keeping the hematocrit at 30% or more, the patient's oxygen-carrying capacity is sustained. By maintaining the urinary output at 30 ml/hour or more, one can be relatively confident that the effective intravascular volume is being preserved and that acute tubular necrosis or bilateral cortical necrosis, the most common causes of death for patients with abruptio placentae, will be avoided.

Internal jugular vein catheterization

In cases of severe abruption, one should anticipate the need for large amounts of intravenous fluids and a central

venous pressure catheter should be inserted to monitor their administration.

Management of coagulopathy

Close to 40% of patients with severe abruptio placentae have plasma fibrinogen concentrations below 150 mg/dl, and in 28% of them the fibrinogen level is less than 100 mg/dl as a consequence of acute DIC. Simultaneous with the drop in fibrinogen, patients with DIC also show prolonged PTT and PT, increased D-dimer concentration, and low platelet count.

DIC has many etiologies including sepsis, giant hemangiomas, and malignancies. The syndrome occurs rather frequently in obstetric conditions such as abruptio placentae, amniotic fluid embolization, and prolonged fetal death in utero. In the case of abruption, DIC seems to result from a massive release of thromboplastin into the circulation, causing intravascular formation of fibrin, consumption of coagulation factors, and subsequent activation of the fibrinolytic system.

For the evaluation of the hemostatic system in patients with abruptio placentae, most laboratories use a DIC profile. This is a battery of laboratory tests, including PT, PTT, D-dimer, quantitative fibrinogen determination, and platelet count. Normal values for the DIC profile are shown in Box 13-3.

The DIC profile is useful for evaluating and following the patient's coagulopathy, but abnormal results are not necessarily an indication for therapy. In fact, without clinical evidence of excessive bleeding, no therapy is warranted. Vaginal delivery can be managed in the presence of extremely depleted clotting components if episiotomy and unusual trauma are avoided. However, to minimize excessive blood loss at the time of delivery, it is safer to replace critically depleted coagulation factors, particularly platelets and fibrinogen.

The coagulopathy will resolve within hours in the postpartum period with appropriate blood replacement and preservation of the intravascular volume. However, the uterus is occasionally a source of excessive bleeding because high levels of FDP (fibrin degradation products) inhibit myometrial contractility. Nevertheless, there are extremely effective measures to combat postpartum uterine atony.

BOX 13-3

Normal values for DIC profile

Test	Normal results
Fibrinogen	150–600 mg/dl
Prothrombin time (PT)	11–16 seconds
Partial thromboplastin time (PTT)	22–37 seconds
Platelet count	12,000–350,000/mm^3
D-dimer	<0.5 mg/L
Fibrin degradation products (FDP)	Less than 10 µg/dl

The use of heparin for the treatment of DIC, complicating abruption, should be avoided. DIC in the patient with abruption originates in the premature separation of the placenta, and treatment is delivery of the fetus and the placenta. The use of heparin in these patients may aggravate the blood loss and increase the need for further transfusions. Another unfounded belief is that the presence of DIC in a patient with abruptio placentae is an indication for immediate cesarean section. In reality, in the presence of a generalized hemostatic defect, any type of operative intervention should be avoided if at all possible.

A new high-tech weapon is now available for the treatment of obstetrical bleeding, particularly in severe bleeding associated with abnormalities of the hemostatic system. Human recombinant factor VIIa (Novoseven, Novo Nordisk Pharmaceuticals Inc., Bagsvaerd, Denmark) is a remarkable drug for the control of obstetrical bleeding. The medication complexes with tissue factor and promotes the activation of factors IX and X and synthesis of thrombin. It is given as a bolus injection of 60–100 µg/kg. The results are dramatic and clearly observable after 10 minutes.

Evaluation of fetal presentation and size

The basic obstetric assessment of fetal position and size is frequently forgotten when dealing with this extreme emergency. Because of the rigidity of the uterine wall and the presence of a closed, uneffaced cervix, it is often difficult to clinically evaluate the fetal presentation and size. Therefore, a sonogram should be obtained in every case of abruptio placentae in which there is even the slightest doubt about the fetal presentation. If a malpresentation is detected, pregnancy should be interrupted by cesarean section, with the exception of infants weighing less than 800 g, which may be delivered vaginally even if they are in transverse lie. A failure to properly evaluate the fetal presentation may result in uterine rupture following oxytocin stimulation. External version should not be attempted in patients with abruption and a rigid uterus.

Delivery

Unless there is a malpresentation, every effort should be made to deliver patients with abruption and fetal death vaginally. Amniotomy should be carried out as soon as possible, followed by the insertion of an intrauterine pressure catheter. Oxytocin infusion should be used regardless of maternal age and parity unless there is clear evidence of active spontaneous labor. The rigidity of the uterus or the presence of a high intrauterine resting pressure should not deter the use of oxytocin. In patients with a fetal death

and an unripe cervix, misoprostol, 400 µg intravaginally, or high-dose oxytocin, 50–100 mU/minute, may be necessary.

The uterine monitoring pattern during spontaneous or induced labor in patients with severe abruptio placentae is different from the pattern observed in normal labor at term. In women with abruption the uterus remains rigid at all times and there are periodic contractions superimposed on the increased resting pressure of the uterus. The resting pressure measured with an intrauterine pressure catheter is elevated, usually around 40 mmHg, and contractions are seen as small waves on top of the resting pressure. Despite the monitoring appearance of poor labor the cervix starts to change, and after complete effacement, dilation is usually rapid.

Pritchard (1973) demonstrated that there was no specific time limit for obtaining a vaginal delivery in patients with abruptio placentae and fetal death. In the past there was a dictum that these patients should be delivered with in 4–6 hours. Today we know that with appropriate maintenance of the maternal status, the time period for obtaining vaginal delivery may be safely extended up to 24 hours. If there is an abnormal fetal presentation or if cephalopelvic disproportion is suspected, the patient should be delivered by cesarean section. Patients with fibrinogen concentrations of less than 100 mg/dl benefit from the administration of 10–20 units of cryoprecipitate immediately before and during cesarean delivery. This amount of cryoprecipitate contains enough fibrinogen to secure adequate hemostasis during surgery and to prevent additional blood loss.

The following is a summary of measures to be taken in the initial management of the patient with abruptio placentae causing fetal demise:

1. Initiate transfusion of PRC regardless of the initial vital signs and the initial hemoglobin and hematocrit.
2. Give enough blood and crystalloid solutions to maintain a hematocrit of at least 30% and a urinary output of at least 30 ml/hour.
3. Obtain a sonogram to confirm fetal death and assess fetal presentation. If there is no fetal malpresentation, start an intravenous infusion of oxytocin. Remember that high doses of oxytocin may be required, that monitoring of uterine activity is unreliable, and that the best index of progress in labor is cervical change.
4. Obtain a DIC profile. Patients with consumption coagulopathy will most probably require administration of fresh frozen plasma or cryoprecipitate if cesarean section or episiotomy is carried out.
5. Do not give heparin. There is no place for heparin in the management of obstetric bleeding. Heparin use in abruptio placentae is dangerous and contraindicated.
6. Do not perform a cesarean section unless there is a clear indication for the procedure. Remember that DIC by itself is not an indication for cesarean section but rather a strong contraindication. Surgical procedures should be avoided if at all possible in the presence of existing or impending generalized hemostatic defect.
7. The presence of a long, hard cervix is not an indication for cesarean section. In most patients the cervix will efface and dilate rapidly after oxytocin induction or vaginal prostaglandin administration.
8. In difficult cases when bleeding and hemostatic defects are causing shock and DIC, human recombinant activated factor VII may save the patient's life. Use 60–100 µg/kg IV, which may be repeated 2 hours later.

Management of abruptio placentae with alive fetus

The complexity of the management of a patient with abruptio placentae increases if the fetus is alive when the patient is admitted to the hospital. Both the mother and the fetus are at risk for loss of life. Few conditions require more sophisticated obstetric care. There are two main subgroups of patients: those with a palpably hypertonic uteri and those with palpably soft uteri.

If the infant is alive and the uterus is rigid, the abruption is probably large but less than 50%, and the chances of fetal distress during labor are more than 90%. In this case, the patient should be prepared for an immediate cesarean section unless there are very special circumstances that preclude surgical intervention (i.e., maternal shock, previable fetus, etc). The preparations for cesarean section should include evaluation of the patient's hemostatic profile and preparation for transfusion. Overt coagulopathy when abruption is not associated with fetal demise is extremely rare. However, coagulopathy and bleeding may develop during or immediately after the surgical intervention.

If the uterus is soft the pregnancy should be interrupted by induction of labor. In these cases the abruption will probably not be greater than 25%, the chances of significant coagulopathy are extremely low, and the prospects for a vaginal delivery with a favorable outcome are excellent. If the uterus becomes hypertonic during labor or if the FHR monitoring becomes nonreassuring, it must be assumed that abruption has extended and a cesarean section should be done. In the absence of uterine rigidity, fetal distress, or obstetric contraindication for vaginal delivery, the large majority of patients should have a vaginal delivery.

Figure 13-4 summarizes the overall plan of management for patients with abruptio placentae.

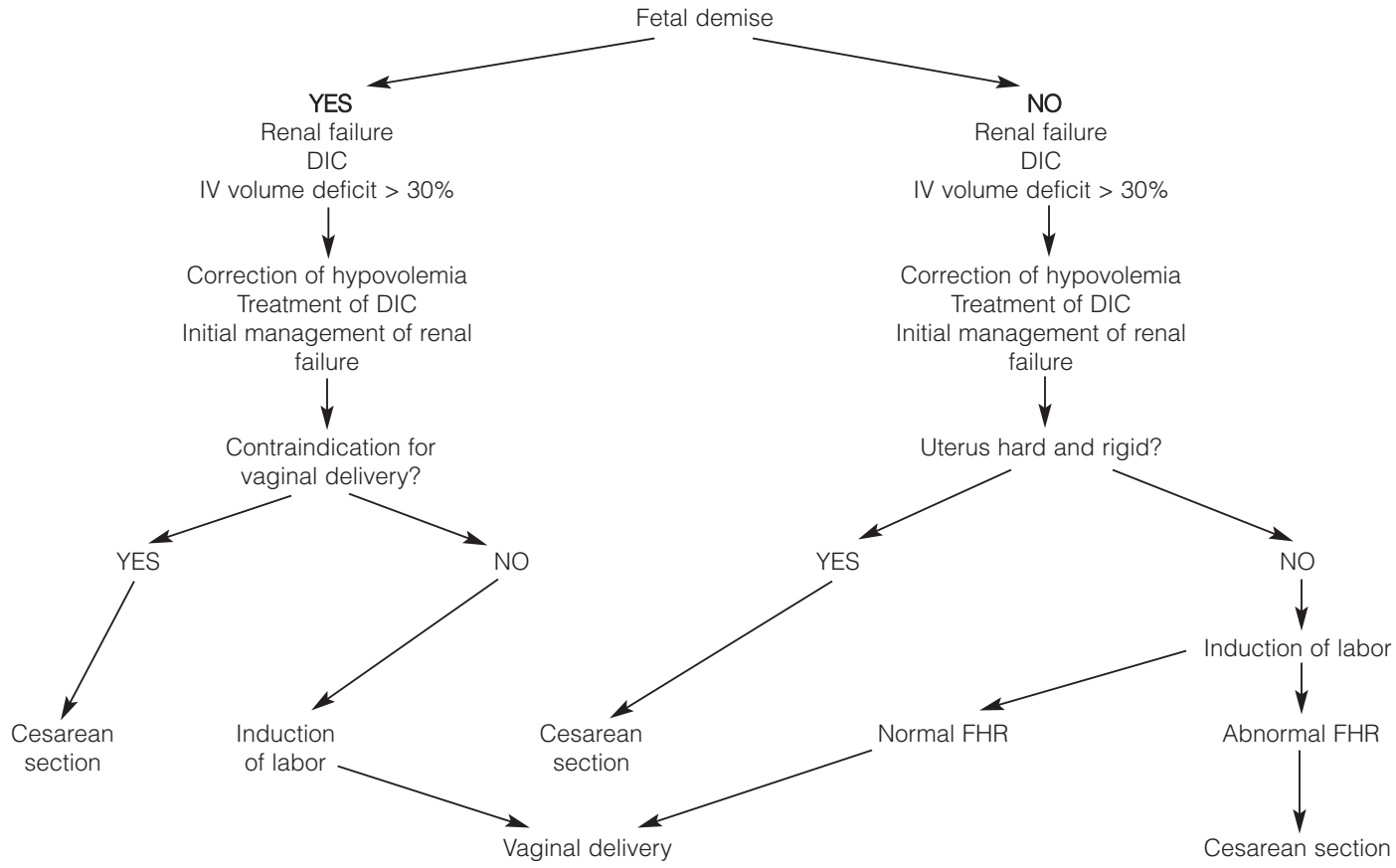

Figure 13.4. Management of abruptio placentae.

Prognosis for future pregnancies

Patients who have abruptio placentae have a higher incidence of complications. Approximately 14% of future pregnancies will end in spontaneous abortion and 9.3% of the cases will have repeated abruption. It has been suggested that the risk of repetition after two consecutive pregnancies with abruptio placentae is 25%.

Delivery before term has been recommended for patients with prior abruption due to the significant risk of recurrence and because a repeat abruption may be more severe. However, there are no data to substantiate this recommendation. Most likely, corrections of factors such as poor nutrition, low folate intake, low weight gain, and smoking would have a far greater effect on reducing the incidence of recurrence than would early delivery with its potential for fetal morbidity.

Other Causes of Third Trimester Bleeding

After excluding placenta previa and abruptio placentae, the most likely diagnosis is bleeding of unknown origin or marginal placental separation. Unfortunately the latter is a diagnosis that can be confirmed or ruled out only after delivery. Patients with third trimester bleeding of unknown origin have a higher than normal incidence of preterm labor (17%) and perinatal mortality (14.2%). Although these risks are less than those associated with abruptio and previa, caution and appropriate monitoring of these patients should be exercised. Other causes of third trimester bleeding etiologies for antepartum bleeding are shown in Box 13-4. The list of conditions shown in that Box indicates that at one point in the management of third trimester bleeding, there is a need for a

BOX 13-4

Causes of third trimester bleeding

- Cervicitis
- Cervical erosions
- Endocervical polyps
- Cancer of the cervix
- Vaginal, vulvar, and cervical varicosities
- Vaginal infections
- Foreign bodies
- Genital lacerations
- Bloody show
- Degenerating uterine myomata
- Vasa previa
- Marginal placental separation

direct cervical examination with a speculum. Except for vasa previa and marginal placental separation these complications usually pose a minimal risk to the fetus.

Vasa previa

Vasa previa is an anomaly in which the umbilical vessels have a velamentous insertion on a low-lying placenta and traverse the membranes in the lower uterine segment in front of the fetal presenting part. Due to the absence of the protective Wharton's gelatin the vessels may be easily lacerated at the time of membrane rupture, causing severe fetal bleeding. Also, fetal hypoxia and death may be caused when the vessels are compressed by the fetal presenting part, particularly during uterine contractions. Consequently, it is not surprising that fetal mortality in vasa previa approaches 75–100%. There is little, if any, increase in maternal complications. However, vasa previa is a rare condition (1 out of 2000–3000 deliveries).

The diagnosis of vasa previa should be considered in all cases of third trimester bleeding associated with an FHR monitoring trace suggestive of fetal compromise or cord compression (Dougall and Baird, 1987). In these cases, vaginal blood should be examined for fetal hemoglobin, as previously described in the discussion about placenta previa, and emergency cesarean delivery should be performed if there is evidence of fetal bleeding. Since vasa previa occurs more frequently in patients with twins, careful fetal monitoring is necessary in these situations.

Peripheral placental separation

Most patients with third trimester vaginal bleeding, no evidence of placenta previa or abruption, and with negative findings on speculum examination have a peripheral placental separation or "marginal sinus bleeding" of the old literature. In these cases, postpartum placental examination shows clots at the junction of the membranes and the border of the placenta. This condition does not cause alterations in the maternal hemostatic system but is associated with preterm labor and premature rupture of the membranes.

In a normal placenta maternal blood enters the intervillous space from the spiral arteries which are terminal branches of the uterine arteries. The exit of blood from the intervillous space into the maternal venous circulation was erroneously thought to be by means of a venous sinus running around the periphery of the placenta. In fact, this anatomic structure does not exist. The venous effluent of the placenta goes to the periphery of the intervillous space, forming lakes that are not separated anatomically from the central portion of the intervillous space. The blood drains from these lakes into numerous large venous channels located in the chorionic-decidual interface adjacent to the placenta and from there into the uteroplacental veins. These venous channels or venous sinuses are fragile and rupture easily if there is a separation of the decidual layer brought about by uterine contractions, trauma, or significant increase in the venous pressure.

Little is known regarding the natural history of marginal sinus separation. Usually bleeding stops after a few days and the pregnancy proceeds uneventfully until term. Other patients have repetitive episodes of mild bleeding. A minority of patients continue to bleed and require preterm delivery. Preterm labor, preterm rupture of membranes, and chorioamnionitis also occur frequently in patients with chronic bleeding.

The diagnosis of marginal placental separation can rarely be confirmed by ultrasound before birth. The majority of patients with marginal placental separation have normal ultrasound findings.

The management of these patients is expectant. However, the obstetrician should be aware of the possibility of complications and should follow these patients at frequent intervals. There are suggestions in the literature that administration of tocolytic agents to these patients prolongs gestation without increasing the frequency of abnormal outcomes (Sholl, 1987).

POSTPARTUM BLEEDING

Postpartum bleeding is a relatively common obstetrical complication causing significant maternal morbidity and mortality. An important factor in the maternal mortality resulting from postpartum bleeding is late recognition of the severity of the bleeding with a resulting delay in blood replacement. The physiologic increase in blood volume that occurs during pregnancy and the IV fluids received during delivery allow pregnant women to tolerate large blood losses without a concomitant marked change in vital signs. They respond to the blood loss by increasing the cardiac output, maintaining blood pressure and pulse rate within normal limits until the mechanism of compensation is exhausted. They then rather suddenly develop signs and symptoms of hemorrhagic shock. In untreated patients, the hemoglobin/hematocrit values also remain within normal limits despite extensive blood losses. Unfortunately, when the woman with postpartum bleeding decompensates, the opportunity for therapeutic intervention is limited and coagulopathy, renal failure, and death are difficult to avoid. The only way to avoid this frightful sequence of events is aggressive treatment of postpartum bleeding even in the presence of apparently normal vital signs and a normal hemoglobin concentration.

Etiology

Postpartum bleeding may be early or late. Early bleeding occurs during the third phase of labor or immediately following the delivery of the placenta. Late bleeding may occur any time from 1 day until 2 or 3 weeks postpartum. The most common cause of early postpartum bleeding is uterine atony. Other common causes are retained placental fragments and lacerations of the vagina or the cervix. Unusual causes include placenta accreta, uterine inversion, and abnormalities of the hemostatic system. In patients having cesarean section or vaginal birth after cesarean section uterine rupture, dehiscence of the uterine scar, poor hemostasis of the uterine incision, and poorly repaired extensions of the uterine incision in the lateral walls of the vagina are common causes of bleeding. The etiology of late bleeding is usually limited to retained placental fragments, subinvolution of the placental implantation site, and maternal abnormalities of the clotting system, in particular Von Willebrand's disease and platelet storage disorders.

Diagnosis

The diagnosis of postpartum bleeding is obvious. What it is not clear in many instances is the etiology and the extent of the bleeding. Both questions should be answered correctly at the time of the initial assessment in order to have a successful outcome.

The most common etiology of postpartum bleeding immediately following a vaginal birth is uterine atony. The diagnosis is usually evident by palpation of the uterus and by cessation of the hemorrhage, once the uterus contracts adequately following massage or treatment with uterotonic drugs. However, even in cases where uterine atony seems to be the obvious diagnosis, proper evaluation of the cause of bleeding following a vaginal birth requires a systematic inspection of the cervix and vagina looking for lacerations. The completeness of this examination cannot be overemphasized. The presence of abundant blood in the vagina, the precarious hemodynamic situation of the patient, and the discomfort of the examination conspire to make this assessment difficult. However, the examination cannot be finished until the obstetrician is 100% sure that the bleeding is not due to tissue trauma during the delivery.

Assessment of postpartum bleeding also requires abdominal or transvaginal ultrasound or a combination of the two. This examination is necessary even in cases where uterine atony seems to be the obvious cause of the bleeding, because in many occasions ultrasound will permit the identification of a piece of placenta inside the uterus. In cases of uterine atony the ultrasound examination will reveal a slightly enlarged uterine cavity which may contain fluid or clots.

Retention of placental fragments is not common when postpartum bleeding occurs after a cesarean section. The most common etiologies of postpartum bleeding after cesarean section are uterine atony, inadequate hemostasis of the uterine incision, or incomplete repair of extensions of the incision. The diagnosis of the last two possibilities is one of exclusion when patients continue bleeding, once the uterus is firmly contracted with the use of uterotonic drugs.

Late postpartum bleeding usually occurs within 2 weeks of the patient's discharge from the hospital. Uterine atony is not a consideration in these cases unless the bleeding occurs in the first few days following delivery. After vaginal birth the most common causes are retained products of conception, subinvolution of the placental implantation site, and abnormalities of the hemostatic system. Women who deliver by cesarean section share the same causes but retention of products of conception is rare.

Treatment

The initial management of women with postpartum bleeding is dominated by the need to assess the extent of the hypovolemia and respond quickly to the decreased intravascular volume and decreased oxygen-carrying capacity. It should be noted that the vital signs may be unreliable markers of the severity of the bleeding. The "tilt test" is useful, and an increase in more than 10 beats in heart rate or a decrease of more than 10 mm of mercury in diastolic blood pressure when the patient is tilted from the supine to the sitting position are indicators of a blood loss exceeding 30% of the total blood volume. When the patient is hypotensive and tachycardiac the blood loss usually exceeds 2000 ml.

The first step in the management of women with postpartum bleeding is to establish intravenous access with one or two large-bore (16-G) catheters. At this time blood should be obtained for CBC with platelets, fibrinogen, PT, PTT, and blood type and antibody screen. Normal saline solution should be infused rapidly to maintain the vital signs within normal limits until PRC are available. The severity of the bleeding will determine if type-specific or crossmatched PRC will be used for transfusion. There is an ongoing discussion regarding the risks and benefits of using colloid solutions in the treatment of hypovolemia. A widely criticized systematic review by the Cochrane injury group concluded that administration of albumin for the treatment of hypovolemia is associated with greater mortality than treatment with crystalloids alone (Cochrane Injuries Group Albumin Reviewers, 1998). The therapeutic expansion of the intravascular volume should be simultaneous with diagnosis of the cause of the bleeding and elimination of

the bleeding source. Expansion of volume without control of the bleeding will only lead to more bleeding. The reader will find more information about transfusion therapy and treatment of hemorrhagic shock in the section of this chapter about treatment of placenta previa.

Successful treatment of postpartum bleeding requires elimination of the source of the bleeding. The most common causes of the bleeding are uterine atony, lacerations and trauma of the lower genital tract, retained placental products, and disorders of the hemostatic system.

Uterine atony

Uterine atony is the inability of the myometrium to adequately contract following delivery, causing continuous and severe bleeding from the placental implantation site. Uterine atony is associated with uterine overdistension, prolonged labor, multiparity, intrauterine infection, and use of uterine relaxing agents. It may occur after vaginal delivery and after cesarean section. The diagnosis is usually made by the observation that the uterus is soft and boggy, contracts following massage, and relaxes again resulting in more bleeding.

The first step in the management of postpartum uterine atony is the administration of uterine contraction stimulants, also called uterotonic agents. Since most women with early postpartum bleeding are already receiving oxytocin the traditional sequence has been to increase the rate of oxytocin administration, followed by IM Methergine, followed by prostaglandins if the bleeding continues. There are multiple problems with this approach to postpartum bleeding. In first place most obstetrical units use only 10 or 20 units of oxytocin diluted in 1 L of saline or LR following delivery of the infant. Studies have demonstrated that the use of 40–50 units of oxytocin in 1 L of LR or saline is an effective measure to prevent postpartum bleeding following cesarean section (Munn et al., 2001). Low concentrations of oxytocin do not prevent and are ineffective to treat postpartum bleeding, and it is necessary to use as much as 80–100 units dissolved in 1 L of electrolyte solution. Methylergonovine is a commonly used uterotonic agent. It is given in doses of 0.2 mg IM every 2–4 hours and can cause hypertension. It is contraindicated in women with preeclampsia. The best uterotonic agents are the prostaglandins. The injectable form of 15-methyl prostaglandin F 2α ("Hemabate") is extremely effective. The dose is 250 μg IM every 15–20 minutes for a maximum of eight doses. It frequently causes nausea and vomiting, diarrhea, and chills. However, the best product available for the treatment of postpartum bleeding is misoprostol (Hofmeyr et al., 2005). It is given in a dose of 1 mg (five tablets of 200 μg) per rectum and it should be the first-choice drug for the management of this obstetrical emergency.

There are occasions when uterine atony does not respond to the administration of uterotonic agents. In that case the next step is to proceed to uterine tamponade using packing with gauze (Hsu et al., 2003), a Foley catheter with a 30-cc balloon, a Sengstaken-Blakemore tube (Seror et al., 2005), an SOS Bakri tamponade balloon (Bakri et al., 2001), or in situations where none of this is possible to use a condom with the open end closely tied around a size 16 rubber catheter that will be used to inflate the condom with water (Akhter et al., 2005).

Uterine tamponade is an effective way to control postpartum bleeding. The use of packing with gauze is controversial but if it is done properly it may stop the bleeding. A Foley catheter with a 30-cc balloon may be inflated up to 100 ml without bursting. It is quite effective to control postpartum bleeding, but the shape of the balloon does not correspond to the elongated uterine cavity. The Sengstaken-Blakemore balloon was designed to control bleeding from esophageal varices. It consists of two balloons: one smaller and spherical in shape, the second being larger, elongated, tubular in shape. Ideally the spherical balloon should be removed and the tubular balloon used for uterine tamponade. However, removal of the spherical balloon sometimes causes leakage of the tubular balloon and the expensive device cannot be used. The recently available SOS Bakri tamponade balloon is a tubular balloon designed specifically for this obstetrical emergency, which can tolerate up to 500 ml of fluid. Every obstetrical unit should have at least one of these balloons available for postpartum bleeding.

When uterine tamponade fails, the following step is selective arterial embolization. This procedure is performed by an interventional radiologist who catheterizes the hypogastric artery, identifies the source of the bleeding, and embolizes the bleeding vessels with small particles of Gelfoam. This procedure is extremely effective in providing bleeding control. In the absence of an interventional radiologist and in the face of continuous bleeding, it is necessary to proceed to surgical intervention consisting in compression sutures to keep the uterus contracted.

Compression sutures are the best surgical approach for the treatment of uterine atony. They preserve the anatomical integrity of the uterus, attack the root of the problem by keeping the uterus contracted, are easy to perform, and have minimal morbidity. The best known procedure is the B-Lynch stitch. It is performed using a long absorbable suture (we prefer 0 chromic or 0 plain catgut) which is anchored in the anterior aspect of the lower uterine segment, passed over the fundus of the uterus, anchored in the posterior aspect of the lower uterine segment, brought back anteriorly passing over the fundus of the uterus, anchored near the entrance point on the anterior aspect of the lower segment, and then tied while the uterus is massaged and manually compressed to reduce its size to a minimum.

A better technique for surgical compression of the uterus was described by Pereira et al. (2005). In addition to the longitudinal B-Lynch stitch, one or more circumferential sutures are placed, encircling the uterus in the transverse plane. The transverse sutures are anchored anteriorly and posteriorly and they are passed through the broad ligament, being sure that the round ligament and the Fallopian tube are not included in the suture. It is also important to avoid the vessels running on the left and right sides of the uterus. This method achieves a degree of uterine compression much better than the B-Lynch stitch alone. Uterine compression sutures have almost completely replaced uterine artery ligation, hypogastric artery ligation, and postpartum hysterectomy for the surgical treatment of uterine atony.

Cervical and vaginal lacerations

Cervical and vaginal lacerations are frequently associated with the use of forceps or vacuum for delivery. In the majority of cases they will be easily observed by a careful examination of the lower genital tract. The most difficult challenge is presented by extended vaginal lacerations because the tissues are fragile and the sutures are frequently cut through the tissue, provoking further bleeding. In this situation, packing the vagina with gauze may be necessary. Vaginal packing is not easy due to the elasticity of the vagina and should be carried out methodically, starting with packing of the vaginal fornices. The pack may be safely removed in 6 hours but many prefer to leave it in for 12 hours.

It is important to have adequate anesthesia for the repair of cervical and vaginal lacerations. Most treatment failures are the consequence of patient discomfort and movements that conspire against good visualization and adequate treatment of the lesion.

Retained placental fragments

Retained placental fragments may occur in any delivery but they occur more frequently in preterm deliveries, prolonged third stage of labor, and following manual or instrumental delivery of the placenta. Manual inspection of the placenta is an ineffective method of assessing the integrity of the organ, and the obstetrician should not rely on placental inspection to rule out retained products. The possibility of retained products is large in patients with postpartum bleeding, a well-contracted uterus, and a normal speculum examination. However, retained products should be strongly suspected in all cases of apparent uterine atony.

The diagnosis of retained placental tissue is made by bedside ultrasound which will reveal a mass of tissue of varying size inside the endometrial cavity. The ultrasound appearance of placental tissue is frequently similar to the endometrium and myometrium, but a careful examination in the longitudinal and the transverse planes will reveal the retained tissue.

The treatment of retained placental tissue consists of removal of the tissue using ring forceps or by suction curettage. The completeness of the operation should be always verified by bedside ultrasound. Good anesthesia is necessary to have a fast, safe, and successful procedure.

INDIAN EXPERIENCE OF EARLY PREGNANCY LOSS

Present day knowledge acknowledges that the overall pregnancy loss is about 31%, of which 22% of pregnancy loss occurs prior to implantation and therefore is clinically not recognized. This section deals with the clinically recognized early pregnancy losses postimplantation. The risk of spontaneous abortion for a woman with no history of previous reproductive wastage is about 15%. It is observed that the risk of repeated abortion in a woman with no living child increases subsequently. Genetic, endocrine, developmental, and anatomic defects, infections, uterine abnormalities, abnormal placentation, psychological factors, and immunologic causes have been identified in the etiology of abortions.

Chromosomal defects, usually aneuploidies have been reported in 50% of single, first trimester and about 20% of second trimester spontaneous abortions. Although repetitive chromosomal abnormalities are not a common cause of recurrent abortions, the frequency of aneuploidy and polyploidy among sporadic abortions can still make them important causes merely by chance. Unbalanced form of a parental balanced chromosomal rearrangement has been recognized in 3% of couples with recurrent abortions (Pai, 2006). Hormonal causes such as luteal phase defect has been reported in 60% of patients with recurrent early miscarriages. However, in random abortions, its incidence may not be so high. Progesterone administration has been shown to give therapeutic benefits (Pai, 2006). The risk of abortion is higher in women with polycystic ovaries. Infertility clinics report a higher incidence of abortions (12–44%) in patients of polycystic ovary syndrome treated successfully (Narvekar NM and Narvekar AN, 1998) for optimal functioning of the corpus luteum during early pregnancy and production of progesterone to support consistent growth of pregnancy. It is important to understand the antecedent events leading to the formation of a healthy corpus luteum. During folliculogenesis, there is a complex interplay between GnRH pulsatility, FSH release, intrafollicular events, and peripheral steroid feedback (Agarwal and Buyales, 1995; Anklesaria and Savalia, 1998; Shah, 1998). Disturbances in the chain of events predisposes to luteal phase defect.

Factors which regulate folliculogenesis influence the luteal phase and luteal rescue during onset of pregnancy. The patterns of GnRH release, circulating androgen levels, prolactin and inhibin concentrations, and the effective induction of progesterone receptors in the endometrium will all affect corpus luteum function, successful implantation of the embryo, and the ability to be rescued by chorionic gonadotropin. Thus luteal phase efficiency depends on a complex interplay of endocrine factors. Other endocrine causes contributing to early pregnancy loss include maternal thyroid dysfunction and uncontrolled diabetes. The incidence of hypothyroidism complicating pregnancy is 9/1000 pregnancies. These women have a higher risk of abortion, premature birth, still birth, and fetal anomalies. The incidence of hyperthyroidism in pregnancy is 2/1000 pregnancies (Reddy and Shenoy, 2001). Diabetes affects pregnancy adversely unless it is well controlled. The risk of abortion in diabetic pregnancies is enhanced (Shivkar et al., 2003). A study from Kashmir, investigating spontaneous abortions, reported impaired carbohydrate tolerance in 9.84% of cases (Mukherji et al., 2002; Roy Chowdhury and Bandopadyaya, 2002).

Presence of antiphospholipid antibodies has been recognized to lead to repeated pregnancy losses. Immunological causes contribute to early pregnancy losses. The immune system is a complex integrated system that has evolved to protect the individual from nonself tissues. The term *allogenicity* is used to describe genetic dissimilarity between individuals of the same species. As the individual's complement of antigens is unique, the immune system can recognize as alien the cells of another member of the species. As the zygote formed by the union of the sperm and ovum has equal genetic endowments from either partner inclusive of the HLA genes that determine the offspring's transplantation antigens, pregnancy can be regarded as a graft–host relationship. But in nature, the embryo appears to be indifferent to the maternal immune response. This is the immune paradox. Thus, for a successful outcome of pregnancy, the mother's immune system must be tolerant of the semiallogenic fetus. In some circumstances when the maternal immunotolerance is breached, an abortion will ensue as a result of alloimmune rejection of the embryo/fetus. Progesterone/retroprogesterone provide immunomodulation and antiabortive effects. Women with three or more spontaneous abortions, in whom chromosomal, anatomic, microbiological, endocrine, and medical causes of recurrent abortions have been excluded, antiphospholipid antibodies negative, coagulation profile normal, and blood proteins normal are candidates for immunotherapy. Success rates of 66% in clinical trials using husband's leukocytes and 86% following use of autologous leukocytes were reported (Shah et al., 1998). Similarly, an interesting case from New Delhi of a previous early pregnancy loss due to immunological cause was recognized on investigation (increased CD_{19} and CD_{56+} cells) and successfully treated with lymphocyte (donor + husband) immune therapy. Lastly, psychological factors also play a role. These are not always easy to identify. A psychiatric evaluation is often beneficial.

INDIAN EXPERIENCE OF THIRD TRIMESTER BLEEDING

Bleeding in late pregnancy or APH may be of placental origin (placenta previa, abruptio placentae), due to local causes, or of unclassified origin. The incidence of antepartum bleeding has been quoted to be 2.5–3.8% (Menon and Sokhi, 1961; Das, 1975; Bhatt, 1986, Bhide et al., 1990; Arora et al., 2001; Chauhan and Krishna, 2001). In present day practice, sonography helps to settle the diagnosis of placental localization, and a speculum examination to inspect the lower genital tract at an appropriate time later helps to exclude any local pathology contributing to the bleeding episode. To determine the efficacy of sonography in determining the cause of APH, a study from Rohtak (Sen et al., 2002) revealed that placenta previa was detected in 30% of cases. The value of transabdominal sonography was as follows: sensitivity (96%), specificity (80%), and positive predictive value (88%) with a false positive rate of 20% and false negative rate of 3.34% in contrast to transvaginal sonography which revealed the following: sensitivity (100%), specificity (95%), and positive predictive value (97%), a false positive rate of 5% and no false negative results. This opinion was confirmed by Chauhan and Krishna (2001), who further stated that the fear of risks of transvaginal sonography in precipitating an episode of bleeding was misplaced; however, to allay the fears of clinicians, the transperineal approach can be utilized safely and effectively, particularly when the cervix is not visualized during abdominal sonography. Transvaginal color Doppler imaging improves the diagnostic accuracy. Placental lacunae exhibiting marked turbulence from within the placenta extending into the surrounding tissues should alert the clinician to the possibility of placenta accreta. MRI to visualize the placenta has been reported upon favorably in literature. Its advantages over ultrasonography are better imaging of soft tissue structures, clearer definition of the cervix, and reduced margin of error resulting from overfilling of the bladder. It is now possible to diagnose antenatally a case of placenta accreta, increta, or percreta with confidence with the help of MRI and to plan timely action.

Analytical reviews on APH excluding local causes reveal that placenta previa, abruptio placentae, and unclassified causes account for APH. Their distribution as reported in Indian studies has been presented in Table 13-2.

Table 13-2. Distribution of the causes of antepartum bleeding and fetal outcome

Authors	Year	Placenta previa	Abruptio placenta	Unclassified APH
Bhatt	1971–1975	36.8%	51.09%	12.04%
Daftary et al.	1981	40.0%	50.0%	10.0%
Menon and Sokhi	1951–1961	18.7%	66.05%	14.8%
Arora et al.	2001	46.4%	25.0%	28.6%
Chauhan and Krishna	2001	33.3%	45.6%	22.1%
PNMR		PNMR 25.0%	PNMR 53.5%	PNMR 28.0%
Low Apgar (<5)		41.0%	40.0%	30.0%

PNMR = perinatal mortality.

Table 13-3. Perinatal mortality in antepartum bleeding and its causes

Authors	Year	PNMR—contribution of principal causes			
		Placenta previa	Abruptio placenta	Prematurity	Perinatal asphyxia
Arora et al.	2001	25.5%	53.5%	67.0%	38.0%
Bhide et al.	1990	10.0%	54.0%	56.0%	35.0%
Khosla et al.	1989	27.0%	51.0%	66.0%	41.0%
Pinto and Prabhu	1971	32.0%	68.0%	55.0%	45.0%

In general, about a third of patients presenting with antepartum bleeding have placenta previa. Placental abruption is a more common event and unclassified causes account for about 25% of all cases of APH. Sonography enables the clinician to be more certain of the diagnosis antenatally.

The risk factors in cases of APH include high maternal age, high parity, previous cesarean section, previous spontaneous or induced abortion, previous curettage, cigarette smoking, and cocaine addiction. Associated risk factors include increased risk of placenta accreta, multiple gestations, maternal anemia, tumors distorting the uterus, and fetal malpresentations. Perinatal risks are also higher; these are attributed to prematurity, low birth weight, birth asphyxia, and a higher incidence of fetal malformations. An analytical study on perinatal morbidity and mortality in APH (112 cases) by Arora et al. (2001) from Pondicherry revealed the following data. The incidence of APH was 2.53%. The booking status revealed that 62% of the patients were nonbooked emergency admissions. The age distribution revealed that 43% of these cases were aged 21–25 years only. The average gravidity in the study was 2.4. Of the patients with placenta previa, 44% suffered the first episode of bleeding before 32 completed weeks of gestation unlike the cases of abruptio placentae who generally presented with bleeding after 32 weeks of gestation. The incidence of fetal malpresentations was 23% in women with placenta previa, but much lower of 11% in cases of abruptio placentae. The incidence of intrauterine fetal death in cases of APH was much higher in cases of abruptio placentae. The cesarean section in placenta previa was 65% as against 50% in accidental hemorrhage. Higher perinatal morbidity was attributed to low birth weights, prematurity, birth asphyxia, trauma, and fetal congenital malformations.

The management of APH has undergone a vast change. In all women with a non-life-threatening episode of bleeding, the medical attitude is that of attempting to gain time with conservative expectant management under hospital supervision. Sonography helps to determine the underlying cause. Facilities to meet any emergency with availability of adequate blood transfusion, implementing emergency obstetric intervention at short notice, and satisfactory neonatal care are necessary during the period of antenatal hospitalization. Management consists of bed rest, hematinics, monitoring of fetal well-being, tocolysis, timely administration of steroids, and well-planned elective delivery on reaching satisfactory fetal maturity. At present, the fetal salvage rate has improved greatly. Perinatal mortality is higher in abruptio placentae as compared to placenta previa (Table 13-3).

Table 13-3 shows that many babies are delivered preterm and are often born with a low Apgar score. In many centers in India, quality neonatal care is nonexistent, general pediatricians continue to care for newborns; intensive care facilities are very few in number and often not available.

INDIAN EXPERIENCE OF POSTPARTUM HEMORRHAGE

Postpartum hemorrhage (PPH) is an emergency every obstetrician has to face, often unexpectedly. It complicates 3–6% of all deliveries. It is the third most common cause

Table 13-4. Uterotonic drugs for use of third stage PPH prophylaxis

Medication	Dose	Primary route alternatives	Frequency of dose	Side effects	Remarks/ Contraindications
Oxytocin	10–40 U/L in normal saline or Ringer's	IV/IM/Intramyometrial. IV in umbilical cord vein	Continuous infusion	Usually none; water retention or intoxication	Action short; repeat doses often needed
Methergine	0.25 mg	IM/slow IV/ intramyometrial	Every 2–4 hours	↑ BP, nausea, vomiting	Hypertension, preeclampsia, heart disease
15-Methyl F2α	0.25 mg	IM/intramyometrial	Every 15–90 minutes for maximum of eight doses	Nausea, vomiting, asthma, flushing, fever and chills, diarrhea	Cardiac, respiratory, renal disease
Dinoprostone	20 mg	Oral/per rectum	Every 2 hours	Same as above	Hypotension
Misoprostol	400–600 µg	Oral/per rectum/vaginal	Every 2–4 hours	Shivering, fever	Rural set-up

of maternal deaths in the developed world, but is the leading cause of maternal mortality (about 25%) in India. Nutritional deficiency, poor general health, anemia, poorly supervised delivery, lack of transport facilities and blood transfusion services combine to add to the woes of underdeveloped countries and contribute to adverse maternal outcome. The use of uterotonic agents and the adoption of the policy of active management of labor go far in the prevention and control of atonic PPH (Table 13-4).

Atonic PPH: The commonest causes predisposing to atonic PPH include retained products, membranes, and placental tissue and infection. A timely exploration of the uterine cavity and removal of products digitally or blunt curettage along with uterotonic agents helps to control bleeding (Bhalerao, 2004; Kore et al., 2000; Reddy and Shenoy, 2001) in most cases. Ananthasubramaniam and others (1988) reported successful control of atonic PPH with injection of $PGF_{2\alpha}$ in 83% of patients who had not responded to oxytocin or ergometrine. Shivkar's intrauterine balloon pressure therapy has helped to save many lives, but it needs wider evaluation (Shivkar et al., 2003). Intrauterine packing may still have a place in rural India as a life-saving procedure. Timely replacement of blood is important. Always exclude local traumatic causes, if in spite of the above measures, if the response is not satisfactory and consider timely transfer to an appropriate facility or consider surgical intervention (bilateral tying of uterine vessels, bilateral ligation of hypogastric arteries, B-Lynch suture, or hysterectomy as a life-saving measure). Facilities for radiologic selective embolization of the pelvic artery are not generally easily available.

Secondary PPH occurs between 24 hours and 6 weeks after delivery, although the first bout is usually small and often ignored, it can assume life-threatening proportions. It often follows cesarean section, and it is generally due to infection. In a review of maternal mortality from West Bengal (Darjeeling), the authors (Mukherji et al., 2002) reported that 65% of maternal deaths occurred in the postpartum period and of these, 31.2% were attributed to secondary postpartum bleeding. Again in another study (Roy Chowdhury and Bandopadyaya, 2002) from West Bengal (Bankura), secondary PPH was reported in 18 cases following cesarean section. Thus secondary PPH should not be treated lightly. All cases should be investigated, observed, and treated effectively.

Traumatic PPH accounts for 6–15% of all cases of PPH. It should be suspected particularly following an operative vaginal delivery or following an episiotomy or perineal injury. Clinically, if the uterus is well contracted in the presence of brisk vaginal bleeding, it is imperative to inspect the lower genital tract (cervix, vaginal walls, perineum, and paraurethral regions) for injuries under a good light and to promptly repair the same.

Pelvic hematomas: Perineal hematomas occur as a result of shearing forces causing rupture of blood vessels or following failure to ligate a bleeder during surgical repair of episiotomy or perineal tear. If small, they get resolved spontaneously with passage of time, but large hematomas cause severe pain. The patient appears pale and restless; there may be unexplained tachycardia and fall in blood pressure. Inspection of the perineum often reveals swelling of the affected side of the perineum, covered with dusky or cyanotic shiny skin. Vaginal or rectal examination reveals the bulge of the hematoma. Treatment comprises surgical evacuation of the blood clot and ligation of any bleeders present, followed by closure in layers. In the event of retroperitoneal hematomas, surgical exploration may be called for; however, successful management with selective arterial embolization has also been reported (Vedantham et al., 1996).

Uterine inversion is a complication that occurs in 1:2000 to 1:50,000 pregnancies. It often follows mismanagement of the third stage of labor—cord traction of a fundal placenta when the uterus is relaxed; occasionally it

may follow secondary to sudden rise in intra-abdominal pressure after delivery, like retching, sneezing, or bout of strenuous coughing when the uterus is relaxed. This is a life-threatening complication and can lead to sudden shock and obstetric collapse, short cord, or sudden removal of placenta during MRP (manual removal of placenta) before the uterine tone returns. Immediate reposition generally succeeds, sedation may be necessary; O'Sullivan's hydrostatic method deserves a trial before resorting to surgical correction. Isolated cases of successful management of uterine inversion have been reported in Indian literature.

IMPORTANT POINTS

1. Classification of a placenta previa as total, partial, or low-lying has little value for patient management that is determined by the frequency and severity of bleeding episodes. This classification, however, has prognostic value because the frequency and severity of complications is greatest with total placenta previa.
2. The incidence of placenta previa is four times greater in patients with prior cesarean than in patients without uterine scars. Placenta accreta occurs more frequently when implantation occurs on the uterine scar.
3. The incidence of preterm delivery, the number of bleeding episodes, the severity of bleeding, and the number of units of blood transfused are significantly greater for patients with previa who bleed before 28 weeks.
4. There is no justification for vaginal digital examination in patients with painless vaginal bleeding in the third trimester.
5. An accurate diagnosis of placenta previa requires examination with endovaginal ultrasound.
6. Before 24 weeks only a cautionary significance should be given to the finding of placenta previa in routine ultrasound examination of asymptomatic patients. In 97% of these patients the placenta has moved away from the cervix by term.
7. Pregnant patients who have acutely lost between 15 and 30% of their blood volume in the third trimester exhibit orthostatic changes in pulse rate and diastolic blood pressure.
8. The probability of acquiring infection with transfusion therapy is small. *The risk of acquiring hepatitis C is 1% and will decrease when screening for this virus is available*. The risk of infection with HIV is 1 in 400,000 to 1 in 1,000,000.
9. Autologous blood donation for routine vaginal delivery or elective cesarean section should be discouraged since the likelihood of requiring transfusion during these procedures is low.
10. Typing and screening should be the first test ordered in anticipation of blood transfusion. It allows a more efficient use of resources and a more rapid response of the blood bank than does the type and crossmatch procedure.
11. Patients with placenta previa selected for expectant management should be hemodynamically stable and with pregnancy of less than 36 weeks.
12. Delivery before 36 weeks in patients with placenta previa is mainly for fetal or maternal reasons. After 36 weeks, there are no advantages in pregnancy prolongation and patients should be delivered.
13. The most important finding in the ultrasound examination of women with abruption is a globular, thick placenta, usually > 6 cm in diameter. A retroplacental clot is not frequently seen.
14. When abruption is severe enough to cause fetal demise, the average blood loss, mostly retroplacental, is 2500 cc. Therefore transfusion of PRC should be instituted in these patients shortly after admission, regardless of their initial vital signs or hemoglobin/hematocrit concentration.
15. To maintain adequate organ perfusion in a patient with severe abruption it is necessary to keep a hematocrit of at least 30% and a urinary output of at least 30 ml/hour.
16. With appropriate maintenance of the maternal status, vaginal delivery in patients with abruptio placentae and fetal death may take up to 24 hours.
17. Patients with abruptio placentae, alive fetus, and soft uterus likely have a separation less than 25% and the probability of vaginal delivery is good.
18. There are no data to substantiate early delivery for patients with a history of abruptio.
19. Human recombinant activated factor VII is the best pharmacologic agent available for the treatment of severe obstetrical bleeding.

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14

Rh Alloimmunization

CHAPTER OUTLINE

Before the discovery of the Rh system by Landsteiner in 1940, little was known about the etiology of erythroblastosis fetalis, a condition in which the fetus becomes edematous and often dies in the uterus from severe anemia and high-output cardiac failure. After this discovery, it was quickly learned that maternal Rh alloimmunization, with placental transfer of IgG antibodies, was the phenomenon responsible for the fetal red cell destruction. This was followed by the finding that spectrophotometric analysis of the amniotic fluid was an excellent index for measuring the severity of the fetal anemia and by the realization that early delivery and intrauterine transfusions (IUTs) could be lifesaving maneuvers for the compromised fetus. Finally, it was found that the administration of D-immunoglobulin to mothers at risk is an extremely effective way of preventing the initial immune response responsible for the problem. In the last decade the main advances are the clarification of the genetics of the Rh factor and the discovery of a noninvasive method, the peak velocity of the fetal middle cerebral artery, or mid-cerebral artery (MCA), to detect the occurrence of fetal anemia. Despite these advances the incidence of Rh alloimmunization remains constant at about six cases per 1000 births. This incidence is significantly greater in countries with limited availability of D-immunoglobulin.

PATHOPHYSIOLOGY

Erythroblastosis fetalis is a disease in which the red blood cells of the fetus and the newborn are hemolyzed by maternal alloantibodies (antibodies capable of reacting with red cells from the same species but not with red cells of the individual producing the antibodies) that have crossed the placenta. The resulting anemia leads to fetal heart failure, massive edema (hydrops fetalis), and intrauterine death. It also may cause varied degrees of neonatal hyperbilirubinemia (hemolytic disease of the newborn). Approximately 97% of all cases of erythroblastosis fetalis are caused by maternal antibodies directed against the RhD antigen present in the fetal red cells. The

BOX 14-1

Irregular antibodies associated with fetal or neonatal hemolytic disease

Blood group system	Related antigen
Kell	K
	k
	Ko
	K_{pa}
	Js^a
	Js^b
Rh (non-D)	E
	e
	C
	c
Duffy	Fy^a
	Fy^b
Kidd	Jk^a
	Jk^b
	Jk^3
MNSs	M
	N
	S
	s

remaining cases are caused by immunization against other fetal antigenic groups such as C, c, E, e, K, k, Fy^a, M, and Jk^a (Box 14-1). Maternal alloimmunization may be also the result of the transfusion of Rh-positive blood to an Rh-negative female. In response to this immunologic stimulation, the mother develops 19S and 7S antibodies, the latter being able to cross the placenta and destroy the fetal red cells.

During normal pregnancy, fetal red cells cross the placenta in 5% of the cases during the first trimester and in 46% by the end of the third trimester (Bowman et al., 1986). However, in the majority of cases maternal Rh sensitization is the consequence of fetal–maternal bleeding happening at the time of delivery. Passage of fetal blood into the maternal circulation at the time of parturition is the rule rather than the exception, but only 10–15% of Rh-negative mothers who have Rh-positive husbands become sensitized at delivery. This happens because in most cases the amount of fetal cells transferred to the mother is small and insufficient to produce a primary immune response. Other factors also influence the probability of primary alloimmunization. One of them is the size of the inoculum; it is accepted that the greater the number of fetal cells entering the maternal circulation, the greater the possibility of maternal sensitization, although some mothers have been immunized with as little as 0.25 ml of fetal Rh-positive cells. Another factor is the coexistence of ABO incompatibility between mother and fetus; if the mother is group O and the father A, B, or AB, the frequency of sensitization is decreased by 50–75% because the maternal anti-A or anti-B antibodies destroy the fetal red cells carrying the Rh antigen before they can elicit an immune response. Furthermore, 30–35% of Rh-negative subjects are non-responders (cannot be immunized) to the Rh-positive antigen, a characteristic that seems to be genetically controlled.

When an immune response is elicited during pregnancy (incidence less than 1%) or at delivery (incidence 10–15%) in an Rh-negative mother who carries an Rh-positive baby, the initial maternal response will be the development of anti-Rh IgM antibodies with a molecular weight too large to cross the placenta. This is followed by the synthesis of anti-Rh IgG antibodies that cross the placenta and stick to the fetal red cells, accelerating their destruction in the infant's reticuloendothelial system. The time between the fetal–maternal bleeding and the initiation of the primary immune response in the mother is not exactly known and probably has some biologic variation. Usually there is an interval of several weeks between the time of the fetal–maternal bleeding and the appearance of anti-Rh antibodies in the maternal serum. That is why prophylactic administration of D-immunoglobulin to the mother shortly after delivery inhibits the immune response. Even when the administration of D-immunoglobulin is delayed up to 2 weeks after transfusion of Rh-positive cells, the procedure is protective in 50% of the cases.

Once Rh alloimmunization has started, the mother may produce large amounts of antibodies (secondary response) in response to small amounts of fetal Rh-positive blood leaking through the placenta. The anti-Rh antibodies cross the placenta and attach to the infant's red cells, making them susceptible to destruction in the fetal reticuloendothelial system. Depending on the severity of the hemolysis, the clinical picture may include congestive heart failure, hepatomegaly, splenomegaly, peripheral edema, and placental hypertrophy. The marked hepatomegaly and splenomegaly present in hydropic stillborns result not only of the development of large foci of compensatory extramedullary hematopoiesis but also of the accumulation of fluid because of congestive heart failure. If untreated, about 20–30% of fetuses affected by erythroblastosis die in utero. Kernicterus (bilirubin deposits in the basal nuclei of the brain) and jaundice are not components of erythroblastosis fetalis during intrauterine life, because accumulation of the pigment is prevented by its removal through the placental circulation and metabolism in the maternal liver. However, after birth the newborn liver cannot effectively handle the large amount of pigment released during the brisk hemolytic process, and this leads to rapid increases in serum bilirubin and eventual tissue deposition.

GENETICS

The genetics of the Rh factor has been elucidated in the last 10 years. The Rh factor is codified by two genes the RHD and the RHCE that are in close proximity on the short arm of chromosome number 1 (Mouro et al., 1993). The nucleotide coding sequence of the two Rh genes is 96% identical. The RHD gene encodes only for the RhD antigen while the RHCE gene encodes for the other four antigens (E, e, C, c). A nucleotide difference in the RHCE gene—cytosine to thymine—determines the expression of the C instead of the c antigen. Another single nucleotide change results in the formation of the E rather than the e antigen. Rh-negative individuals are homozygous for a complete deletion of the RHD gene. Rh-positive individuals may have one copy (heterozygous) or two copies (homozygous) of the RHD gene. This has practical importance because a homozygous Rh-positive father (DD), if mated with an Rh-negative mother, will necessarily pass to his offspring a D gene and, as a result, the offspring will be Rh positive in 100% of the cases. If the father is heterozygous (D), the chances of his child receiving the paternal D gene and being Rh positive are 50%.

The majority of Caucasian Rh-negative mothers are "ccee." For that reason Rh alloimmunization to antigens other than D, C, and E is rare. The C and E antigens usually cause immunization via blood transfusion rather than as a consequence of fetal–maternal bleeding during pregnancy. Other blood group systems different from the Rh have antigens with potential to cause fetal hemolytic disease. The most common are the K (Kell), Fy^a (Duffy), and Jk^a (Kidd). An antigen frequently found in routine antenatal testing is the Lewis group (Le-a and Le-b). The Lewis antigens do not cause fetal hemolytic disease and differ from all of the other red cell antigens in that they are not synthesized in the red cell membrane but are absorbed into it. Other rare antigenic groups may also cause mild to severe erythroblastosis fetalis (Table 14-1).

Table 14-1. Paternal genotype frequency

Reaction in test tube with anti: C D E c e	Type	Not excluded	Percentage	Homo/ hetero (H)(h)
+ + – + +	CDe/cde	CDe/cDe	32.0	h
		cDe/Cde	2.0	H
			0.1	h
			17.0	H
+ + – – +	CDe/CDe	CDe/Cde	0.8	h
			12.0	H
+ + + + +	CDe/cDE	CDe/Cde	1.0	h
		cDE/Cde	0.3	h
			11.0	h
– + + + +	cDE/cde	cDE/cDe	1.0	H
		cDe/cdE	0.1	h
			2.0	H
– + + + –	cDE/cDE	cDE/cdE	0.3	h
			2.0	h
– + – + +	cDe/cde	cDe/cDe	0.1	H

The general rules of Rh inheritance have exceptions. Some red cells react weakly with anti-D antibodies because they contain a gene that produces only a part of the D antigen. This variant is called Du and it should be absent (Du negative) in a given individual to be considered Rh-negative. A third allele of C and c has also been identified, most commonly in association with D and e, and has been called Cw. Some individuals have a rare state, termed Rh-null in which their red cells lack Rh antigens. As we will see later, some individuals of Asian and African ancestry have parts of nonfunctioning Rh genes that produce false positive Rh determinations with the polymerase chain reaction (PCR) technology.

DIAGNOSIS

The blood type, Rh group, and antibody screening should be determined in all pregnant women at their first prenatal visit. The presence of anti-D antibodies in the serum is diagnostic of maternal Rh alloimmunization. To test for antibodies, maternal plasma is incubated with Rh-positive erythrocytes and with serum rich in antiglobulin antibodies (Coombs' serum) and the red cells will agglutinate if Rh antibodies are present in the maternal plasma. The IgG anti-Rh antibodies have a relatively small molecular weight and are not capable of bridging the intercellular distance of 250 A that exists between red cells in solution to cause agglutination. This distance results from red cells repelling each other because of their negative surface charge. The addition of Coombs' serum to the maternal plasma decreases the intercellular distance and facilitates the agglutination of red cells when anti-Rh antibodies are present.

The concentration of anti-D antibodies is determined by a titration procedure in which progressively double dilutions of the maternal serum are incubated with group O Rh-positive erythrocytes and the agglutination of the erythrocytes is used as the end point of the reaction. Titer values correspond to the greatest dilution with positive agglutination. For example, a titer of 32 indicates that the tube with the greatest dilution where agglutination was detected had a dilution of 1:32. In most first-immunized pregnancies, the concentration of antibodies is so low that they can be detected only in undiluted serum and may not appear until late in pregnancy. The explanation for those cases of late appearance of antibodies is that fetal–maternal bleeding generating a maternal antibody response is more common in the later stages of gestation.

There are variations in antibody titers among different laboratories, and the obstetrician managing an immunized

pregnancy should use the same laboratory for all of the antibody titer determinations of a given patient. For maximal accuracy, serum samples should be stored and the procedure repeated in the original sample each time that a titer is determined in a subsequent sample. Also, it is important to know the critical titer level associated with intrauterine death for the reporting laboratory. For most laboratories the critical anti-D value is between 8 and 32.

All pregnant women should be screened for antibodies in the first prenatal visit. The screening should include Rh-negative women who have received anti-D immune globulin in a previous pregnancy because postpartum administration of anti-D immune globulin does not guarantee prevention of Rh alloimmunization. An antibody screening should also be obtained during the initial prenatal evaluation of Rh-positive mothers especially those who have had blood transfusions, unexplained fetal losses, or infants with unexplained jaundice.

MANAGEMENT

Rh-negative women presenting for obstetrical care can be categorized in two different groups: (a) Rh-negative nonimmunized women and (b) Rh-negative immunized women. To the last group it is necessary to add Rh-positive women immunized against non-D Rh antigens or against other blood group systems. These two sets of patients are managed differently. In Rh-negative nonimmunized women the objective of management is *prevention* of Rh alloimmunization. In women who are already immunized the objective of management is *early detection and adequate treatment* of fetal anemia.

Management of Rh-Negative Nonimmunized Women

Rh-negative nonimmunized women do not have detectable alloantibodies in the initial prenatal evaluation. In these cases the first thing to do is to determine the Rh phenotype of the baby's father. If the father is Rh negative the baby will be Rh negative, the possibility of alloimmunization does not exist, and the pregnancy should be managed like any other normal pregnancy without any further testing or treatment related to the Rh factor. If the baby's father is Rh positive, there is 50 (father heterozygous) to 100% (father homozygous) probability that the fetus will inherit one copy of the RHD gene and therefore Rh alloimmunization may occur during pregnancy. In these cases it is not necessary to determine the Rh genotype of the father because even in the best of the circumstances (father heterozygous for the D antigen), the probability that the fetus will be Rh positive is substantial and the plan of management will be identical to that for the homozygous father. If the father is Rh positive, it is necessary to design a strategy to detect Rh alloimmunization if it occurs during the first 28 weeks of pregnancy and to prevent its occurrence during the last 12 weeks and at the time of delivery when fetal–maternal bleeding is more common.

Detection of Rh alloimmunization

The possibility that Rh sensitization may occur before delivery is small (about 1%). To identify the few Rh-negative women who will develop antepartum sensitization, the antibody screening should be repeated at 20, 24, and 28 weeks of gestation. If anti-D antibodies are detected, the woman has developed Rh alloimmunization and her management becomes similar to that of Rh-negative immunized women. If the antibody screening does not show evidence of alloimmunization, the patient should receive anti-D immune globulin at 28 weeks of gestation and further antibody screenings will be unnecessary. Also, at the time of delivery it will be necessary to determine the mother's eligibility for a second dose of anti-D immune globulin.

The need for antibody screening every 4 weeks in nonimmunized Rh-negative women is not universally accepted because Rh alloimmunization rarely happens during the antenatal period and because the first immunized pregnancy rarely produces severe fetal hemolytic disease. For these reasons some prefer to limit the testing to the antibody screening that is performed before the administration of Rhogam at 28 weeks. However, testing every 4 weeks will avoid missing the development of antibodies in the occasional patient who becomes immunized before delivery and will prevent the rare poor fetal outcome that may result from inadequate surveillance.

Prevention of Rh alloimmunization

The antepartum administration of anti-D immune globulin at 28 weeks to Rh-negative women decreases the incidence of third trimester alloimmunization from 18 to 20/1000 to 2/1000 patients. After administration of anti-D immune globulin, the antibody screening will detect anti-D antibodies in the patient's serum, but the titer should not be greater than 4 at term. An anti-D titer greater than 4 at term most probably results from alloimmunization rather than from anti-D-immunoglobulin administration. The antepartum administration of anti-D immune globulin is not cost-effective. Many women will receive one or two doses of a relatively expensive medication, and only a few will benefit from it. However, anti-D immune globulin administration decreases the incidence of Rh alloimmunization and is the procedure of choice.

The Rh-negative gravida who remains unsensitized (negative antibody screenings) during pregnancy and receives anti-D immune globulin antepartum should have her eligibility for postpartum administration determined

immediately after delivery and anti-D immune globulin given when the following conditions are fulfilled:

1. The infant is Rh positive.
2. The direct Coombs' test on umbilical cord blood is negative. This test reveals whether or not the infant's red cells are covered by irregular antibodies.
3. The crossmatch between anti-D immune globulin and the mother's red cells is compatible.

The usual dosage of anti-D immune globulin is 300 mg. This amount is capable of neutralizing the antigenic potential of up to 30 ml of fetal blood (about 15 ml of fetal cells) and prevents Rh alloimmunization in 90% of the cases. In the other 10% of the cases D-immunoglobulin is ineffective, most probably as a consequence of insufficient antigenic neutralization following a large transfusion of fetal cells into the mother. A large fetal–maternal hemorrhage occurs in 1 out of every 300–500 deliveries, and it should be suspected with the birth of a pale baby, a fetal hemoglobin concentration of less than 10 g, abruptio placentae, midforceps operations, and traumatic deliveries. These indicators are not completely reliable, and ideally the volume of fetal blood transfused to the mother should be quantified with the use of the Kleihauer-Betke stain. This method is based on the fact that an acid solution (citric acid phosphate buffer, pH 3.5) elutes the adult but not the fetal hemoglobin from the red cells; fetal erythrocytes appear in a smear stained dark red and surrounded by colorless ghosts that are adult erythrocytes without hemoglobin. This test can detect as little as 0.2 ml of fetal blood diluted in 5 L of maternal blood. The Kleihauer-Betke test is not useful and should not be used to determine the need for D-immunoglobulin administration. In fact, about 50% of Rh-negative mothers who become sensitized have negative postpartum Kleihauer-Betke testing. The Kleihauer-Betke test is difficult to perform and may produce false positive results as a consequence of multiple factors affecting the acid elution of hemoglobin from the red cells. Also, the presence of reticulocytes and adult red cells containing fetal hemoglobin may cause false positive results.

In USA, a crossmatch of the anti-D immune globulin against the mother's red cells is carried out before the administration of this product. This practice had its origin in the initial trials to determine the effectiveness of anti-D immune globulin prophylaxis, at which time there was a fear of causing hemolysis in the recipient. Today it is known that the infusion of plasma containing anti-D antibodies is innocuous and does not cause intravascular hemolysis. However, the practice continues because an important benefit of the anti-D immune globulin crossmatching is its ability to detect a large fetal–maternal hemorrhage. In fact, if more than 20 ml of fetal blood has entered the maternal circulation, the anti-D immune globulin reacts and agglutinates the fetal erythrocytes present in the maternal blood and the crossmatch becomes incompatible. Because of its simplicity, the D-immunoglobulin crossmatch is widely used in place of the Kleihauer-Betke stain to screen mothers in need of high dosages of D-immunoglobulin. However, the threshold sensitivity of the D-immunoglobulin crossmatch is high, and the Kleihauer-Betke test should be the procedure of choice to assess the volume of the fetal–maternal bleeding.

Anti-D immune globulin can be given any time up to 4 weeks after delivery. The maximal protective effect is obtained if the antibody is administered within 72 hours following delivery. This limit was chosen arbitrarily in the original experiments in which the value of D-immunoglobulin in preventing Rh alloimmunization was proven. Other experiments have shown that administration of anti-D immune globulin several days and even weeks after delivery still has a protective effect although the efficiency of the protection is reduced. Therefore, anti-D immune globulin should be given to any eligible Rh-negative mother as soon as possible after delivery, and treatment should not be withheld if more than 72 hours have passed in the postpartum period. The administration of anti-D immune globulin to eligible mothers after delivery decreases the incidence of Rh sensitization from 15 to 1 or 2%. The 1-in-10 failure rate results from undetected large fetal–maternal bleeding or from alloimmunization occurring before delivery. Anti-D immune globulin should also be given to all nonimmunized Rh-negative women after spontaneous or induced abortions, after amniocentesis, and after ectopic pregnancies. Since the half-life of anti-D immune globulin is 24 days, approximately 20%

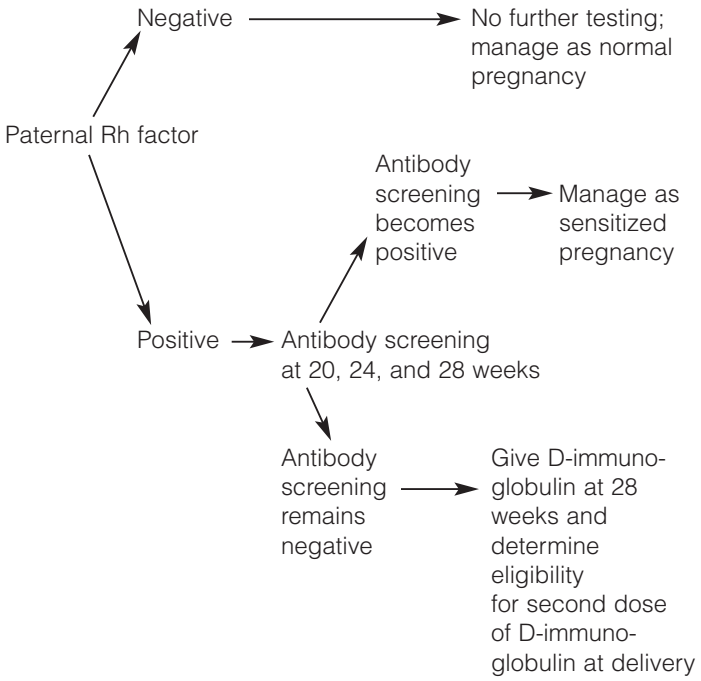

Figure 14-1. Management of Rh-negative nonimmunized women.

of women receiving treatment at 28 weeks will have no demonstrable antibodies at 40 weeks. For that reason some experts recommend a second dose of anti-D immune globulin if the pregnancy continues after 40 weeks.

A summary of the management of Rh-negative nonimmunized women is shown in Figure 14-1.

Management of Rh-Negative Immunized Women

The management of Rh-negative women immunized in a prior pregnancy or with immunization secondary to the administration of incompatible blood products requires, as a first step, the determination of the paternal and fetal Rh phenotype and genotype.

Paternal Rh phenotype and genotype

Determination of the paternal Rh phenotype is the first step. If the father of the baby is Rh negative the fetus will not be affected and further tests are unnecessary. If the father is Rh positive it is necessary to determine if he is homozygous or heterozygous for the RHD gene. The only exception to this rule is if the couple had an Rh-negative infant in a prior pregnancy, because in this case the father is heterozygous.

The father's genotype is indirectly determined by serologic testing for the antigens produced by the RHD and the RHCE genes and comparing the results with genotype frequency tables (Table 14-1). This is possible because of the closely linked inheritance of the RHD and RHCE genes. For example, a Caucasian Rh-positive father with positive serologic testing for Dcce, DCEe, or Dce antigens will have 90% or more probability of being heterozygous. The probability will decrease with the number of children he has parented that are Rh positive. There are mathematical models that take into consideration the ethnicity and the paternal history of Rh-positive neonates (Kanter, 1992) to determine the number of alleles in the paternal RHD gene. If the father is heterozygous, the fetus has a 50% probability of being Rh negative and determination of the fetal Rh becomes mandatory to avoid unnecessary testing in the 50% fetuses that will be Rh negative. If the father is homozygous, the fetus will be Rh positive and amniocentesis to determine the fetal Rh will be unnecessary.

Fetal Rh determination

The fetal Rh genotype can be determined using cells collected by chorionic villous biopsy (CVS) or amniocentesis. The fetal Rh phenotype can be determined by serologic testing using fetal blood. CVS has the advantage of being done early in pregnancy and the potential disadvantage of increasing the severity of the alloimmunization if the fetus is Rh positive. Fetal blood sampling is a more complicated procedure and has greater morbidity and mortality than CVS or amniocentesis but it will allow the fetal Rh phenotype to be known rapidly by conventional blood bank serology. Amniocentesis is the method of choice to obtain fetal tissue for Rh factor determination because of its simplicity and safety,

To determine the fetal Rh genotype in amniocytes, it is necessary to use DNA technology. The fetal cells contained in the amniotic fluid are cultured in order to obtain an adequate amount of DNA. The genomic DNA is used for genetic amplification by PCR (Simsek et al., 1995). The primers for this reaction are highly specific for the RHD gene. The end point is whether or not the RHD gene is present in the amniocytes and can be amplified by the PCR. However, PCR technology cannot determine if there is one or two alleles of the RHD gene. A different DNA primer is used to amplify the RHCE gene to determine the C/c and E/e composition.

The PCR test is erroneous in 1–2% of the cases. The causes of PCR errors are contamination, failed amplification, and genetic rearrangements of the RHD gene. The worst consequence of this is when the PCR erroneously reveals an Rh-negative fetus because this will result in lack of surveillance for hemolytic anemia and potential fetal death. To avoid this problem it is prudent to repeat the antibody titer at 4 weeks' intervals in Rh-sensitized women with an Rh-negative fetus diagnosed with PCR. A fourfold increase in titer will make the accuracy of the PCR determination of the fetal Rh suspicious. There are also false Rh-positive results with the PCR. Some individuals of African ancestry possess only a part of the RHD gene (Singleton et al., 2000). The incomplete gene or pseudogene cannot codify for the D antigen and serologically they are Rh negatives. However, the incomplete gene will be copied by the PCR and the Rh-negative fetus may falsely appear to be Rh positive by amniocentesis and PCR.

In the near future the fetal Rh can be determined from the free fetal DNA that is present in maternal plasma in relatively high concentrations. This approach first requires determining that the DNA is fetal in origin. Then PCR is used to amplify RH gene-specific sequences to confirm or deny the presence of the RHD gene (Lo et al., 1998; Finning et al., 2002).

The management of sensitized Rh-negative women with an Rh-positive fetus is different if the pregnancy is the first affected one or not.

First affected pregnancy

The first affected pregnancy is the only pregnancy in which maternal anti-Rh antibody titers can be used to determine the risk of fetal anemia. The reason for this limitation is that the correlation between antibody titers and transfer of fetal cells into the maternal circulation that

exists in the first affected pregnancy is lost during subsequent gestations. Also, in the majority of first immunized pregnancies the anti-Rh antibody concentration is low and rarely exceeds the critical level of most laboratories. The critical level means that no death due to fetal hemolytic disease has occurred within 1 week of delivery when the antibody titer was at that level or lower.

Serum antibody titers

Patients in the course of their first sensitized pregnancy should have antibody titers every 4 weeks unless the following occur:

1. The titer is found to be at or above the critical level (usually 32) on the initial evaluation.
2. The titer reaches or exceeds the critical level at any time during gestation.
3. There is a significant rise in titer (two-tube dilution) between two consecutive samples, even if the upper dilution does not reach the critical level (e.g., an increase from 4 to 32 with a critical level of 64).

If any of these conditions occur, there is no further use for antibody titers for following the first sensitized pregnancy and further management will be based on fetal assessment using the mid-cerebral artery peak systolic velocity (MCA PSV) and the concentration of bilirubin in the amniotic fluid.

If the antibody titer remains under the critical level up to 36 weeks of gestation, the patient with a first sensitized pregnancy should be delivered by elective induction of labor between 38 and 40 weeks, and the birth of a nonaffected (Rh-negative) or mildly affected Rh-positive infant should be anticipated. In these cases the neonatologist should be notified in advance of the induction of an Rh-negative immunized mother so that evaluation and treatment of the newborn can be started in the delivery room and continued without delay.

Women with a first sensitized pregnancy followed with antibody titers that have a sudden antibody titer elevation when they are more than 34 and less than 37 weeks' gestation should have amniocentesis and delivered if the fetal lung maturity is adequate. If the fetal lung maturity tests indicate pulmonary immaturity and the bilirubin level is low (less than 0.05), the pregnancy should be allowed to continue as long as weekly amniocentesis shows fetal pulmonary immaturity and a low bilirubin concentration. These babies usually have mild hemolytic disease and should be delivered as soon as their lungs reach adequate maturation.

Women with a previous affected pregnancy

After the first affected pregnancy, the ability to predict fetal anemia from the maternal anti-D titers is lost and different methods are necessary to evaluate the likelihood of fetal anemia. In these cases the past obstetric history is the predominant indicator of the outcome. Sensitized patients with negative past obstetrical history and titers remaining at or below 64 have a 4% incidence of intrauterine death before 37 weeks. In contrast, patients with similar titers but with histories of delivering affected infants have a 32% stillbirth rate before 37 weeks. When the titer is above 64, patients with negative obstetrical histories have a stillborn incidence of 17.2%, whereas those with histories of affected infants have a stillborn rate of 67.8%. Since titers are not predictive of outcome, women with prior affected pregnancies should be followed with serial determinations of the PSV of the fetal middle cerebral artery (MCA PSV) and with amniocentesis to determine the concentration of bilirubin in the amniotic fluid.

Middle cerebral artery peak velocity

The MCA PSV is an accurate noninvasive method for the diagnosis of fetal anemia (Mari et al., 1995). The correlation between the MCA PSV and fetal anemia becomes stronger as the fetal hemoglobin decreases (Mari et al., 2000). Also, MCA peak velocity values can be used to predict the fetal hemoglobin concentration (Mari et al., 2002).

The technique for measuring the MCA peak velocity is not complicated and has a high index of reproducibility. Since the majority of fetuses are in cephalic presentation, the fetal head is relatively fixed and does not move excessively during the examination. The ultrasound probe is used to obtain a view adequate for the measurement of the biparietal diameter and the vascular structures are identified with color Doppler. The MCA of the cerebral hemisphere closer to the ultrasound transducer is interrogated a few millimeters after its origin from the internal carotid artery but without including any part of this artery and taking care that the angle of insonation is as close as possible to 0° (Figure 14-2). The fetus should be resting, since activity will cause falsely elevated PSV

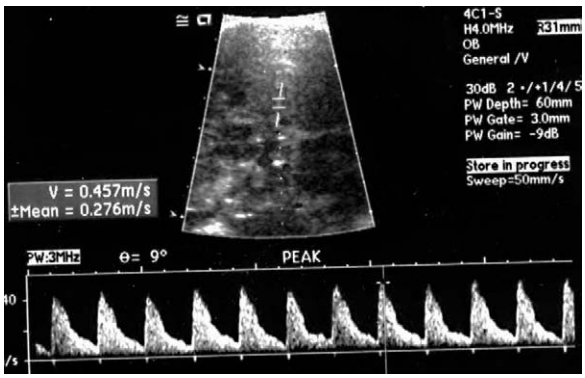

Figure 14-2. Determination of middle cerebral artery peak systolic velocity.

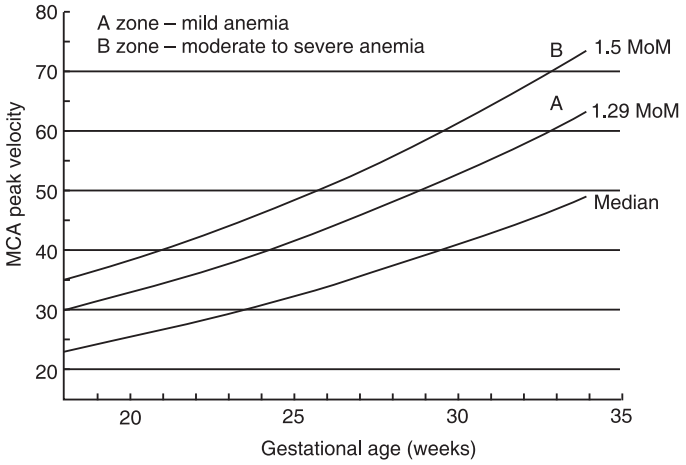

Figure 14-3. Normal values for middle cerebral artery peak systolic velocity with gestational age. (From Moise KJ, Jr. Management of rhesus alloimmunization. Obstet Gynecol 2002; 100: 600–11).

values (Sallout et al., 2004). The distal part of the MCA should not be used for this measurement and if it is not possible to interrogate the proximal part of the MCA closer to the ultrasound probe, it is better to examine the proximal part of the MCA from the cerebral hemisphere far from the ultrasound probe (Abel et al., 2003). Typical waveforms are obtained and the PSV of at least three of them is measured and averaged. The threshold for the diagnosis of fetal anemia is a value equal to or greater than 1.5 multiples of the median (MoM) for the gestational age (Figure 14-3). Abnormally elevated MCA PSV has a sensitivity of 100% and a false positive rate of 12% for the diagnosis of fetal anemia, and some investigators recommend cordocentesis and IUT as the next step following an abnormal MCA PSV. However, the false positive rate of the MCA PSV is at least 12% and a more conservative approach will be to perform amniocentesis to determine the concentration of amniotic fluid bilirubin. With this approach, cordocentesis and intravascular transfusion will be limited to fetuses showing abnormally elevated MCA PSV plus elevated amniotic fluid bilirubin.

Amniotic fluid bilirubin

Spectrophotometric analysis of the amniotic fluid to determine the concentration of bilirubin is the traditional method for evaluating the severity of the fetal hemolytic process and for determining the optimal time for IUT or for delivery of the infant. Usually the first amniocentesis is performed at 20 weeks but in women who start off with a high titer, who have had a baby that was hydropic or died in uterus, or whose ultrasound evaluation demonstrates early signs of fetal hydrops, the first amniocentesis may be done at 16 weeks. The decision regarding when to repeat the procedure will be dictated by the results of the amniotic fluid analysis, as will be discussed later.

Before performing an amniocentesis, the best site for the procedure should be determined using real-time ultrasound. The use of ultrasound has increased the success rate in obtaining adequate samples for amniotic fluid analysis to nearly 100%. Ultrasound allows identification of the placenta and delineation of the placental edges, and in the majority of cases amniocentesis can be performed safely without entering the placenta. Color Doppler is invaluable for visualization of the umbilical cord and gives the operator almost absolute certainty that the pocket selected for amniocentesis does not contain loops of cord. Once the tap site has been selected, the abdomen is prepared with aseptic technique using a Betadine solution. Local anesthesia is not necessary. Depending on the depth of the pocket, a 3.5–7.0-in. long, 22-G disposable needle is inserted to the depth previously determined. The tip of the needle should be visualized with ultrasound and the needle should be advanced until it reaches the center of the pocket of fluid.

Mild contractions occasionally occur following amniocentesis, but they usually subside after 30–40 minutes. In rare cases, contractions may continue and result in premature labor. Patients undergoing amniocentesis should be instructed to report if the contractions continue and become stronger, and if that is the case, therapy with tocolytic agents may be indicated.

A small button of red cells is frequently found after centrifugation of the amniotic fluid even when the amniocentesis yields clear fluid. This is not a "bloody tap," a term that is reserved for gross, visible contamination of the fluid with fetal or maternal blood. Bloody taps are less common since amniocenteses are done under ultrasound guidance. In the large majority of cases, the blood is maternal in origin, but it may be a mixture of maternal and fetal cells, especially in cases of transplacental amniocentesis. If fluid grossly contaminated with blood comes out of the needle after amniocentesis, the best thing to do is to let the fluid escape to see if spontaneous clearing occurs. If the hematocrit value after clearing is more than 5%, the determination of bilirubin will be distorted and should not be used for patient management. If the fluid is grossly contaminated, the chances of adequate spontaneous clearing are low, and the amniocentesis should be postponed for 1 week.

Infection is a rare complication of amniocentesis. The resulting chorioamnionitis usually leads to preterm labor and results in preterm delivery. The treatment is evacuation of the uterus. Adherence to aseptic technique is the key to the prevention of this problem.

The peak absorption of meconium in amniotic fluid is similar to the Soret's band of hemoglobin and as a consequence, meconium causes a marked rise in bilirubin values,

a change that does not disappear after centrifugation. For this reason, meconium-stained specimens should not be used for patient management. Another source of error in the evaluation of fetal anemia by amniocentesis is an increased amount of fluid. With polyhydramnios the bilirubin content of the amniotic fluid is diluted, resulting in falsely low bilirubin values.

In women with multiple pregnancy, each fetus should be evaluated separately. In the case of twin pregnancy, both, neither, or only one of the twins may be affected and each one of the amniotic sacs should be aspirated. In these cases, the help of ultrasound is invaluable. It allows (a) visualization of the membrane separating the sacs and (b) its penetration by the needle if a single puncture is chosen as the procedure of choice. If each sac is to be entered, 1 ml of indigo carmine may be injected into the sac entered first. The fluid obtained from the second sac must be clear; if it shows a blue color, the tip of the needle is in the first sac.

About 5–10 ml of amniotic fluid is required for spectrophotometric analysis. The fluid should be kept in a brown bottle to protect it from exposure to the sunlight, which destroys some of the bilirubin and causes false low readings. The fluid is centrifuged at 4000 rpm for 20 minutes and analyzed by spectrophotometry. When normal amniotic fluid is examined in a spectrophotometer using water as a blank, the optical density (OD) readings between 350 and 650 nm form an almost straight line. If the amniotic fluid contains bilirubin, the OD readings will show a peak at 450 nm, and the size of the peak will be proportional to the amount of pigment in the fluid. Rather than using continuous scanning between 350 and 650 nm, the majority of laboratories measure the OD at 375, 450, and 525 nm. The results are plotted on semilogarithmic paper, and a straight line is drawn between the readings at 375 and 525 nm. The difference between the point at which the line crosses the 450-nm mark (expected value) and the actual reading at this wavelength is the delta OD at 450 nm (ΔOD450), which is used for patient management.

During normal pregnancy the ΔOD450 values change with gestational age and it is necessary to use adequate norms to correlate the laboratory values with the fetal situation. The original Liley curve has been used for this purpose for more than 40 years. In his original description, Liley (1961) recorded the ΔOD450 of 101 immunized patients on semilogarithmic paper (gestational age in weeks on the ordinate, ΔOD450 values on the abscissa) and divided the graph into three zones (Figure 14-4). The upper zone or zone 3 corresponded to severely affected infants, the low zone or zone 1 to nonaffected or mildly affected babies, and the middle zone or zone 2 included fetuses severely and mildly affected.

If the amniotic fluid shows a ΔOD450 value in zone 1, there is no immediate danger of intrauterine fetal death, and the procedure should be repeated in 4 weeks. If the ΔOD450 values remain in zone 1 in repeated amniocentesis carried out every 4 weeks, the patient

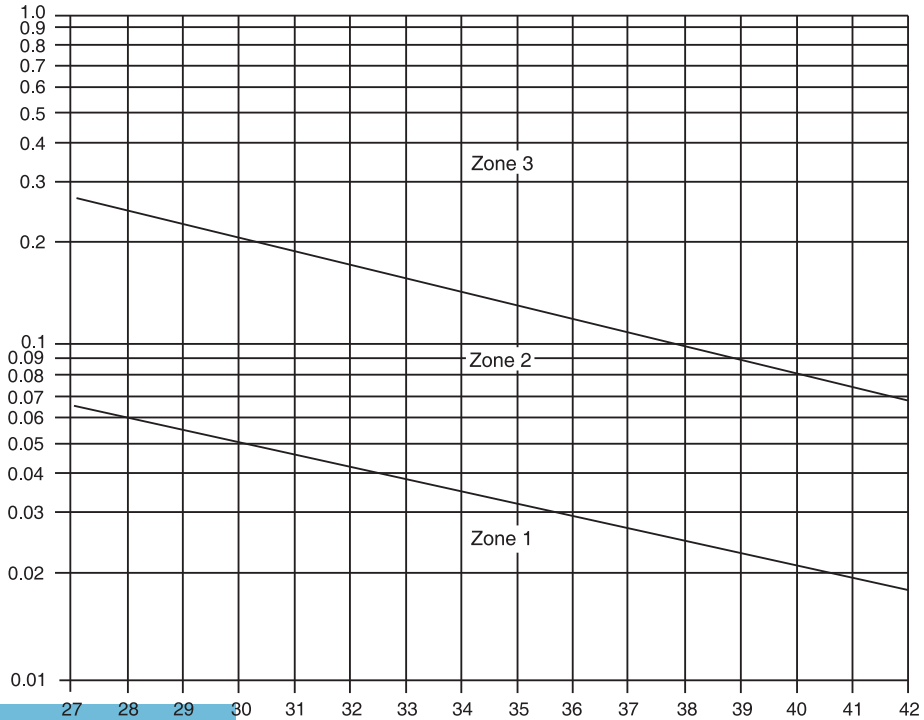

Figure 14-4. Liley graph to estimate severity of fetal hemolytic anemia.

should be delivered at term, and the birth of a nonaffected (Rh-negative) or a mildly affected baby should be anticipated. If at any time the amniotic fluid shows a ΔOD450 value in zone 2, the procedure should be repeated in 1 week, since values in this zone may correspond to moderately or severely affected infants. If the following amniocentesis shows a ΔOD450 value in zone 1, there is no need to repeat the amniocentesis before 4 weeks. If the following amniocentesis shows a decreasing trend in ΔOD450 value but the lower value is still within zone 2, the amniocentesis should be repeated in 2 weeks. If the following amniocentesis shows a ΔOD450 value similar to the previous one and still within zone 2 (horizontal trend), the procedure should be repeated in another week, and if the horizontal trend continues, cordocentesis and evaluation of the fetal hematocrit are indicated with exception of those patients with adequate fetal lung maturity who are better managed by immediate delivery.

If the initial amniotic fluid examination shows a ΔOD450 in zone 3 or if any ΔOD450 value previously in zone 1 or 2 moves to zone 3 (rising trend), the infant may be in imminent danger of intrauterine death. In these cases, fetal blood sampling should be done and IUT performed if the fetal hematocrit is less than 30%. IUT may be avoided in fetuses with adequate indices of lung maturation because in these cases delivery is the management of choice. A summary of the management protocol using Liley zones is shown in Figure 14-5.

The main limitation of the Liley curve is that it starts at 26 weeks' gestation, and extrapolation of the lines to earlier gestational ages is inaccurate. Other investigators (Queenan et al., 1993) have developed a curve for fetal assessment from 14 to 40 weeks, divided into 4 zones (Figure 14-6). The lower, first zone corresponds to nonaffected Rh-negative fetuses. Values in the second zone are indeterminate and do not permit a determination of whether the fetus is affected or not. The third zone corresponds to affected Rh-positive fetuses. The upper zone corresponds to fetuses at risk of intrauterine death. In general, a ΔOD450 greater than 0.15 indicates severe immunization and the need for cordocentesis and early transfusion. Values below 0.09 indicate mild disease or no disease. Values between 0.09 and 1.5 will require repeat amniocentesis in 1 week. After 26 weeks the need for intervention can be determined using the Liley graph.

Amniotic fluid bilirubin and MCA PSV can be used together in the diagnosis of fetal anemia. PSV should be the initial test because it is not invasive and has better predictive values than amniotic fluid bilirubin concentration (Nishie et al., 2003; Pereira et al., 2003). When the MCA PSV is above normal limits, amniocentesis to determine the amniotic fluid bilirubin concentration should be performed before cordocentesis to avoid invasive procedures in nonanemic fetuses. In several of these cases the DOD450 will demonstrate values below the transfusion zone and IUT can be avoided or postponed.

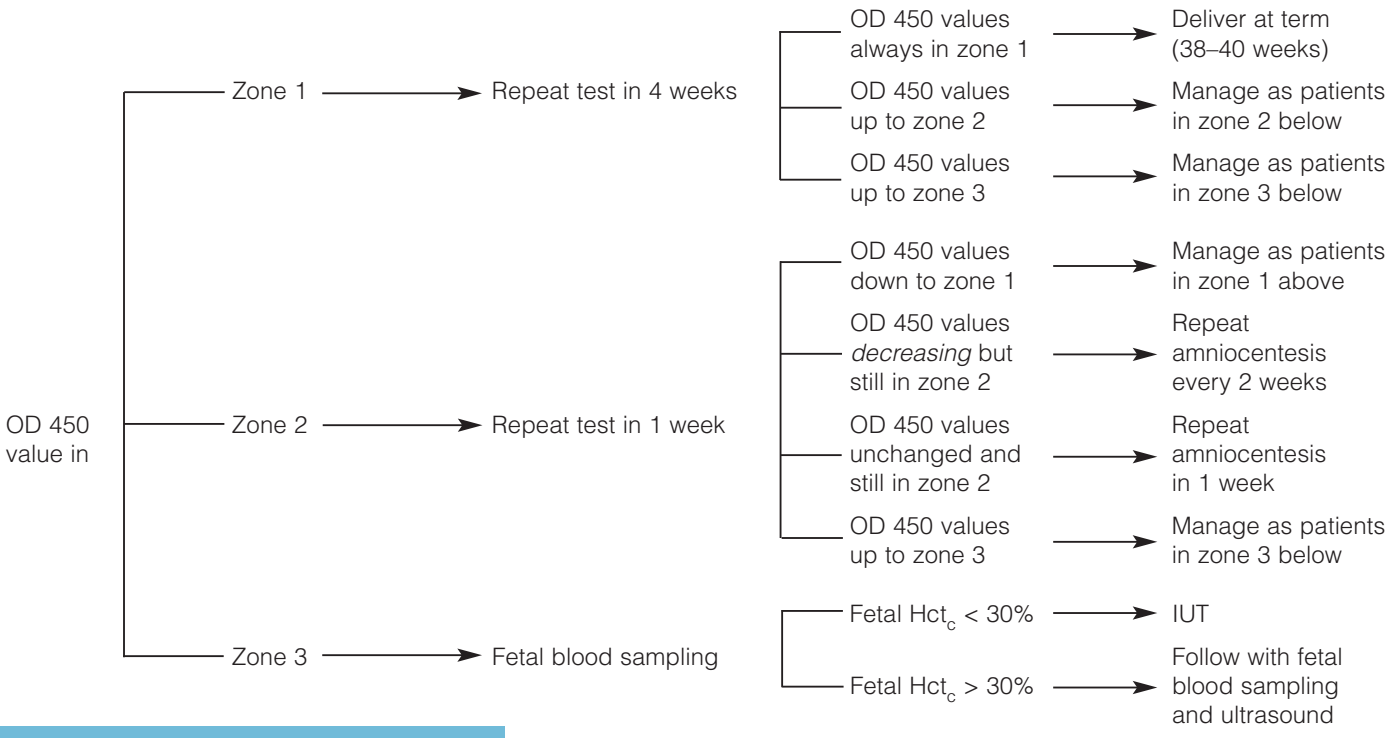

Figure 14-5. Management of Rh alloimmunization by amniotic fluid analysis.

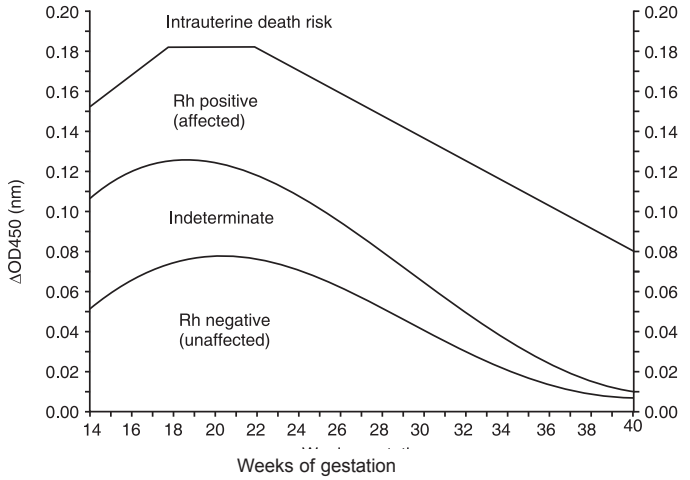

Figure 14-6. Curve for OD450 values from 14 to 40 weeks' gestation. (From Queenan et al. Deviation in amniotic fluid optical density at a wavelength of 450 nm in Rh-immunized pregnancies from 14 to 40 weeks' gestation: a proposal for clinical management. Am J Obstet Gynecol 1993; 168: 1370–6).

Ultrasound assessment

High-resolution ultrasound is a valuable tool in the management of sensitized Rh-negative patients. Modern equipment allows a clear visualization of the fetal structures and early diagnosis of the presence of fetal ascites, pericardial effusion, liver enlargement, and placental swelling. For these reasons, some investigators believe that the accuracy of ultrasound in detecting signs of fetal hemolytic disease is better than amniotic fluid bilirubin measurements (Frigoletto et al., 1986; Reece et al., 1989).

There are two important caveats in the use of ultrasound as the main indicator of fetal hemolytic disease. In the first place, fetal hydrops usually develops when the fetal hematocrit is below 20% and ultrasound will only detect advanced degrees of fetal anemia. Secondly, in many patients the onset of fetal hydrops is rather sudden and its detection by ultrasound will require the performance of frequent evaluations. Proponents of the use of ultrasound for the assessment of fetal anemia point out that ultrasound screening has no false positives like the MCA PSV and the amniotic fluid bilirubin. Once fetal ascites is detected, the fetus is anemic and IUT is necessary. However, MCA PSV and amniotic fluid bilirubin determinations can detect fetuses with moderate and severe hemolysis when ultrasound evaluation is still normal. Therefore, it is only in special circumstances that ultrasound should be used as the main criterion to judge the extension of the hemolytic process and the need for intervention.

Fetal blood sampling

The introduction of cordocentesis by Daffos et al. (1983) dramatically changed the management and the therapy of the Rh-sensitized patient. Umbilical cord blood sampling allows a precise measurement of the fetal hematocrit and hemoglobin concentration to determine the severity of the hemolytic process and the need for IUT. Also, the same technique may be used for direct intravascular transfusion to the fetus, a technique that has successfully allowed "in utero" treatment of hydropic fetuses unresponsive to transfusions into the peritoneal cavity.

For fetal blood sampling or transfusion the placental insertion of the umbilical cord is found using high resolution ultrasound and color flow mapping. Then, under ultrasound guidance a needle is introduced into the umbilical vein and fetal blood is drawn for determination of fetal blood group and Rh, direct Coombs' test, hemoglobin, and hematocrit. A hematocrit of less than 30% is an indication for IUT. Cordocentesis requires a degree of expertise and has the potential for serious complications. Cordocentesis is technically more difficult when performed between 16 and 20 weeks.

The main indication for fetal blood sampling in the Rh-sensitized patient is a combination of a MCA PSV > 1.5 MoMs above the mean and an amniotic fluid bilirubin values in the high middle zone or in zone 3. Another clear indication is the finding of fetal hydrops by ultrasonographic examination. When fetal blood sampling is limited to these two indications, only those fetuses that have clear indication of severe hemolytic disease are exposed to the risks of cordocentesis.

The most common complication of umbilical fetal blood sampling is bleeding which is usually transient. However, blood loss from cordocentesis may be severe and may cause fetal death. Cordocentesis may also cause fetal–maternal bleeding and a large increase in antibody concentration with worsening of the hemolytic process. Also, thrombosis of the umbilical vessels and severe vasospasm with secondary fetal bradycardia are procedural complications. The risk of fetal death following cordocentesis is approximately 1.5% after 24 weeks and it may be as high as 5% before 24 weeks.

Intrauterine transfusion

Since its introduction in 1963, IUT has been instrumental in saving hundreds of infants affected by hemolytic disease secondary to maternal Rh alloimmunization. However, IUT results are not uniform. They are modified by variables such as the experience and skills of the obstetrician performing the procedure, the severity of the fetal disease, the placental implantation site, the maternal obesity, and the fetal lie, among many other factors.

There are two types of IUT: intraperitoneal and intravascular. In both methods, the procedure is carried out under visual control with real-time ultrasound. In intraperitoneal IUT the blood is injected into the peritoneal cavity and

transported by the lymphatic system into the fetal bloodstream. In intravascular transfusion, the blood is injected directly into the umbilical circulation. The two types of IUT are not mutually exclusive. They complement each other and either one or both of them may be used depending on the circumstances. Although the direct intravascular approach is the procedure of choice, it is not without problems and it is preferable to perform an intraperitoneal transfusion if the approach to the umbilical cord is difficult (posterior placenta, maternal obesity) or if a sample of fetal blood cannot be obtained after several attempts. The overall survival rate of fetuses transfused intravascularly is 84.8%, 80.1% for hydropic, and 89.5% for nonhydropic fetuses.

In the severely hydropic fetus, the intravascular approach offers the best possibility for successful fetal therapy. If access to the umbilical cord is difficult, it is possible to transfuse through the intrahepatic portion of the umbilical vein. Another access to the intravascular compartment of the fetus when everything else fails is the right ventricle of the heart.

IUT has a potential for serious complications. Perinatal death was approximately 11.0% (7.4% fetal and 3.9% neonatal) in a series of 254 fetuses treated with 740 IUTs (Van Kamp et al., 2005). Infection, rupture of membranes, and emergency delivery occur occasionally. The procedure-related complication rate is 3.1% per procedure.

Early delivery and glucocorticoids

The classical approach to the management of sensitized Rh-negative mothers was early delivery depending on the severity of the fetal hemolytic process. This has changed and at present most maternal–fetal medicine specialists perform the last transfusion at about 35–36 weeks and deliver at 37–38 weeks' gestation. If delivery before 36 weeks is necessary, the use of steroids to accelerate the maturation of the fetal lungs is recommended. Betamethasone 12 mg IM daily for 2 consecutive days or dexamethasone 6 mg every 12 hours for four doses are equally effective. We found (Arias et al., 1979) that glucocorticoid treatment has little immediate effect on the lecithin to sphingomyelin (L/S) ratio, and the studies by Caritis et al. (1977) show that RDS (respiratory distress syndrome) prevention occurs even if the infants with hemolytic disease treated with steroids are delivered when they still have immature L/S ratios.

Corticosteroids cause a decrease in ΔOD450 values. It is necessary to avoid the false sense of security given by the drop in delta ΔOD450 values that follows glucocorticoid treatment and to deliver the infant 24 hours after the second dose of betamethasone. Amniocentesis to assess fetal lungs maturity should be used generously after 34 weeks because delivery is the treatment of choice when the fetal lungs are mature.

Other treatment modalities

There are treatment modalities for women with Rh alloimmunization which have been used in cases of severe immunization with high initial titers and history of pregnancy losses due to fetal hydrops. They include plasmapheresis and administration of promethazine and IgG. The best evidence of benefit is for IgG administration. Voto et al. (1997) treated 69 women with extremely severe Rh alloimmunization. Thirty received IgG before 20 weeks, 400 mg/kg/day for 5 consecutive days every 2–3 weeks, followed by IUTs after 20 weeks and 39 received IUTs only. They found a significantly lower incidence in the number of fetal deaths in women treated with the combination of IUT and IgG.

ALLOIMMUNIZATION TO RH ANTIGENS DIFFERENT FROM D

When the mother has alloimmunization by the E or C antigens as a consequence of prior childbirth and the father is the same, it is not necessary to find the paternal Rh genotype because obviously the E or C antigens in the fetal blood originated in the father. In contrast, when the mother develops Rh alloimmunization against E or C following transfusion of blood products, it is necessary to know the paternal genotype. If the father is negative for these antigens, there is no possibility of fetal hemolytic disease and no further testing or treatment is necessary. However, if the father is positive for the antigen or antigens causing maternal alloimmunization, the pregnancy should be followed similarly to the more common anti-D alloimmunization.

Alloimmunization against the E and C antigens is the most frequently found after D and Kell. The E antigen traditionally has been considered to be less immunogenic than D and cause less severe hemolytic disease of the newborn. The contrary was demonstrated in a study of 62 newborns with positive direct Coombs' test born to mothers sensitized against the E antigen, and 42 had mild, 8 modest, 5 severe, and 1 very severe hemolytic disease of the newborn. Overall 21% of affected infants required exchange transfusion (Moran et al., 2000). This study also found that there was no correlation between anti-E titers in the maternal serum and the severity of the fetal anemia, an observation that has been found in other studies (Babinzki and Berkowitz, 1999; To et al., 2003). There are no published reports about the value of using MCA PSV in anti-E cases. Based on this information, it seems prudent to manage cases of anti-E alloimmunization with serial amniocentesis.

Anti-c alloimmunization is another relatively frequent cause of hemolytic disease of the newborns. In a study of 46 newborns with positive direct Coombs' test born to mothers sensitized to c, 26% had severe hemolytic disease (Hackney et al., 2004). Contrary to anti-E, there was good correlation between anti-c titers and hemolytic disease and amniotic fluid spectrophotometry. Therefore, patients with anti-c can be followed similarly to patients with anti-D.

INDIAN EXPERIENCE OF ERYTHROBLASTOSIS FETALIS

The commonest cause of erythroblastosis fetalis in obstetric practice is Rh incompatibility. The incidence of Rh-negative in Western countries is about 15%. But its incidence in India varies between 3 and 5.7% (Bhakoo, 1986; Gupte and Kulkarni, 1994; Salvi, 1998). The incidence of Rh sensitization during pregnancy is about 1.9% (Salvi, 1998) and the perinatal loss due to Rh alloimmunization has been reported to be between 1 and 2.5% (Shah and Shroff, 2004). Factors protecting against Rh sensitization include maternal–fetal blood group ABO incompatibility and immunological nonresponder status. The main causes of Rh sensitization in present-day practice are the following: Lack of awareness in many places in India, particularly in rural set-ups where the practice of routinely testing all pregnant mothers for their ABO and Rh blood groups is not being observed. In small rural towns, facilities for laboratory testing for isoimmunization are nonexistent. Lastly the benefits of protecting nonimmune Rh-negative mothers from isoimmunization with the use of prophylactic inj. anti-D immunoglobulin is either unknown or ignored because of cost considerations.

Fetomaternal hemorrhage (FMH), fetomaternal leak (FML), or transplacental leak (TPL) is the cause of isoimmunization. As little as 0.1 ml of leak can cause sensitization. The commonest antecedent event is delivery, but it is known to follow abortions, ectopic pregnancy, antepartum hemorrhage, etc. It is often precipitated during diagnostic obstetric procedures like chorion villus sampling (CVS) or amniocentesis. FMH has been reported during external version for breech presentations and following operative obstetric interventions (forceps delivery, cesarean section, and manual removal of placenta). In present-day practice of liberalized abortion laws and widespread acceptance of MTP (induced abortions), the incidence of Rh sensitization threatens to rise, unless the practice of protecting Rh-negative women undergoing MTP with anti-D prophylaxis is also universally accepted and practiced. Although sensitization commonly follows delivery, small asymptomatic and unsuspected fetomaternal leaks have been reported to occur during pregnancy. This led to the practice of offering all Rh-negative nonimmunized patients the benefit of antenatal inj. anti-D in the third trimester of pregnancy and again after delivery if indicated. Wherever facilities for assessing the quantum of FMH using the Kleihauer–Betke test are available, these should be availed of. In such patients, 20 µg/ml of FML calculated on the basis of the Kleihauer–Betke test would suffice to prevent isoimmunization. It also helps to save scarce resources.

Table 14-2. Incidence of FML following MTP (Indian Survey)

Author	Year	Incidence
Bakshi and Rosario-Pinto	1978	First trimester–1.0% Early second trimester (13–16 weeks)– 4.5% Late second trimester (17–20 weeks)–14.0% MTP accomplished by D&C–42.8%
Ambiye et al.	1985	First trimester–6.0%
Ramanan et al.	1980	First trimester–15% MTP using D&C–23.0%

Assessment of the incidence of FMH reveals that it occurs in 6.7% during the first trimester, in 13.9% during the second trimester, and in 29% during the third trimester (Reddy, 1999; Salvi, 1998). Its incidence following amniocentesis was reported to be 15–25%, and higher still after abortions. The incidence following MTP is higher than following spontaneous abortions, and the risks increase with gestation size (from first to second trimester) both following spontaneous and induced abortions (Desai, 1988). Reports from several Indian centers containing the incidence of TPH (transplacental hemorrhage) or FML following induced abortions (MTP) have been tabulated in Table 14-2.

The risks of sensitization also depend on the quantum of leak. The estimated risk of sensitization following an FMH of 0.1 ml was 1% , following FMH of 0.5–1.0 ml the risk was 25.0%, and following FMH of > 5.0 ml it was 65%. The quantum of FML was lower in women undergoing MTP by the method of suction evacuation as compared to those in whom a D&C was adopted to perform the MTP. The above data clearly established the role of the method of MTP and gestation size on the frequency of FMH and its effect on Rh sensitization (Daftary and Desai, 2006). Overall about 16% of Rh-negative women are at risk of isoimmunization, this risk is reduced to 1.5–2.0% if immunoprophylaxis with inj. anti-D immunoglobulin 300 µg is started antenatally at 28 weeks of gestation. A repeat top-up dose of inj. anti-D prophylaxis at 34 weeks is desirable or soon after delivery if the newborn is Rh-positive and the direct Coombs test on the cord blood is negative, to reduce the risks of immunization to the minimum (Daftary and Desai, 2006). Should the newborn be Rh-negative, there is no need

to administer the anti-D immunoprophylaxis. Deka et al. from New Delhi (2004) advocated determination of fetal Rh group by PCR on amniotic fluid obtained by amniocentesis. In case of Rh-negative pregnant women whose fetus is Rh-negative, the need for antenatal anti-D immunoprophylaxis is completely obviated (Deka et al. 2004).

The basic pathology of Rh isoimmunization results from the hemolysis of fetal RBCs as a result of maternal serum antibodies crossing the placental barrier into the fetal circulation and causing progressive hemolysis over time leading to fetal anemia and its grave consequences. A wide range of sonographic findings (Suresh, 1998) have been documented in response to fetal anemia. These changes not only include fetal organs and organ systems but also the fetal environment. These findings include hepatosplenomegaly, increase in portal venous diameter, and flow velocity (color Doppler flow studies). On sonography there may be evidence of presence of fluid in serous cavities, subcutaneous edema, disturbances of liquor distribution causing hydramnios or oligohydramnios, and some placentomegaly. Serial sonography is also useful in monitoring fetal growth pattern and well-being. Interventional sonography plays an important role in fetal cord blood testing, A fetal blood hematocrit of < 40% is indicative of fetal anemia. The lower the reading, the worse the prognosis. A hematocrit reading of < 30% after 26 weeks of gestation calls for prompt measures to improve fetal status or to save the fetus. In affected patients, serial testing of amniotic fluid and the charting of optical density at 450 µ on Liley's charts guides the clinician in deciding whether to continue keeping the patient under observation, to terminate pregnancy, or opt for performing an intrauterine fetal transfusion (cordocentesis followed by intravascular blood transfusion or intrauterine intraperitoneal transfusion). In earlier times the fetal prognosis following fetal hydrops was poor, but in present times with the facilities for intrauterine fetal transfusion being widely utilized, the prognosis has vastly improved. Successful intrauterine fetal blood transfusions have been achieved in India, but these cases are sporadic (Salvi, 1998).

IMPORTANT POINTS

1. The Rh factor is codified by two genes, RHD and RHCE, located in close proximity to each other in the short arm of chromosome number 1. Rh-negative individuals lack the RHD gene. Rh-positive persons may have one (heterozygous) or two (homozygous) alleles in the RHD gene.
2. The RHCE gene contains the information for the synthesis of the Cc/Ee antigens. One nucleotide change is responsible for the synthesis of C or c and E or e antigens.
3. In the majority of cases Rh alloimmunization results from the passage of fetal Rh-positive cells into the bloodstream of Rh-negative mothers at the time of delivery.
4. The distinction between homozygous and heterozygous Rh-negative fathers is made by serologic testing against the five antigens produced by the RHD and RHCE genes and comparing the results with genotype frequency tables based on allelic frequencies or using mathematical models which take into consideration serology, ethnicity, and paternal reproductive history.
5. Some individuals have a gene that produces only a part of the D antigen. This variant is called Du and it should be absent for a given individual (Du-negative) to be considered to be Rh-negative.
6. Some antigens frequently found in routine antepartum testing belong to the Lewis group. The Lewis antigens do not cause fetal hemolytic disease.
7. Usually there is an interval of several weeks between the time of the fetal–maternal bleeding and the appearance of anti-Rh antibodies in the maternal serum. The administration of an adequate amount of D-immunoglobulin shortly after delivery inhibits this immune response.
8. In as many as 10% of the cases, postpartum administration of the usual dose (300 µg) of D-immunoglobulin is ineffective to prevent the development of Rh alloimmunization. In most cases this is the consequence of insufficient antigenic neutralization by the D-immunoglobulin of a large fetal–maternal transfusion. A large fetal–maternal transfusion should be suspected with the birth of a pale baby, a fetal hemoglobin of less than 10 g/dl, abruptio placentae, midforceps operations, and traumatic deliveries.
9. Maternal antibody titers are useful for the follow-up of patients exclusively in their first immunized pregnancy. They are not useful during subsequent pregnancies.
10. There are two methods to indirectly determine the presence of fetal anemia: (a) measurement of the PSV of the fetal middle cerebral artery (MCA PSV) by Doppler ultrasound and (b) determination of the bilirubin concentration in the amniotic fluid. An MCA PSV > 1.5 MoMs or a bilirubin concentration in the zone 3 of the Liley curve strongly suggest the presence of fetal anemia and should be followed by direct evaluation using umbilical cord blood. The advantage of using the peak MCA velocity is that it is a noninvasive procedure without risk to mother or fetus.
11. Traditionally, the first amniocentesis was carried out at 24–26 weeks because the Liley curve used to evaluate the severity of fetal hemolysis starts at this gestational age. More recently, the Queenan's curve may be used to assess the severity of the fetal hemolysis from 14 to 40 weeks.
12. Direct intravascular IUT can reverse fetal hydrops and result in better than 80% good outcomes in these seriously compromised fetuses.

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15

Abnormal Labor and Delivery

CHAPTER OUTLINE

The approach to problems occurring during labor and delivery has substantially changed in the last decade. The most significant of these changes has been the acknowledgement that vaginal delivery is not the fundamental goal of good obstetrical care. Vaginal deliveries after prolonged labors, operative vaginal deliveries, and breech presentations are therefore quickly disappearing from modern obstetrical practice and being replaced by cesarean deliveries. Modern obstetrical practice is also characterized by the condensation of all labor abnormalities into a single condition, the "lack of progress in labor." Labor either progresses normally, progresses with minimally tolerable abnormalities, or there is a "lack of progress in labor" which is treated by cesarean section. In addition, there is a generalized fear of any situation associated with neurological damage of the fetus. This fear is reflected in no-tolerance policies for abnormal fetal heart rate (FHR) monitoring patterns that frequently are grouped under the term "fetal intolerance to labor."

Multiple factors are responsible for the present state of obstetrical practice. Among them:

1. Advances in anesthesia, blood banking, and pre- and postsurgical care which have made cesarean section a relatively safe operation
2. Medical–legal concerns that have transformed obstetrical practice into a discipline with zero tolerance for any risk factor associated with fetal/neonatal brain damage and cerebral palsy
3. An information explosion, which has generated more knowledgeable patients who believe in the safety and convenience of cesarean delivery and demand a surgical approach for their delivery
4. Increasing number of indications for cesarean delivery

BOX 15-1

Abnormalities of labor

- Lack of progress in the latent phase of labor
- Lack of progress in the active phase of labor
- Lack of progress during the second stage of labor

Many may disagree with the current trends and characteristics of obstetrical care, but there is no indication that they will change in the near future. To reflect more closely on what happens today in most labor and delivery units in USA, we classify labor abnormalities into three groups depending on the stage of labor when the abnormalities occur (Box 15-1). Another reason for this classification is the increased severity and poor prognosis of lack of progress in labor depending on the phase of labor when it occurs. Indeed, the prognosis of a labor abnormality and the risk for cesarean delivery increase dramatically when it occurs in the second stage of labor, it is less when it occurs in the active phase, and it is even less when it occurs during the latent phase. With respect to the treatment of labor abnormalities, we have purposely avoided offering instrumental vaginal delivery other than simple interventions as an option for the treatment of these disorders. The reason is that instrumental vaginal delivery is rapidly disappearing from obstetrical practice, and new generations of obstetricians are not adequately trained in this treatment modality.

NORMAL LABOR

Labor and delivery is a complex physiologic process resulting in the expulsion of the products of conception from the uterus into the outside world. This process is characterized by increased frequency, intensity, and duration of uterine contractions, by progressive effacement and dilation of the cervix, and by descent of the fetus through the birth canal. Normal labor usually occurs after 38 weeks of gestation, and the mechanism of its initiation has not been completely clarified despite extensive investigations on the subject. Experimental evidence strongly suggests that the fetus is the primary trigger of labor by means of a mechanism that involves the hypothalamic production of corticotrophin-releasing hormone and subsequent activation of the pituitary–adrenal–placental circuit. Interested readers will find more information about the mechanism of initiation of parturition in Chapter 7 of this book.

Most of the present understanding of labor and its abnormalities is based on the work of Emanuel A. Friedman (1978). Friedman constructed a graphic representation of labor by plotting cervical dilatation and descent of the presenting part against time. During normal labor cervical dilatation follows a sigmoid-shaped curve (Figure 15-1, line A) with three distinct parts: (a) the latent phase that corresponds to the initial part of labor where there is little progression in cervical dilation, (b) the active phase that is the part of the sigmoid curve where there is a fast progression in dilation, and (c) the deceleration phase that corresponds to the final part of the sigmoid curve where the rate of cervical dilation becomes slow again. The descent of the fetus through the birth canal (Figure 15-1, line B) follows a hyperbolic-shaped curve with little change during the latent and active phases of labor, followed by rapid progress starting at the beginning of the deceleration phase.

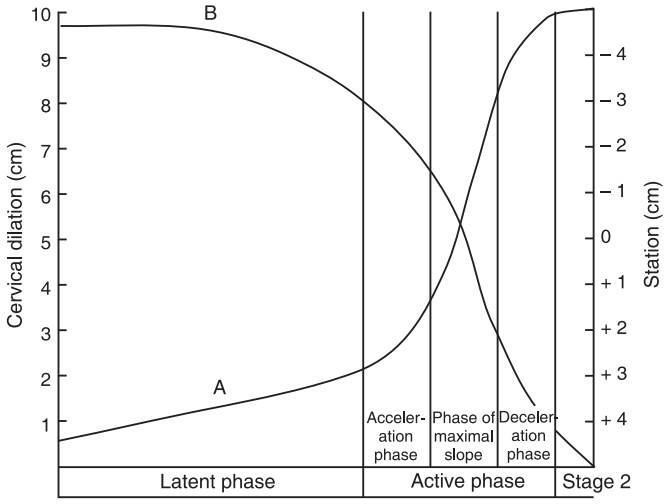

Figure 15-1. Graphic representation of labor (Friedman curve). Line A represents progress in cervical dilation with time and line B, descent of the presenting part with progression of labor.

Further research into the characteristics of human labor suggests the need for some changes to the original description of Friedman. It seems that the deceleration phase of cervical dilatation does not exist and that the cervix dilates in the active phase slower than as described by Friedman (Zhang et al., 2002). The duration of the active phase, from 4 cm to complete cervical dilatation, varies between 5.5 hours (Zhang et al., 2002) and 7.7 hours for nulliparas and 5.7 hours for multiparas (Albers et al., 1996). Another criterion that has been modified is the definition of the beginning of the active phase which for Friedman was the beginning of the upswing of the cervical dilatation curve. The objective criteria of 4 cm of cervical dilatation and 80% or more cervical effacement have replaced Friedman's definition.

Approximately 75% of nulliparous and 90% of multiparous women have normal labor and deliver vaginally. The remainder will have labor abnormalities characterized by prolongation of any of the three well-recognized phases of normal labor, the latent phase, the active phase, and the descent of the presenting part. Some of these women resume normal labor spontaneously or with the help of oxytocin stimulation. In the other cases, the

abnormality of labor will reach a point where—in the opinion of the health care provider—there is no further progress and surgical intervention is necessary.

LACK OF PROGRESS IN LABOR

Most clinicians diagnose lack of progress in labor when there is no change or minimal change in cervical dilatation in a 2-hour period during the latent or the active phases of labor, or no change or minimal change in descent of the presenting part during 1-hour during the second stage of labor in the presence of adequate uterine activity (regular contractions 2–3 minutes apart, lasting more than 40 seconds). In general, labor abnormalities have their origin in conditions affecting the "power" of the expulsive forces, the fetal "passenger," or the maternal "pelvis" (Box 15-2).

BOX 15-2

Causes of labor abnormalities

Power
- Hypotonic dysfunction
- Hypertonic dysfunction
- Poor maternal expulsive efforts

Passenger
- Size
- Presentation
- Position
- Attitude
- Congenital abnormalities

Pelvis
- Cephalopelvic disproportion (CPD)

Power

During normal labor the uterus contracts every 3–4 minutes and each contraction increases the intrauterine pressure (IUP) 25–75 mmHg above a baseline of 5–20 mmHg. Although rarely used in obstetrical practice, uterine work can be expressed as Montevideo Units by subtracting the baseline pressure of each contraction from the peak pressure and adding the results from all the contractions occurring in a 10-minute period. Most women in spontaneous labor will have three contractions in 10 minutes and will produce approximately 100–200 Montevideo Units. A patient having strong contractions every 2 minutes will generate more than 300 Montevideo Units. In the second stage of labor the uterine work is complemented by maternal expulsive efforts that become an important part of the "power" required to achieve vaginal delivery.

Abnormalities of uterine work and maternal expulsive efforts are a common cause of abnormal labor patterns. The most common abnormalities are hypotonic dysfunction, hypertonic dysfunction, and inadequate maternal pushing efforts. The most important contributor to lack of progress in labor is hypotonic dysfunction, or uterine inertia that is characterized by a decrease in the frequency and intensity of uterine contractions. In some instances hypotonic labor is manifested by biphasic contractions that are a sign of ineffective uterine work. Hypotonic labor may be primary when it is due to an intrinsic failure of the uterine muscle or secondary when it results from pharmacologic intervention such as excessive sedation or regional anesthesia. Hypertonic dysfunction is characterized by frequent, intense, and painful contractions having no effect on cervical dilatation or effacement. Some investigators describe subtypes of hypertonic dysfunction: (a) uterine tachysystole is an increase in the frequency of uterine contractions and (b) hyperstimulation is tachysystole associated with FHR abnormalities. Inadequate maternal pushing efforts are usually secondary to maternal fatigue or to epidural anesthesia. To have a quantitative measurement of the "power" of the uterus it is necessary to use an intrauterine pressure catheter (IUPC). Evaluation of the intensity of contractions by external monitoring with tocodynamometer or by palpation of the uterus is inaccurate.

The Passenger

Evaluation of the fetal "passenger" is important in the assessment of labor abnormalities. The most important variables are fetal weight, presentation, position, and attitude. An abnormally large fetal weight, or fetal macrosomia, defined as fetal weight equal to or larger than 4000 g, is a relatively frequent finding in patients with abnormal labor. Unfortunately, our ability to determine the fetal weight at term clinically and by ultrasound is limited. Abnormal fetal presentations (brow, shoulder, face), positions (occiput posterior, occiput transverse), and attitude (extension, asynclitism) are other important causes of abnormal labor. They are relatively easy to diagnose with careful digital pelvic and ultrasound examinations.

Fetal abnormalities such as hydrocephaly, fetal ascites, and fetal tumors may be a cause of abnormal labor. Most women have one or more ultrasound examinations during pregnancy and these gross abnormalities have been ruled out. It is a good idea to do a rapid fetal survey with ultrasound to rule out malformations in the rare patient with abnormal labor who has not had an ultrasound examination during pregnancy.

The Pelvis

Abnormalities of the maternal pelvis are rare and are usually recognized before labor starts. Most cases are women with multiple pelvic fractures following motor vehicle accidents or women with paraplegia or spina bifida. However, the clinical assumption that there is a disparity

between the diameters of the fetal head and the dimensions of the maternal pelvis (cephalopelvic disproportion, or CPD) is the most frequent explanation given for the development of lack of progress in labor. Unfortunately, the diameters of the pelvis cannot be measured objectively due to concerns about fetal radiation exposure. The majority of CPD cases are most probably the result of a mixture of myometrial dysfunction, abnormal fetal presentation, and borderline pelvic measurements.

LACK OF PROGRESS DURING THE LATENT PHASE OF LABOR

Diagnosis

According to Friedman, the latent phase of labor is the interval from the onset of labor, defined as the time when uterine contractions become regular, to the beginning of the active phase of labor, defined as a sudden upward change in the slope of the cervical dilatation curve (Friedman et al., 1961). The mean duration of the latent phase of labor is 8.6 hours in the nullipara and 5.3 hours in the multipara and is prolonged when its duration exceeds 20 hours in the nullipara and 14 hours in the multipara patient. In obstetrical practice it is extremely difficult to use Friedman's definition of latent phase and prolonged latent phase. The fundamental problem is that the definitions of the onset of labor and the beginning of the active phase are subjective and imprecise. Therefore it is better to adopt more objective criteria and define the end of the latent phase and beginning of the active phase as cervical dilatation of 4 cm and cervical effacement ≥ 80%. According to this definition, lack of progress during the latent phase will be the lack of change or minimal change in cervical effacement and dilation during a 2-hour period in a woman having regular uterine contractions before the beginning of the active phase of labor.

The most important element in the diagnosis of lack of progress during the latent phase of labor is the assessment of cervical effacement. Multiparous women may have a cervical dilatation of 3 or 4 cm without being in the active phase of labor while a cervical effacement of ≥ 80% usually indicates labor independent of parity. Also, although assessment of cervical effacement has important variability among clinicians (Holcomb and Smeltzer, 1991), there is large degree of concurrence in the evaluation of advanced stages of cervical thinning.

The most frequent problem with the diagnosis of prolonged latent phase of labor is the distinction between false labor and latent phase of labor. A common method to make this differentiation is by observing the patient for a period of at least 2 hours. Patients in false labor will show a pattern of irregular contractions that eventually decrease in frequency and intensity, and will have no cervical changes during the observation period. Patients in latent phase will show persistent regular uterine contractions usually increasing in intensity and frequency and will show some cervical changes such as softening and effacement of the cervix. Another method to differentiate false labor from latent phase of labor is by "therapeutic rest." For this purpose, the patient is given a 15-mg dose of morphine sulfate. Patients in false labor sleep for a few hours and awake without contractions. Patients in latent phase continue contracting and show cervical changes following the rest period.

Another problem is making the distinction between late latent phase and early active phase of labor. The majority (64.4%) of women presenting to the hospital in labor will be in established labor with cervical dilatation of 4 cm or more, approximately 29% will be in early labor, and 11.3% will be in latent phase. Patients presenting in early labor and in latent phase of labor are at high risk for cesarean section (Gharoro and Enabudoso, 2006). Women presenting in latent phase have an incidence of cesarean delivery of 26% (Simon and Grobman, 2005). A useful parameter to distinguish between late latent phase and early lack of progress in the active phase is the patient's parity. A multipara making little progress at 4 cm of dilatation will most probably be in latent phase. A nullipara under the same circumstances will most probably be in early secondary arrest. The degree of cervical dilatation is also important: 60% of the patients will be in active phase if the cervix is 4 cm dilated, and 90% if it is 5 cm. Cervical effacement is a good criterion to recognize patients in active phase. Most patients will be in active phase if their cervix is effaced ≥ 80%. If effacement is 50% or less they, most probably, are in latent phase.

Ultrasound may be used to distinguish between normal labor and prolonged latent phase, and false labor and early lack of progress in the active phase. For this purpose the cervical length is assessed with endovaginal ultrasound before, during, and after a uterine contraction. During normal labor the cervix will shorten about 50% while the change will be little in women with labor abnormalities (Saito et al., 2003).

Etiology

In nulliparous patients the most frequent cause of lack of progress during the latent phase is an unripe cervix at the beginning of labor. In multiparas the most common cause is false labor, which is the final diagnosis in more than 50% of patients initially diagnosed with prolonged latent phase.

Management

There are two modes of management for patients with a prolonged latent phase: "therapeutic rest" and oxytocin

BOX 15-3

Oxytocin administration for induction or augmentation of labor

- Dilute 30 units of oxytocin in 500 ml of normal saline
- Use continuous IV piggyback administration with Harvard pump or similar device
- If the cervix is already dilated, monitor with pressure catheter and scalp electrode
- Initiate oxytocin infusion at 0.5–2.0 mU/minute
- Increase the dose by 1–2 mU/minute every 20–30 minutes, until an adequate pattern of contractions is achieved

stimulation. Both methods have approximately the same effectiveness and are capable of eliminating the labor abnormality in about 85% of the cases. The selection of the type of management should be based on considerations such as the state of fatigue and anxiety of the patient, the etiology of the problem, and the convenience of the patient and the obstetrician.

If therapeutic rest is chosen as the plan of management, 15 mg of morphine should be given IM. The majority of patients will be sleeping within 1 hour and be awake 4–5 hours later either in active labor or in no labor. There are two possible problems with therapeutic rest. The first is the possibility of giving this dose of narcotic to a patient who in reality is in the active phase of labor and who may deliver shortly after treatment a depressed infant because of the relatively large dose of morphine given to the mother. If this occurs, the pediatrician should be notified and ready to administer adequate treatment if the baby has respiratory depression at delivery. The second problem is that the treatment may be ineffective and morphine administration may cause further prolongation of the latent phase.

If oxytocin stimulation is chosen as the mode of treatment, the medication must be started at 0.5–1.0 mU/minute and increased gradually at 30–40-minute intervals (Box 15-3). Patients in prolonged latent phase usually do not need large doses of oxytocin to develop adequate contractions, and the majority of them respond to dosages less than 8 mU/minute. The main problem with this approach is that induction may be prolonged, especially if the cervix is unripe. In that case, the prolonged latent phase and the long induction will combine to produce patient fatigue and anxiety. Amniotomy is not useful in patients with lack of progress in the latent phase of labor and should be avoided.

Prognosis

Prolonged latent phase is an abnormality of labor that is associated with increased incidence of cesarean section, chorioamnionitis, and postpartum bleeding (Simon and Grobman, 2005). Thick meconium, 5-minute Apgar score less than 7, and admission to the neonatal intensive care unit, or NICU, are also associated with prolonged latent phase of labor (Maghoma and Buchmann, 2002). With the use of multivariate linear logistic regression models, investigators have determined that prolonged latent phase is independently associated with these abnormal outcomes (Chelmow et al., 1993). Therefore, the presence of this labor abnormality should alert the clinician to the risk of further complications during labor.

LACK OF PROGRESS DURING THE ACTIVE PHASE OF LABOR

Diagnosis

Lack of progress during the active phase of labor, 4–10 cm of cervical dilation, is a significant complication of labor demanding cesarean delivery in more than 50% of the cases. It is characterized by lack of change or minimal change (less than 1.5 cm/hour) in cervical dilatation for 2 hours during the active phase of labor. It occurs in 5–10% of all women in labor and is twice more frequent in nulliparous than in multiparous patients.

Etiology

The most common causes of lack of progress during the active phase of labor are CPD, abnormal uterine contractility (primary or secondary uterine inertia), and fetal malpositions. The high incidence of disproportion makes it necessary to rigorously evaluate the fetal–pelvic relationship in every patient exhibiting this abnormality of labor. CPD occurs more frequently when the lack of progress is detected early in the active phase, between 4 and 6 cm. Lack of progress because of fetal malpositions, especially occiput posterior (OP) position of the fetal head, typically occurs at the end of the active phase (≥8 cm of cervical dilatation). Abnormal uterine contractility may cause lack of progress at any time during the active phase of labor.

Management

The management of lack of progress during the active phase of labor depends on the etiology of the problem. Since CPD is a frequent and important cause, the first thing to do following the diagnosis is to evaluate the fetal–pelvic relationship to determine if CPD is present. A search should be performed for clinical indicators of CPD (Box 15-4) and clinical pelvimetry (Box 15-5) should follow. A useful test to assess for the presence of CPD is the Mueller-Hillis maneuver. It consists of applying fundal pressure at the peak of a uterine contraction and assessing, with a hand placed in the vagina, if such a pressure produces downward mobility of the fetal head. If the fetal

BOX 15-4

Clinical indicators suggesting CPD

Abdominal examination
- Large fetal size
- Fetal head overriding the pubic symphysis

Pelvic examination
- Cervix shrinking after amniotomy
- Edema of the cervix
- Head not well applied against the cervix
- Head not engaged with leading point at –2 station
- Caput formation
- Molding (cranial bones overlapping)
- Deflexion (anterior fontanelle easily palpable)
- Asynclitism (sagittal suture is not in the middle of the pelvis)

Others
- Maternal pushing before complete dilatation
- Early decelerations
- Negative Mueller-Hillis test
- Reverse Mueller-Hillis test

BOX 15-5

Clinical pelvimetry findings suggestive of CPD
- Narrow subpubic arch
- Bi-ischial diameter less than 8 cm
- Prominent ischial spines
- Flat sacrum
- Diagonal conjugate diameter less than 11.5 cm

head moves downwards the test is negative and the possibility of CPD is slight. If there is no movement of the fetal head the test is positive and the possibility of CPD is high.

Another important and frequent cause of lack of progress during the active phase of labor is inadequate uterine activity. Therefore, and unless other etiology is apparent, an IUPC should be inserted to obtain a precise evaluation of uterine activity. If the contractions are more than 3 minutes apart, last less than 40 seconds, and provoke a rise in IUP less than 50 mmHg, it may be assumed that a deficiency in the expulsive power of the uterus is the cause of the problem and stimulation with oxytocin is in order. Oxytocin must be administered as shown in Box 15-3. If excessive sedation or regional anesthesia is the causal agent of the uterine inertia, oxytocin stimulation should be concurrent with discontinuation of the labor-inhibiting factors. In most cases the dose of oxytocin required to overcome the arrest of dilation is not greater than 12 mU/minute. The use of continuous oxytocin infusion of 24 mU/minute or more, for the purpose of stimulating the pregnant uterus, is dangerous and not recommended. Some patients with lack of progress in the active phase of labor and normal clinical pelvimetry show adequate uterine contractions when the IUPC is applied. In these patients the uterus is working adequately, the possibility of CPD is large, and stimulation with oxytocin is unnecessary and may be dangerous.

Friedman and Sachtleben (1963) found that 85% of patients in secondary arrest of cervical dilation who respond to oxytocin do so within 3 hours. An adequate response consisted in an upswing of the cervical dilation curve. Therefore, 3 hours of oxytocin augmentation constitutes an adequate trial of labor. If no change in cervical dilation is observed after 3 hours, further attempts to achieve a vaginal delivery are unwarranted, and the patient should have a cesarean delivery. In patients who respond properly to oxytocin augmentation, the slope of the postarrest curve of dilation is equal to or larger than that observed before the arrest. In these cases the prognosis is good, and the chances for vaginal delivery are excellent. When the patient does not respond to oxytocin stimulation or the postarrest, slope of cervical dilation is less than it was before the arrest, and there is a strong possibility that CPD is present.

A cause of lack of progress or poor progress in the active phase of labor is fetal malposition, especially OP and occiput transverse (OT) positions of the fetal head that can be easily diagnosed by means of bedside ultrasound examination. Typically malpositions cause lack of progress in the final stages of cervical dilatation (>8 cm of dilatation) and the clinical picture corresponds to the prolonged deceleration phase described by Friedman. In multiparas the most frequent malposition is OP (40.7%) and second is OT (25.4%). In 60% of nulliparous patients the fetal head position will be OT and in 26.3% will be OP. Fetal malpositions frequently resolve spontaneously and hence when they are found the patient should be supported and reassured.

In summary, the management of lack of progress during the active phase of labor depends on the etiology of the problem: fetal malpositions should be managed expectantly, uterine inertia should be treated with oxytocin stimulation, and CPD resolved by means of cesarean section. In the majority of cases the differential diagnosis between these conditions is not difficult: inadequate uterine activity can be easily recognized with IUP monitoring, fetal malpositions can be easily recognized with ultrasound examination, and CPD will be the diagnosis if the other conditions are ruled out and other variables suggesting CPD are present (Boxes 15-4 and 15-5).

Prognosis

Almost 70% of patients presenting with lack of progress in the active phase of labor have simultaneous arrest of descent and will require delivery by cesarean section. The other 30% will resume progress spontaneously or with oxytocin stimulation and may deliver vaginally. An important factor in the prognosis is the patient's parity:

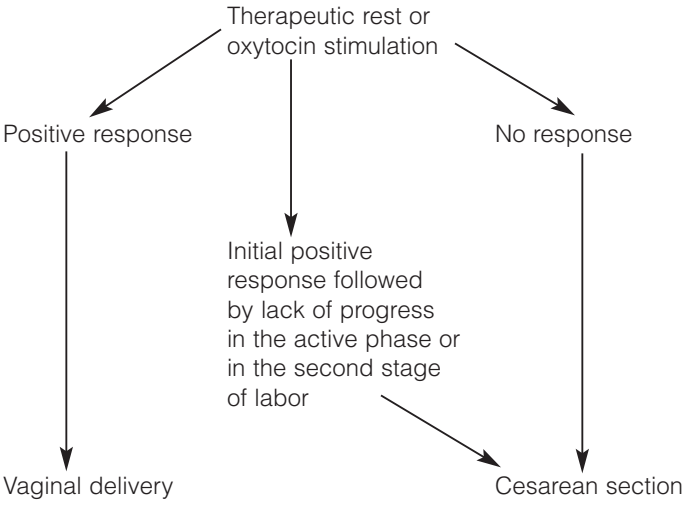

Figure 15-2. Management of lack of progress in the latent phase of labor.

approximately 80% of multiparas with lack of progress in the active phase respond to therapy and dilate further, while most nulliparous patients fail to respond to treatment. Also, lack of progress in the active phase of labor is usually caused by CPD and there is a poor prognosis when the diagnosis is made before the cervix reaches 6 cm of dilatation. The presence of associated labor disorders, particularly lack of descent and a higher station of the presenting part at the time of diagnosis, makes the prognosis worse. When the lack of progress in the active phase of labor occurs at +1 or lower station the possibility that it may be resolved with oxytocin stimulation is good. When the presenting part is above 0 station, CPD is a strong possibility and cesarean delivery may be the best management. Recurrences of lack of progress during the active phase of labor must be treated by cesarean section.

A summary of the management plan for lack of progress in labor during the active phase of labor is presented in Figure 15-2.

LACK OF PROGRESS IN THE SECOND STAGE OF LABOR

Lack of progress in the second stage of labor is a serious complication characterized by protracted descent, less than 1 cm/hour, or no descent of the presenting part into the birth canal during the second stage of labor (from complete cervical dilatation to delivery). Descent of the presenting part into the mother pelvis usually starts at the end of the active phase of labor and is easily observable during the second stage of labor. The normal rate of descent is 3.3 cm/hour for nulliparas and 6.6 cm/hour for multiparas. Slow or protracted descent occurs when the maximal slope of descent is 1.0 cm/hour or less in nulliparas or 2.0 cm/hour or less in multiparas.

Several risk factors for arrest of descent during the second stage have been identified (Feinstein et al., 2002). These risk factors include nulliparity, fetal macrosomia, epidural anesthesia, male gender, and induction of labor.

Diagnosis

Arrest of descent occurs when there is no progress in the movement of the fetus through the birth canal in the second stage of labor for 1 hour as documented by appropriately spaced vaginal examinations. In some patients descent does not occur at all from the very beginning of labor and this abnormality is named failure of descent. The diagnosis of lack of progress in the second stage of labor requires documentation that descent has not occurred or has been abnormally slow during 1 hour. The evaluation of the fetal descent is complicated by the development of molding and caput at the end of labor. In many cases a pelvic examination shows that progress is being made when in reality what is felt as a positive change is caput formation. This error is so common that Friedman recommends assessing the station of the presenting part by both abdominal (Figure 15-3) and pelvic examinations in all cases of suspected abnormalities of descent. To evaluate the descent of the presenting part by abdominal examination, the first and second Leopold maneuvers should be carried out and the station assessed from –5 to 0. This method is not as precise as station assessment by pelvic examination, but with the use of both methods it is possible to avoid mistakes caused by caput formation during labor.

Etiology

In the nullipara, CPD is the cause of more than 50% of the cases of arrest of descent. In multiparas with arrest of descent the incidence of CPD is approximately 30%. The incidence is larger when the arrest occurs at a high station or when the patient is receiving uterotonic stimulation.

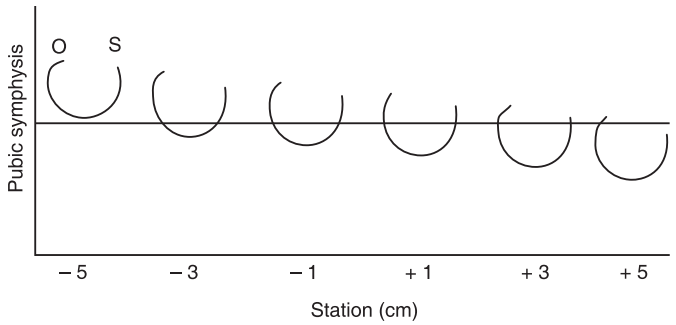

Figure 15-3. Assessing the station of the presenting part by abdominal examination. The graph shows the progressive descent of a fetal head (O, occiput; S, sinciput) through the pelvis. The head eventually crosses a line that represents the pubic symphysis. The station is evaluated using a range of –5 when the head is floating to +5 when the head is deep inside the true pelvis. (From Chrichton D. S Afr Med J 1974; 48: 784).

Other reasons for lack of progress in the second stage of labor are inadequate uterine activity, fetal malpositions, epidural anesthesia, and fetal macrosomia. OT or OP malpositions were present in 75.9% of all patients with arrest of descent in Friedman's series (Friedman and Sachtleben, 1970). However, almost all nulliparas with fetal malposition have several factors operating simultaneously, and it is difficult to isolate the role of malposition alone. Epidural anesthesia was present in 80.6% of nulliparas with arrest of descent. This does not mean that the regional block was the cause of the problem but indicates that it may be a contributory factor.

Protracted descent frequently occurs when the infant is macrosomic. In Friedman's and Sachtleben's study (1970) 9% of the infants born to mothers with protracted descent weighed more than 4000 g as compared with 4.2% in patients without labor abnormalities. Fetal malpositions of no consequence in normal-size infants frequently represent the difference between vaginal and cesarean delivery in macrosomic babies.

Patients receiving epidural anesthesia during labor have more descent disorders and a higher incidence of operative vaginal deliveries than patients without epidural blocks (Bates et al., 1985). This occurs because epidural blocks interfere with the bear down reflex and impair the ability of patients to push during the second stage of labor. A meta-analysis of almost 2400 women randomly assigned to epidural anesthesia or parenteral analgesia found that epidurals prolong the active phase by an average of 42 minutes and the second stage by an average of 14 minutes (Halpern et al., 1998). With respect to the increase in cesarean section rate, the literature is controversial with some studies finding a significant cesarean rate increase (Thorp et al., 1993) and others finding no differences (Sharma et al., 2002).

Several of the disadvantages of traditional epidural blockade during labor are minimized by using a mixture of low-dose local anesthetic such as bupivacaine with an opioid agonist such as fentanyl for continuous epidural infusion. The analgesia achieved with this methodology is excellent and there is minimal motor blockade with preservation of the patient's ability to push during second stage (Youngstrom et al., 1996). Both continuous and intermittent epidural infusions produce comparable analgesia and maternal satisfaction (Salim et al., 2005).

The effect of epidural anesthesia on the duration of the second stage should be taken into consideration for the management of prolonged second stage of labor. As long as descent continues and fetal monitoring is reassuring, prolongation of the second stage beyond the classical limit of 2 hours for nulliparas and 1 hour for multiparas is permissible for patients receiving epidural anesthesia.

A frequent etiology of protracted descent in the multipara is a decrease in the expulsive forces of the uterus during the second stage of labor. This can be documented by an IUPC and corrected by an intravenous infusion of oxytocin.

Management

The first thing to do in the patient with lack of progress in the second stage of labor is to rule out obvious reasons for the problem such as inadequate contractions, epidural anesthesia, excessive sedation, and fetal malposition. However, the presence of an obvious reason for the abnormality must not distract the observer from ruling out the possibility of CPD. In primiparas with this disorder, the incidence of CPD is about 30%. Also, CPD is the most likely diagnosis in patients with prolonged second stage and macrosomic infants. Clinical pelvimetry and a Mueller-Hillis maneuver must be performed. If the clinical pelvimetry is suspicious or the Mueller-Hillis test gives a negative result, the possibility of CPD is high. An important clinical sign is the presence of a floating head (Debby et al., 2003). This finding is an indication for cesarean section if the membranes are ruptured. If the membranes are still intact, there is a possibility that the head may descend after amniotomy. However, amniotomy in these cases is associated with a high incidence of umbilical cord prolapse.

The treatment of lack of progress in the second stage of labor must be directed to the suspected etiologic agent: (a) epidural block or excessive sedation must be managed with an abatement policy, (b) CPD requires cesarean delivery, and (c) poor uterine contractility requires oxytocin stimulation. Cesarean delivery is the choice in cases of macrosomia combined with malposition.

Oxytocin augmentation is indicated if the uterine contractions seem to be inadequate as evaluated with the IUPC. Oxytocin significantly increases the rate of cervical dilation as well as the rate of cervical dilatation when compared with amniotomy alone or with expectant management (Blanch et al., 1988) Oxytocin must be administered starting at a dose of 0.5–1.0 mU/minute, with increases in doses separated by intervals of at least 30 minutes (Box 15-3). Internal monitoring with fetal scalp electrode and IUPC is important. The possibility of CPD is always there, and hyperstimulation of the uterus should be avoided to prevent uterine rupture. Direct FHR monitoring is mandatory because it has been shown that the fetus becomes progressively acidotic during the second stage (Modanlou et al., 1973).

Abatement of regional anesthesia may be indicated after disproportion has been ruled out. Most patients who respond to abatement of anesthesia or to oxytocin augmentation do so in 1–2 hours. If no response is noticed 2 hours after the beginning of oxytocin stimulation, most probably CPD is present and the pregnancy should be interrupted by cesarean section.

Prognosis

Patients with lack of progress in the second stage of labor have a guarded prognosis. The reason for this is the high frequency of CPD. In Friedman's and Sachtleben's study (1976) 30.4% of patients with arrest of descent required cesarean section, 37.6% were delivered with midforceps, 12.7% had forceps rotations, and 5.1% had failed forceps. In today's world, the 55.4% cases delivered with forceps in Friedman's and Sachtleben's study will be delivered by cesarean for a total incidence of cesarean of 85.8%. The reason for this is that forceps delivery has almost completely disappeared from the obstetrical armamentarium.

The most important prognostic indices in patients with arrest of descent are (a) the fetal station at the time of arrest—the higher the station, the greater the possibility of disproportion; (b) the duration of the arrest—the longer the duration of the arrest, the greater the possibility of disproportion; and (c) the characteristics of the postarrest progression—if the postarrest descent rate is equal to or larger than the prearrest slope, the prognosis for atraumatic vaginal delivery is good.

Prolonged second stage of labor is associated with significant maternal and fetal morbidity independent of the need for operative intervention. Fetal distress, as evidenced by a low Apgar score, is common occurrence in 21.9% of the cases. Shoulder dystocia, with its associated morbidity, occurs in 14.1% of the cases. In many cases the cesarean is performed when the fetal head is impacted in the maternal pelvis and despite precautions extension of the hysterotomy incision occurs and blood loss is larger than usual. Postpartum bleeding is common occurrence in 12.5% of the cases.

The management of abnormalities of the second stage of labor is similar to the management of abnormalities during the active phase of labor and is shown in Figure 15-4.

ABNORMAL FETAL PRESENTATIONS

The usual presentation at the time of parturition is cephalic and the usual mechanism of labor involves internal rotation of the fetal head to an occiput anterior (OA) position with subsequent delivery. Situations that deviate from this are known as abnormal fetal presentations and they used to be a management problem for the obstetrician. Today, most abnormal fetal presentations are managed by cesarean section and the role of the obstetrician is limited to the performance of external version in persistent breech presentations after 36 weeks, breech delivery when patients present in advanced labor with the lower part of the fetus already in the vagina or protruding to the outside, and manual or one-blade forceps rotation of persistent OP presentations.

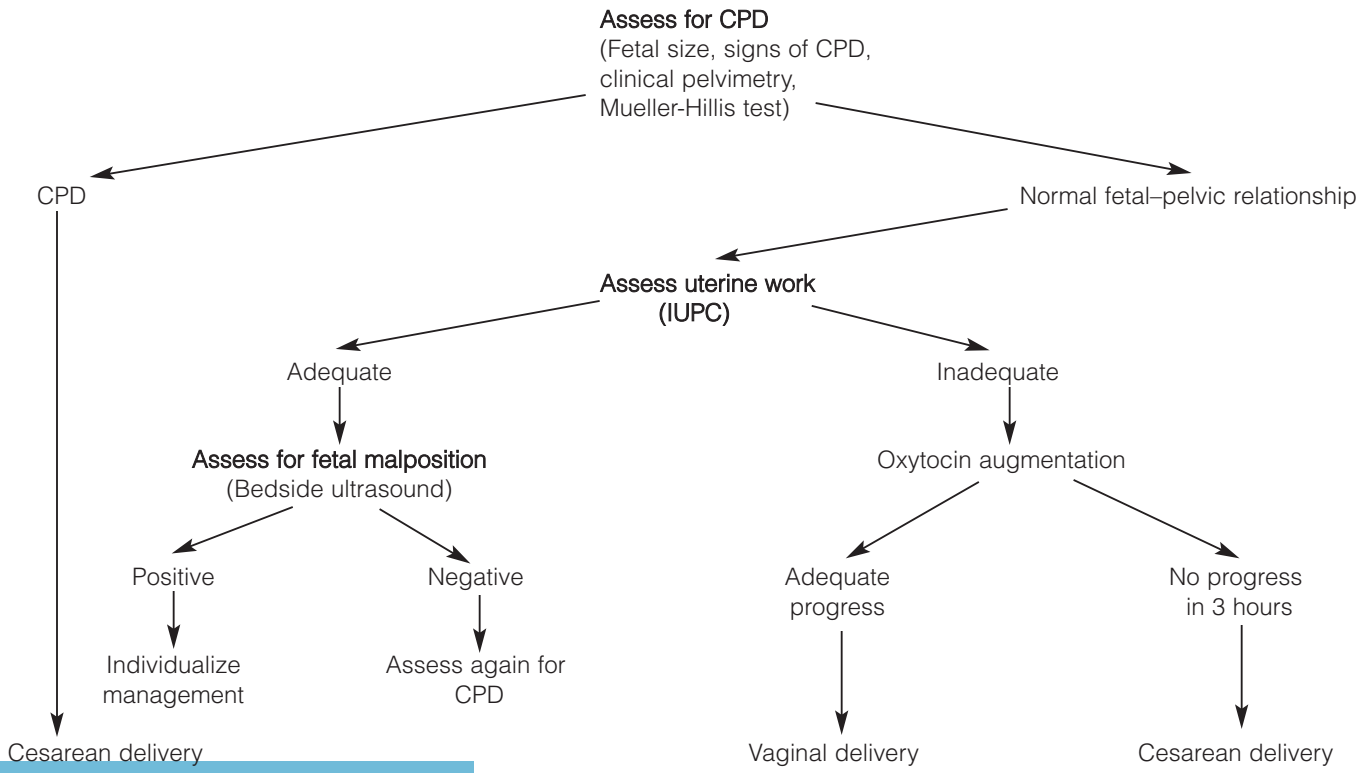

Figure 15-4. Management of lack of progress in the active phase and in the second phase of labor.

Breech Presentation

Breech presentation occurs in 3–4% of all deliveries. Fetal and neonatal mortality and morbidity are considerably higher for the fetus in a breech presentation than for the fetus in a cephalic presentation. In one study (Brenner et al., 1974) the overall fetal mortality for breech deliveries was 25.4% compared to 2.6% for nonbreech. In another study (De Crespigny and Pepperell, 1979) breech deliveries were 3.3% of the total deliveries and accounted for 24.3% of the perinatal mortality. This poor fetal outcome persists when some factors such as prematurity and congenital abnormalities are excluded.

A considerable part of the fetal and neonatal morbidity and mortality found in breech presentations is due to associated factors. The most important of these factors are preterm delivery, congenital malformations, preterm rupture of membranes, placenta previa, and abruptio placentae. In addition to these conditions there are a series of problems, some occurring exclusively and some others happening frequently in cases of breech presentation such as umbilical cord prolapse, entrapment of the fetal head and extension of the fetal arms at the time of delivery, and traumatic injuries to the fetus. Some of these problems are unpredictable and may happen even in well-selected cases.

External cephalic version

External cephalic version is a prophylactic maneuver to decrease the number of fetuses in breech presentation that eventually will require cesarean delivery. Spontaneous rotation from breech to cephalic presentation may occur during the last 4–6 weeks of gestation but the probability that it will happen is low and decreases with every week of pregnancy prolongation. Hence external version is recommended and is usually performed at 36 weeks when the chances of spontaneous rotation decrease and the amount of amniotic fluid is at a peak. There are several contraindications to external version, and the procedure should not be performed if any of the conditions listed in Box 15-6 are present. If there are no contraindications the following steps should be followed:

1. External version should be carried out in the labor and delivery suite at 36 weeks of gestation. The operating room should be prepared to perform an emergency cesarean section in case severe fetal bradycardia occurs during or after the procedure. An ultrasound should be performed to assess the fetal position and rule out congenital abnormalities. If not done before, color Doppler should be used to be certain that the umbilical cord is not wrapped around the fetal neck. There is no evidence suggesting or not that the presence of cord around the neck increases the risk of FHR abnormalities in women undergoing external version. However, if the presence of nuchal cord is known before the external version and the procedure has a poor outcome, it will be difficult to justify its performance. A reactive NST (nonstress test) should precede the maneuver.
2. Administer nifedipine 20 mg orally or terbutaline 0.25 mg subcutaneously with the patient lying on her left side and her feet slightly elevated, and wait for 20 minutes. Epidural anesthesia can be used and will increase the rate of success.
3. It is ineffective to attempt an external version if the breech is in the pelvis and the version should begin by dislodging the breech from the pelvis using both hands. When the breech does not come out easily from the pelvis by abdominal upward pressure, an assistant may place his/her fingers in the vagina and push the breech out of the pelvis. The fetus is then moved up and laterally using transabdominal manual pressure on the buttocks. Once the baby has reached a transverse position, the rotation is completed using one hand to push the breech up and the other hand to push the fetal head down. Fetal heart activity must be constantly monitored.
4. The procedure should be interrupted if (a) the version is not easy, (b) the mother is in pain, (c) there is a marked increase or decrease in FHR or an irregular rhythm of the fetal heart.
5. A reactive NST should be obtained after completing the procedure. The patient should be allowed to walk and eat, and FHR monitoring repeated for a short period of time before discharge.

BOX 15-6

Contraindications to external version

1. Indicated cesarean delivery
   - Placenta previa
   - Contracted pelvis
2. Indicated vaginal delivery
   - Fetal death
   - Severe congenital abnormality (anencephaly, etc.)
3. Difficult procedure
   - Rupture of the membranes
   - Oligohydramnios
   - Lack of uterine relaxation (patient in labor)
   - Multiple pregnancy
   - Anterior placenta
   - Pregnancy close to term with engaged breech
4. Increased maternal or fetal risks
   - Sensitized Rh negative mother*
   - Severe hypertension
   - Severe intrauterine growth retardation
   - Fetus with hyperextended head

*If the mother is nonsensitized RhoGAM should be given after the procedure.

6. If the mother is Rh negative, RhoGAM must be given.

Some investigators enthusiastically favor external version and others find no advantage to its use. The reason external cephalic version is not universally accepted is the 1–4% possibility of complications, including fetal losses as high as 1.7% (Van Dorsten et al., 1981). However, some investigators believe that cephalic version is a reasonable management alternative for most persistent breech presentations. This procedure reduces the incidence of cesarean deliveries due to breech presentations and is safe when performed without application of excessive force and with continuous fetal monitoring.

External version is greatly facilitated by the use of uterine relaxants and epidural anesthesia. The fetal manipulation should be gentle, and the procedure must be stopped if the mother has pain or if there is more than 15% increase or decrease in FHR frequency.

Breech delivery

To attempt a vaginal breech delivery in circumstances where there is time to do a cesarean is an invitation to disaster. Although the possibility of a successful vaginal breech delivery is substantial, any outcome less than excellent will be closely scrutinized and may have severe medical–legal consequences. The reason for this is a large randomized clinical trial (Hannah et al., 2000) demonstrating that cesarean section has better outcomes than vaginal deliveries. The results of this trial have been endorsed by the American College of Obstetricians and Gynecologists (ACOG, 2001) and the Canadian Association of Obstetricians and Gynecologists, organizations that recommend cesarean deliveries for breech presentation. Obviously, it is difficult to have a successful legal defense of any adverse occurrence during an elective vaginal breech delivery when authoritative professional associations have recommended against this route of delivery.

Since elective vaginal breech delivery is rare, the only occasion when the obstetrician is faced with the delivery of a fetus in breech presentation is when a woman arrives to labor and delivery in advanced labor with the lower part of the body of the fetus in the vagina or protruding to the outside of the external genitalia. This can be a dangerous situation because there is no time to perform an emergency cesarean and the practitioner is forced to perform a delivery for which he/she is not adequately trained. In this situation the patient should be moved to an operating room while the uterine contractions are inhibited with a tocolytic agent, terbutaline 250 mg IV push. A vaginal digital examination is performed to rule out umbilical cord prolapse. An ultrasound examination is performed to rule out the presence of hydrocephaly. The anesthesiologist is called and the obstetrician has a few seconds to decide if there is time for a cesarean and if the cesarean will be beneficial for the infant and the mother. In general, unless it is impossible to stop the fetus from being born vaginally, is better to do a cesarean section.

If vaginal delivery is unavoidable and the fetus is preterm, the obstetrician should be ready to deal with an entrapped fetal head. The most rapid and effective approach for managing an entrapped fetal head is the use of Duhrssen's incisions in the cervix. These incisions may extend into the lower uterine segment and cause cervical incompetence in future pregnancies. Another approach is to use intravenous terbutaline (300 mg IV push) or intravenous diazoxide (300 mg IV push) to relax the cervix. Terbutaline has less pronounced cardiovascular effects than diazoxide. Another powerful uterine and cervical relaxant is halothane. However, its use requires general anesthesia with endotracheal intubation. Nitroglycerin (250 μg IV) has been used to relax the cervix in patients with retained placentas and may be useful in breech infants with entrapped head.

Another situation with considerable risk to the breech fetus is the intracranial bleeding associated with a rapid delivery of the fetal head. This problem, which occurs more frequently in preterm infants, may be decreased with the use of Piper's forceps. This instrument was originally designed to avoid delays in the delivery of the head. It has been demonstrated that the use of Piper's forceps for the delivery of the head is safer than delivery without the instrument for infants weighing between 1000 and 3000 g (Milner, 1975). The Piper's forceps are also useful to prevent trauma to the fetal mouth and throat during the Mauriceau maneuver as well as the intracranial bleeding associated with the sudden "popping out" of the fetal head.

During the Mauriceau maneuver the middle finger of the obstetrician is introduced into the mouth of the infant while the body rests on the palm of the hand and the forearm. The index and the annular fingers are placed at each side of the baby's nose and pressure is applied to the upper maxillary bone. Two fingers of the other hand are hooked over the infant's neck and are used to apply downward traction. Sometimes voluntary or involuntary traction is exerted with the finger placed in the infant's mouth in order to obtain maximal flexion of the baby's head, and a frequent result is traumatic injury to the baby's mouth and pharynx. Routine use of Piper's forceps eliminates this complication.

Persistent OP Position

In about 5% of all term labors the occiput fails to spontaneously rotate to an anterior position. A persistent OP position is usually manifested by lack of progress in the second stage of labor but it also may cause lack of

progress in the late part of the active phase of labor. Malposition of the fetal head should be suspected when the fetal head remains at –1 or 0 station during the last 1 or 2 cm of cervical dilatation, and the suspicion should be stronger if the presenting part remains at this station after complete cervical dilation. Lack of descent is frequently misdiagnosed as arrest of cervical dilatation because there is a persistent anterior rim of the cervix that fails to disappear despite adequate uterine contractions. However, the anterior rim of cervix is the result rather than the cause of the labor abnormality. Every time that a patient has a persistent anterior rim of cervix and a presenting part at a high station, the presence of an OP malposition should be strongly suspected and the diagnosis confirmed by pelvic and ultrasound examinations.

Persistent OP position is associated with high risk of adverse maternal and neonatal outcomes. In the mother it is associated with increased incidence of operative vaginal delivery and deliveries by cesarean section, third and fourth degree perineal lacerations, chorioamnionitis. and excessive blood loss during delivery (Cheng et al., 2006b). In the neonate it is associated with low 5-minute Apgar scores, academic blood gases, birth trauma, admission to the NICU, and prolonged hospital stay (Cheng et al., 2006b), Persistent OP position tends to recur in future pregnancies (Gardberg et al., 2004).

Etiology

To study the development of the persistent OP position during labor, the fetal position was assessed at the onset of labor in 408 women with term, singleton pregnancies (Gardberg et al., 1998). The authors found that 15% of their patients had OP position at the beginning of labor and 87% of them rotated during labor to an OA position. Most (68%) of persistent OP positions develop through a malrotation during labor from an initial OA position. There is no clear explanation for the malrotation to OP or for the lack of spontaneous internal rotation in cases of persistent OP positions. The problem occurs more often in women with high BMI (body mass index), in Blacks, and when the fetus is large. It seems to be associated with the presence of relatively narrow transverse diameters of the midpelvis. The pelvic shape is not the only factor in the etiology of the OP position. OP positions occur up to three times more often in patients laboring under conduction anesthesia, a fact that suggests a possible etiologic role for a deficiency of the expulsive forces of labor. There is no association between OP position and CPD.

Associated labor abnormalities

The most common labor abnormalities in patients with persistent OP position are protracted descent and arrest of descent. Prolonged latent phase, prolonged active phase, and prolonged deceleration phase may also occur, but descent problems are predominant.

Management

It is important to rule out the possibility of CPD in patients with persistent OP position and abnormal labor. If the infant is large, the mother is short, and the presenting part is above 0 station, CPD should be strongly suspected. Also, if the Mueller-Hillis maneuver fails to show a downward thrust of the fetal head, CPD should be suspected. If CPD is strongly suspected cesarean delivery is indicated.

In many patients with persistent OP uterine contractions of poor quality perpetuate the malposition and prolong the labor abnormality. If a deficiency in uterine contractility is suspected, a pressure catheter should be inserted. If the uterine work is deficient, labor augmentation with intravenous oxytocin is the treatment of choice and in many cases this intervention is followed by spontaneous rotation of the head to an OA position and vaginal delivery. In other cases there is no spontaneous rotation, but the improvement in uterine contractility makes the head descend and eventually deliver in OP position. In this case episiotomy should be performed to avoid a perineal tear.

The patient with persistent OP malposition should be allowed to labor if there is no evidence of CPD or fetal distress and if the uterine work is adequate. The chances that a laboring woman with persistent OP position will have a spontaneous vaginal delivery are only 26% for nulliparas and 57% for multiparas (Ponkey et al., 2003). Approximately 60% of patients delivering vaginally will deliver in OP position. The other 40% will rotate spontaneously and deliver in OA position.

An important question in cases of persistent OP presentation is how long a patient may remain in the second stage of labor before there is significant risk of fetal or maternal complications. The upper limit of normal for the duration of the second stage of labor is 2 hours for the nullipara and 50 minutes for the multipara. However, intervention is not necessarily justified when these limits have been reached. Studies (Cohen, 1977) have shown that in the absence of fetal distress the second stage of labor may be prolonged beyond those limits without unfavorable effects on the infant.

If further descent occurs and the fetal head reaches the perineum, a digital rotation to the OA position (Lowenstein and Zevin, 1971) may be attempted. The following is the technique for digital rotation from OP to OA position:

1. The presentation should be at a low station, visible at the introitus. The exact position of the occiput and the fetal spine should be determined clinically and by ultrasound examination.

2. Using the right hand for a left-sided position and the left hand for a right-sided position, the lambdoid suture should be identified and the tip of the middle finger placed exactly at the angle of the lambdoid suture with the tip of the index finger directly alongside the middle finger on the upper lambdoid suture.
3. The hand that is outside the vagina should be applied in the form of a fist against the anterior shoulder of the infant.
4. The two fingers placed on the lambdoid suture should exert a steady rotary motion in a direction at right angles to the sagittal suture (clockwise) and simultaneously the fist should push the fetal shoulder transversely (counterclockwise) in the direction of the occiput. The counterpressure to the rotary motion of the fingers brings about flexion of the head and correction of asynclitism.

If the digital rotation fails one-blade forceps rotation may be attempted. This is a relatively simple maneuver that may be carried out by individuals with limited forceps experience. The cardinal rule to avoid causing injuries is not to put excessive pressure on the forceps blade when it is slide on the side of the fetal head or when it is moved around the pubic symphysis. Any resistance that cannot be easily overcome with slight digital pressure on the forceps should be enough to abandon the procedure. Another condition for a safe forceps application is to be certain that the leading edge of the fetal skull, not the caput, is at or lower than a +2 station. To perform the procedure, one blade of a Tucker-McLane, Lukhart-Simpson, or similar forceps is introduced upside down in the opposite side (right side blade on the maternal left side or left side blade on the maternal right side) of the maternal pelvis. With the second and third finger, the bladder blade is rotated up and around the pubic symphysis, "wandering" over the fetal ear. When the bladder is under the pubic symphysis the fetal head usually rotates. If the head does not rotate easily the maneuver is ended. The edge of the bladder should not be angled into the fetal head or the maternal pelvis. If the rotation attempt fails and the maternal expulsive efforts are not enough to achieve spontaneous delivery, low forceps should be applied and the infant delivered in OP position or the baby should by delivered by cesarean.

A maneuver frequently used by midwives in attempts to modify an OP position is to place the patient on her hands and knees and perform pelvic rocking movements. A randomized clinical trial demonstrated that this technique is not useful and failed to reduce the incidence of persistent OP position (Kariminia et al., 2004).

A summary of the plan of management for persistent OP malposition is shown in Figure 15-5. It is important to avoid midforceps rotations for OP malpositions because many of the adverse outcomes occur in babies delivered with midforceps operations.

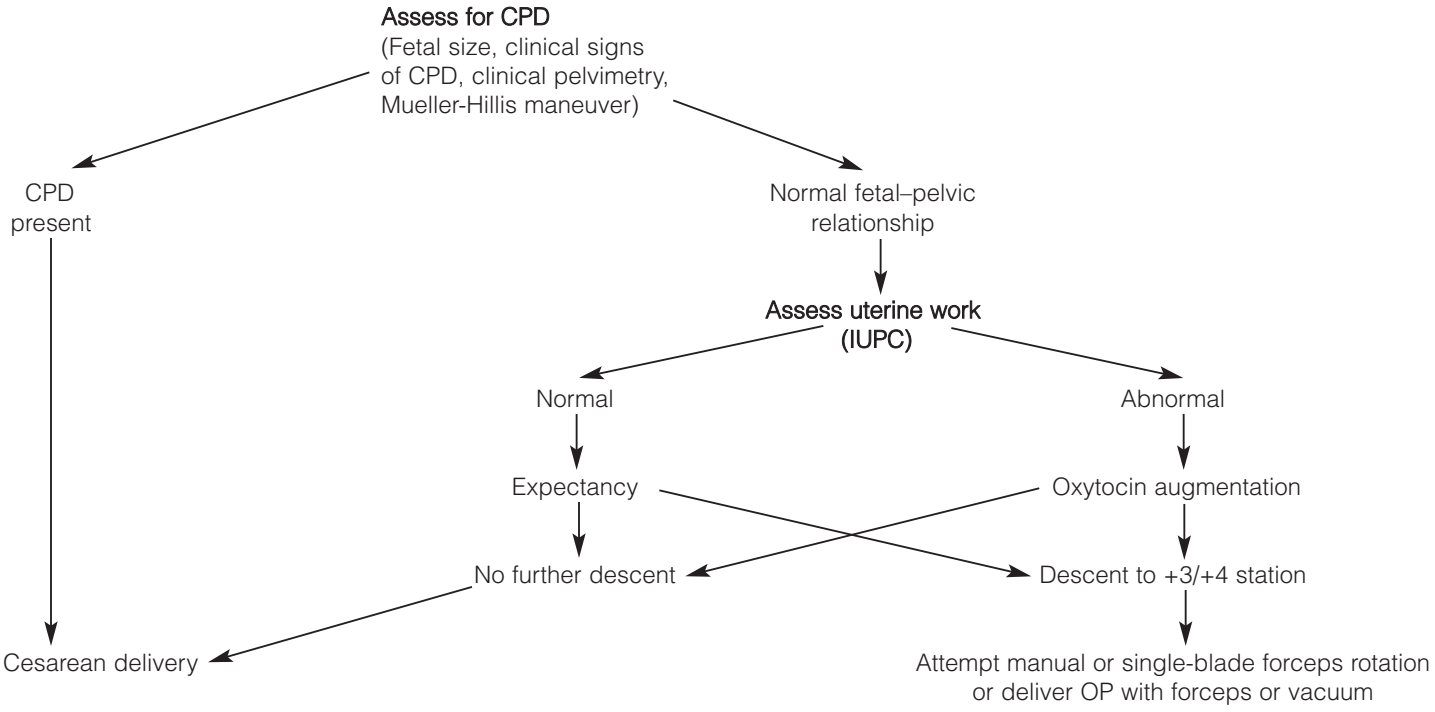

Figure 15-5. Management of persistent occiput posterior position.

Other Abnormal Presentations

Shoulder, face, and compound presentations are rare events in obstetrics. Their management is briefly reviewed here.

Shoulder presentation

Shoulder presentation or transverse lie occurs in approximately 0.3% of singleton pregnancies and in approximately 10% of multiple births. Shoulder presentation implies that the long axis of the fetus is perpendicular to the long axis of the mother. In the majority of cases the shoulder is the presenting part. In other cases the infant's hand and arm prolapsed into the vagina. Occasionally there is no presenting part in the pelvis and the fetal back is above the pelvic outlet. In other cases the fetal back is up against the uterine fundus and the small parts are over the inlet, and the patient presents with the umbilical cord prolapsed in the vagina. An ultrasound examination confirms the diagnosis. Transverse lies are usually associated with multiparity, and more than 80% of the cases occur in patients who are para 3 or more. They occur more frequently in preterm infants.

Cesarean section is the method of choice for the delivery of a fetus in transverse lie with two exceptions, grossly immature fetuses less than 500 g and macerated fetuses up to 1050 g, both of which can be delivered vaginally. In all other circumstances, even in neglected shoulder presentations with fetal death and chorioamnionitis, cesarean section is the recommended procedure. A low transverse uterine incision is adequate in most cases of transverse lie. The prerequisite is to know the exact position of the fetal head and extremities. Once the uterine incision is made the operator's hand must find the fetal head and bring it down to the pelvis. If that is not possible the fetal legs should be brought down and the fetus delivered as a breech. Occasionally, it is difficult to extract an infant in transverse lie through a low transverse incision, especially when the fetal back is over the pelvic inlet, and it will be necessary to do an inverted T incision to deliver the fetus.

Face presentation

Face presentation occurs in about 0.2% of all deliveries. It is characterized by extreme extension of the fetal head so that the face rather than the skull becomes the presenting part. Any factor that favors the extension or prevents the flexion of the fetal head, such as congenital goiter or anencephaly, may be an etiologic factor in cases of face presentation. Face presentation is associated with multiparity because the lack of resistance of the anterior abdominal wall allows the fetus to sag forward and extend the cervical spine. Face presentation may occur in association with CPD. A combination of an inlet contraction and a macrosomic infant is found in up to 39.4% of cases of face presentation.

The diagnosis of a face presentation is made by vaginal examination and confirmed by ultrasound examination. The presentation may be confused with a breech, a mistake that is easily avoided by remembering two rules:

1. The anus has sphincter tone; the mouth does not.
2. The anus is in line with the ischial tuberosities; the mouth and the malar prominences form a triangle.

Spontaneous vaginal delivery of face presentations should be expected in 60–80% of the cases (Duff, 1981). Approximately 50% of patients with the fetal chin in the posterior part of the maternal pelvis rotate spontaneously to mentoanterior position allowing vaginal delivery. This usually happens during the second stage of labor. Therefore, there is no reason to intervene early in cases of mentoposterior positions if dilation of the cervix and descent of the head are proceeding normally.

Maneuvers to convert a face presentation to a vertex or to convert manually or instrumentally a mentoposterior to a mentoanterior position should be avoided. If a patient with a face presentation is making progress during labor, she should be left alone. If arrest of labor occurs, cesarean section is indicated.

Compound presentations

Compound presentations are rather uncommon situations in which one or two of the fetal extremities enter the pelvis simultaneously with the presenting part. The problem occurs in 0.1% of all deliveries. The most common combinations are head–hand, breech–hand, and head–arm–foot. The most common associated complication is umbilical cord prolapse, which may occur in up to 20% of the cases. Compound presentations are associated with multiparity, prematurity, twin gestation, and CPD.

In the majority of cases the prolapsed extremity does not interfere with the normal course of labor and vaginal delivery. In the case of head–hand presentation, the hand of the newborn will be swollen and bluish for 24–48 hours after birth, but recovery without sequelae is the rule. Breech–hand presentations (the second most common) should be managed with the same criteria used to manage any breech presentation. Head–foot and head–arm–foot presentations require a gentle attempt at repositioning the lower extremity. If this fails and the foot or arm does not move inside the uterus, cesarean section is necessary unless the fetus weighs less than 800 g.

OPERATIVE VAGINAL DELIVERY

Achievement of a safe vaginal delivery depends, in many cases, on the ability of the obstetrician to perform an

operative vaginal delivery with forceps or vacuum. However, the ability of the obstetrician to perform forceps and vacuum procedures is severely limited by medical–legal concerns and only outlet or low forceps or vacuum are carried out by obstetricians in USA. The American College of Obstetricians and Gynecologists (ACOG, 2000) recognizes three indications for these procedures: indicated shortening of the second stage of labor, management of prolonged second stage, and presumed fetal jeopardy.

Shortening of the second stage of labor is the most common indication for operative vaginal delivery. Most obstetricians use vacuum extraction for this indication because it is easier to use and has less associated morbidity than forceps delivery. When the procedure is performed following the conditions required for outlet forceps (Box 15-7) the perinatal outcome is similar to that of spontaneous vaginal delivery. Operative vaginal delivery is, in many cases, an adequate plan of management when the second stage of labor in nulliparous patients lasts more than 3 hours in women with epidural anesthesia or 2 hours in women without epidural anesthesia. For the multipara these limits are 2 hours with an epidural and 1 hour without an epidural. These time limits are in agreement with the work of Kilpatrick and Laros (1989). These investigators found that the 95th percentiles for the duration of the second stage in nulliparous patients with and without epidural anesthesia were 185 and 132 minutes, respectively; for multiparous patients they were 61 and 85 minutes, respectively. These values reflect the significant impact of regional anesthesia on the duration of the second stage. In patients without epidural anesthesia the most common cause of prolonged second stage is insufficient expulsive efforts due to maternal exhaustion. However, it is extremely important to rule out CPD before the application of instruments to the fetal head.

Presumed fetal jeopardy in the second stage of labor is another indication for operative vaginal delivery. A common occurrence is the presence of repetitive severe variable decelerations concomitant with contractions and maternal expulsive efforts. In these cases the obstetrician needs to deliver the baby before asphyxia and acidosis become established, and cesarean delivery is the best option. However, in some of these patients forceps or vacuum delivery can be performed faster and with significantly less maternal and fetal morbidity than cesarean section. The decision between operative vaginal delivery and cesarean delivery in cases of presumed fetal jeopardy in the second stage of labor is complex, and several variables should be taken into consideration including, among others, station of the presenting part, familiarity and experience of the obstetrician with operative vaginal delivery, and immediate availability of an operating room and anesthesia. In most cases operative vaginal delivery for suspected fetal jeopardy or for prolonged second stage of labor can be performed without causing maternal or fetal morbidity. However, in some cases the procedure is unsuccessful and ends with the delivery of a depressed infant and with maternal complications secondary to cervical, vaginal, and perineal trauma. In order to avoid a poor outcome, it is necessary to rigorously comply with the conditions necessary for low forceps application (Box 15-7). The safety of these procedures is improved if the biparietal diameter, not the caput, is at +2 or greater station; the fetal size is less than 4000 g; clinical pelvimetry demonstrates a roomy pelvis; and the exact position of the head and the fetal spine is determined with ultrasound prior to the procedure. If any difficulty is anticipated or is found during the procedure, the best management is to inhibit uterine activity with terbutaline, administer oxygen to the mother, and deliver promptly by cesarean section.

BOX 15-7

Prerequisites for the application of outlet forceps

1. Fetal scalp visible at the introitus without separating labia
2. Fetal skull has reached pelvic floor
3. Sagittal suture in the anteroposterior diameter on right or left occipitoanterior or occipitoposterior positions
4. Rotation does not exceed 45°.

VACUUM DELIVERY

Vacuum extractors were designed to limit the amount of traction that could be exerted over the fetal skull in the course of an operative vaginal delivery. The instrument is relatively easy to apply and the outcome and safety are comparable to or better than those with forceps. The basic rules for the safe and successful application of a vacuum device are found in Box 15-8. Vacuum devices should not be used for rotations.

BOX 15-8

Conditions for vacuum extraction

1. The device should be placed on the sagittal suture about 3 cm in front of the posterior fontanelle in order to maintain flexion of the fetal head.
2. The patient should have normal uterine activity and be able to push.
3. Direction of the traction should be parallel to the axis of the birth canal.
4. The obstetrician should be willing to abandon the procedure if delivery does not occur after three to five traction events, total application of 15 minutes, or after two detachments (pop offs) occur.

Vacuum extraction is not free of complications. Scalp lacerations, cephalohematomas, subgaleal hematomas, intracranial bleeding, retinal hemorrhage, and hyperbilirubinemia are associated with vacuum deliveries. A serious complication occurring in 2.6–4.5% of vacuum deliveries is subgaleal hematomas. They are collections of blood in the space between the cranial periosteum and the epicranial aponeurosis. This is a potentially large space that may hold the entire blood volume of the newborn. More common, 14–16%, and less severe are cephalohematomas in which the bleeding is subperiosteal and is limited to one cranial bone, usually the parietal bone.

CESAREAN DELIVERY

In the USA one out of every three women pregnant with a viable fetus will deliver by means of a cesarean operation (Menacker, 2005). This represents a dramatic shift in obstetrical practice that just a few years ago focused on achieving a vaginal birth. As a consequence, the obstetrician is faced today with an increasing number of surgical problems, requiring knowledge and expertise for a successful solution. Although cesarean is a relatively simple and safe operation, it is associated with risks and complications that increase directly with the number of operations.

Cesarean before labor has several advantages. It has a protective effect on the ligaments of the pelvis and women delivered by cesarean have less an incidence of pelvic organ prolapse than those who deliver vaginally. Cesarean before labor eliminates the fetal and newborn complications resulting from deficiencies in the oxygen supply to the fetus during labor and delivery and specifically eliminates the cases of cerebral palsy resulting from hypoxic complications during birth. Box 15-9 shows that elective cesarean with no labor is associated with an incidence of fetal intracranial hemorrhage smaller than in any other type of delivery (Hale and Harer, 2005). A cesarean will eliminate the newborn complications associated with the use of vacuum and forceps and will decrease the incidence of newborn's infections caused by HSV, HIV, *Chlamydia*, hepatitis B virus, and human papilloma virus, which are usually acquired during the passage of the fetus through the birth canal. These advantages of cesarean delivery added to the fear of childbirth have generated an increasing number of cesareans in the absence of medical or obstetrical indications which are performed primarily because of patient's request.

BOX 15-9

Mode of delivery and incidence of fetal intracranial hemorrhage

Mode of delivery	Incidence
Cesarean delivery with no labor	1 per 2750
Spontaneous vaginal delivery	1 per 1900
Cesarean delivery during labor	1 per 907
Vacuum-assisted vaginal delivery	1 per 860
Forceps-assisted vaginal delivery	1 per 664
Cesarean delivery after failed vacuum or forceps	1 per 334

From Hale RW, Harer WB. Elective prophylactic cesarean delivery. ACOG Clin Rev 2005; 10(2): 1, 15–6.

Cesarean has short-term and long-term risks. The risk of maternal death as a direct complication of an elective cesarean at term is not significantly increased as compared with the risk of maternal death following vaginal delivery (Lydon-Rochelle et al., 2001). The risk of intraoperative bleeding large enough to require blood transfusion is about 1%. The risk of postoperative infection is about 2–3%. New risks develop with the performance of repeated cesarean and the incidences of placenta previa, placenta accreta, and abruptio placenta increase dramatically after three cesarean sections. The incidence of placenta previa raises from 0.3 to 4.1% in women with no cesareans and women with 3 prior cesareans, respectively (Miller et al., 1997).

The most serious risk is that associated with placenta accreta and the need for hysterectomy. In a study of 723 women with placenta previa the incidence of placenta accreta was 3, 11, 40, 61, and 67% for first, second, third, fourth, and fifth or more repeat cesareans, respectively. The risk of hysterectomy was 0.7, 0.4, 0.9, 2.4, 3.5, and 9.0% for first, second, third, fourth, and fifth or more repeat cesareans, respectively. Even in the absence of previa and accreta surgical morbidity such as blood loss, accidental cystostomy, bowel injury, admission to intensive care, length of the operation, and days of hospitalization increased in direct relation with the number of cesarean deliveries (Silver et al., 2006).

In view of the increasing number of elective cesareans performed because of maternal request, the National Institute of Child Health and Human Development convened a state-of-the-science meeting in March of 2006 to analyze the short- and long-term benefits and harms to mother and baby associated with cesarean delivery by maternal request versus attempted vaginal delivery (NIH, 2006). Some of the conclusions of the conference were:

1. There is insufficient evidence to fully evaluate the risks and benefits of cesarean delivery on maternal request.
2. Cesarean delivery on maternal request should not be performed before 39 weeks of gestation or without verification of fetal lung maturity.
3. Maternal request for cesarean should not be motivated by unavailability of effective pain management.
4. Given the increased risk of placenta previa and accreta with each cesarean delivery that a woman has,

cesarean delivery on maternal request is not recommended for women desiring several children.

Box 15-10 summarizes some of the maternal and neonatal outcomes following elective cesarean at term in women not in labor and in women having vaginal delivery. It should be noticed that the evidence favoring one type of delivery over the other is weak and further studies on this topic are necessary.

In addition to the problems resulting directly from the cesarean operation, there are important morbidities that depend of maternal factors. One of these factors is maternal obesity, a morbid condition that is increasing rapidly in frequency in USA. Cesarean delivery in women weighing more than 300 lbs may be an unsettling experience for individuals not familiarized with these cases. One common error is to lift the abdominal pannus and perform the skin incision in the suprapubic area, similarly to what is done in persons with normal weight. In morbidly obese women this area is a culture medium for anaerobic bacteria and wound infection is a common outcome. The best incision in these cases is a transverse infraumbilical or even supraumbilical, depending on the size of the abdominal pannus.

Obesity, maternal diabetes, intrapartum chorioamnionitis, and prolonged rupture of membranes are some of the most frequent factors contributing to wound infection following cesarean operation. The incidence of infection may decrease with preparation of the operative site by chlorhexidine wash starting 24 hours before the operation, use of subcutaneous sutures to eliminate dead space and reduce the formation of seromas, and by administration of broad spectrum antibiotic prophylaxis at least 1 hour before the incision is made. Patients on corticosteroids are at risk for poor wound healing. Vertical incisions should be avoided but if they are necessary, closure of the wound requires retention sutures. Vitamin A, 10,000–15,000 units per day, orally, is useful to improve wound healing in patients taking steroids.

Despite prophylactic measures some patients develop hematomas and seromas that require opening the incision. Traditionally open wounds have been managed by secondary intention using dressing changes but more recently they are managed by secondary closure or by secondary intention using negative pressure. Secondary closure is successful in more than 80% of the cases, once the wound is free of infection and necrotic tissue and is starting to granulate, usually 4 days after evacuation of the hematoma or seroma. Negative pressure wound therapy uses continuous negative pressure to evacuate edema fluid and debris and reduce bacterial colonization. The negative pressure increases blood flow and oxygenation of the open wound and promotes the formation of granulation tissue, significantly accelerating the time to complete healing. Sarsam et al. (2005) have published a good review article on management of wound complications.

BOX 15-10

Maternal and neonatal outcomes following elective cesarean at term in nonlaboring women and following vaginal delivery

Outcome	Cesarean	Vaginal
Frequency of postpartum bleeding	+	–
Maternal length of hospital stay	–	+
Neonatal respiratory morbidity	–	+
Postpartum infection	–	+
Anesthetic complications	–	+
Subsequent placenta previa	–	+
Breast-feeding	–	+
Urinary incontinency	+	–
Anorectal function	+	–
Sexual function	+	–
Surgical or traumatic complications	+	–
Pelvic organ prolapse	+	–
Fetal mortality	+	–
Neonatal intracranial bleeding	+	–
Neonatal asphyxia	+	–
Neonatal encephalopathy	+	–
Birth injury	+	–
Neonatal infection	+	–

(+) indicates more favorable outcome.

INDIAN EXPERIENCE ABOUT INTRAPARTUM MANAGEMENT

Partography

The graphic representation of labor described by Friedman as the mean cervical dilatation curve forms the cornerstone of present day partography. A cervicograph based on clinical data in primigravidae delivering normally in the Indian setting (Daftary and Mhatre, 1977) and its application to the management of primigravid labors was reported from Bombay (1977). The basic data of the mean cervical dilatation time curve so developed constituted the *Indian nomogram*. Later on in all future studies, the partogram was enlarged, and two additional lines designated as the "Alert Line" and "Action Line" were drawn to the right of the maximal slope of cervical dilatation. The designated "Alert line" corresponded to the maximal slope of cervical dilatation of the slowest 10% of Indian patients who had delivered normally. Two hours later, another parallel line was drawn and designated as the "Action Line." The patient's partogram was plotted alongside the nomogram when she entered the active phase of labor. Whenever the patient's partogram deviated from the "nomogram" and crossed the "Alert Line," it was apparent that the progress of labor was slower than

expected; at this point in time the patient was clinically evaluated to rule out CPD, fetal malposition, and inefficient pains. Abnormal progress recognized on the partogram is usually the first step in recognizing abnormal labor or *dysfunctional labors* or *dystocia*. It calls for the evaluation of the "3 Ps" namely the powers or efficiency of uterine contractions, if necessary. Observation of the frequency, duration, and intensity of uterine contractions provides the clue to clinical assessment of uterine efficiency. In India, facilities for continuous monitoring of uterine contractions with intrauterine pressure catheters and monitoring fetal well-being with use of fetal scalp electrodes are available in few institutions only; hence clinical monitoring has to be relied upon. Evaluation of *pelvis*, gross CPD is often obvious clinically prior to the onset of labor, and in case of doubt an x-ray pelvimetry is justified to settle the diagnosis. But on occasions, lack of progress during labor may be attributed to the *passenger* like a big sized baby, fetal malposition like occipitoposterior, fetal malpresentation like deflexed head or brow presentation, or fetal malformation like hydrocephalus or fetal ascites. Depending on the assessment of the cause for lack of progress in labor, corrective measures are instituted like amniotomy, oxytocin augmentation of labor, or measures to allay anxiety and provide pain relief to improve uterine efficiency. After close observation of progress during the next 2 hours, if the progress continues to remain tardy, the patient's partogram crosses the "Action Line." This indicates that the corrective therapeutic steps instituted earlier have not been effective and have not yielded the desired results. A follow-up evaluation often reveals the cause to be borderline disproportion, occipitoposterior malposition, or incoordinate pains. The further management decisions should be based on the clinical assessment of the cause of tardy progress and the maternal and fetal conditions prevailing at that time. Follow-up clinical assessment may lead to the decision of either continuation of "Trial of Labor" or planning obstetric intervention. In the latter case it allows sufficient time to alert the theater staff, anesthesiologist, and the neonatologist about any contemplated emergency surgery.

The beneficial results of labor analgesia in providing pain relief and relieving anxiety are evident to all clinicians. However, the services of an anesthesiologist to administer epidural anesthesia are not universally available in India; hence a protocol of a combination of analgesics and antispasmodic drugs in small synergistic doses (assuring safety margins) has been indigenously evaluated and added on to the management protocol. This protocol has been extensively evaluated in many centers in India. The optimizing labor protocol designed to meet the needs of the Indian obstetrician has given satisfactory results. It provides substantial pain relief labor and leads to shorter labors with satisfactory obstetric outcome (Sarin et al., 1982; Ganla et al., 2000; Singh et al., 2000; Daftary, 2001; Chauhan and Gupta, 2003; Khosla et al., 2003; Nanavati, 2004). Epidural anesthesia provides excellent pain relief during labor, and it facilitates cervical dilatation as well; however, the descent process is often slower. Dysfunctional labors complicate about 8–11% of all labors with cephalic presentation. A survey of Indian literature shows that dystocia was the indication for cesarean section in 20–40% of cases: Deshmukh (1985), 23.3%; Bhasker Rao et al. (1985), 26.3%; Singh and Laxmi Devi (2001), 44.4%; Konar et al. (1988), 38.8%; Arora and Oomaguichi (1991), 20.2%; Vijaykar and Rawal (1987), 30.4%; and Daftary and Patki (1996), 29.6%.

Induction of Labor

It is the nonspontaneous initiation of uterine contractions that results in progressive dilatation and effacement of the cervix and descent of the presenting part progressing to vaginal delivery (Nanavati, 2004). The incidence of labor induction in practice ranges between 9 and 18.4% (Nanavati, 2004). These inductions are undertaken in women in whom continuation of pregnancy is likely to adversely affect maternal or fetal health. On rare occasions, labor may be induced for the convenience of the patient or the doctor. The common indications for induction of labor include maternal indications like pregnancy-induced hypertension, diabetes mellitus, intrauterine fetal death, antepartum hemorrhage, hydramnios, congenital fetal malformation, premature rupture of membranes, suspected chorioamnionitis, and other causes. Fetal indications include placental insufficiency and IUGR (intrauterine growth restriction), postdatism, Rh isoimmunization, previous unexplained stillbirths, and deteriorating antenatal tests for fetal well-being. Prostaglandins (PGE_2 oral tablets or gel) have been effectively used for labor induction and give superior results to the older method of amniotomy followed by oxytocin induction. The chances of successful induction of labor are directly related to the status of the cervix. When the Bishop Score is > 7, the success rates of labor induction are high (Krishna et al., 1990; Bhide et al., 1993; Patki et al., 1993; Jina et al., 1994). Prostaglandins compared to oxytocin give a higher success rate of induction of labor, a lower cesarean section rate, and a better obstetric outcome. It is now generally accepted that prostaglandins are indicated for induction of labor followed by oxytocin after a suitable time gap for augmentation of established labor.

Abnormal Fetal Presentations—Breech Presentation

These account for 3–5% (Bhide et al., 1990; Walvekar and Anjaria, 2004) of all deliveries; breech delivery is

associated with a high perinatal morbidity and mortality. The causes of high perinatal wastage are higher incidence of prematurity (20–30%), birth asphyxia (25–42%), congenital defects (approximately 5%), birth trauma (3.6–7.4%), and infection (1.5–3.2%; Patwardhan et al., 1990; Pavse et al., 1990; Shah and Purandare, 1991; Jadhav and Maydeo, 2001). The route of delivery also influences perinatal outcome. In a study from Mumbai, Jadhav and Maydeo (2001) reported that although 60.8% of these patients were delivered by cesarean section, 39.2% were delivered vaginally.

The perinatal mortality rate for vaginal births was 117.3/1000 in contrast to a perinatal mortality rate of 5.4/1000 births in the group delivered by cesarean section (Jadhav and Maydeo, 2001). In another study from Mumbai, Patwardhan et al. (1990) reviewed the outcome of delivery of 427 patients admitted in labor with breech presentation. In the study 48.9% were primigravidae and 51.1% were multiparae. In this series 25% were delivered by cesarean section; the rest were delivered vaginally. Analysis of perinatal outcome revealed that no baby delivered by cesarean section had an Apgar score < 5, whereas the incidence of low Apgar score of < 5 was recorded in 7.3% of vaginal breech deliveries. The incidence of neonatal morbidity was 27% in vaginal breech deliveries as compared to 1.0% in cesarean births. The neonatal mortality was 39/1000 in vaginal breech deliveries as compared to none in the cesarean section group. Many other Indian studies (Bhide et al., 1990; Pavse et al., 1990; Shah and Purandare, 1991; De et al., 1992; Walvekar and Anjaria, 2004) corroborated these findings.

External cephalic version to correct breech presentations close to term has been successfully employed in some centers abroad, but is not widely practiced in India. Studies from Calcutta indicated that although clinicians willingly accept cesarean section as a better option in the management of delivery for breech presentation in primigravidae, they are reluctant to select cesarean section as the mode of delivery in multiparae. This assumption is not true; it does not withstand scientific scrutiny. In an analytical study of perinatal outcome in breech presentations in relation to the mode of delivery in primigravidae and multiparae, it was conclusively shown that cesarean section gives a better perinatal outcome in both primigravidae and multiparae. Vaginal delivery therefore carries higher risk for all pregnant women with breech presentations. The Canadian randomized controlled multicentric "Term Breech Trial" (Walvekar and Anjaria, 2004) to evaluate cesarean versus planned vaginal birth laid to rest all doubts about the optimal route of delivery. This landmark trial conclusively proved the maternal and perinatal benefits of planned cesarean births over planned vaginal birth for term breech.

Planned vaginal births may be justified in India in the following cases. (a) In selected cases of term pregnancies presenting with frank breech presentation, wherein the pelvis is normal, adequate beyond reproach, the baby is of moderate size (2.5–3.5 kg), the services of a well-trained obstetrician are available, and facilities for an emergency cesarean section possible at short notice. Proper counseling should precede the decision for attempting vaginal delivery. (b) Whenever the patient presents in advanced labor. (c) The fetus is preterm and not likely to survive. In rural India particularly, the obstetrician may still be called upon to deliver a breech birth—hence indicating the importance of learning the art of conducting breech deliveries even in present times.

Transverse (Oblique) Lie—Shoulder Presentation

It accounts for 0.3–0.5% of singleton births and occurs in 5–10% multiple births. The route of delivery of choice is cesarean section except in few cases of grossly immature fetuses < 0.5 kg or a dead macerated fetus weighing up to about 1.0 kg. Patients with neglected impacted shoulder presentation causing obstructed labor and rupture uterus continue to be admitted as transferred emergency admissions in our public hospitals. The incidence of rupture uterus reported ranges from 1:224 to 1:490 pregnancies (Sheth, 1991; Pagi et al., 1996). However, in a survey of cases of uterine rupture, booked cases accounted for 12.5% of the total cases analyzed (most of these were following previous cesarean scar rupture) and unbooked transfer cases accounted for rupture uterus in 87.5%. Of these 80% were from rural surroundings.

Occipitoposterior Malposition

These account for about 5% of fetal presentations at term. Given good uterine contractions, a moderate sized baby, and an adequate pelvis, there are bright chances, during labor, of the fetus accomplishing anterior rotation of the occiput and delivering normally. These labors are often somewhat prolonged. Oxytocin augmentation is often required to accomplish the desired result. Most patients presenting with deep transverse arrest are generally associated with android pelvis or outlet contraction. In borderline cases, a vacuum extraction may succeed. However, whenever difficulty is anticipated, cesarean section is the preferred alternative. In cases of persistent occipitoposterior presentations—given time, and ensuring optimum uterine contractions—the clinician may confidently await a vaginal face-to-pubis delivery. These women often need vaginal instrumental assistance. Anticipate perineal injuries—a wide episiotomy prevents bad perineal tears.

Transverse Lie and Shoulder Presentations

Patients diagnosed with this malpresentation antenatally should be properly counseled. A planned cesarean section

is the preferred route of delivery. In India, cases of obstructed labor attributed to neglected impacted shoulder presentation continue to be transferred to our public hospitals, often in a morbid state with threatened or manifest rupture of the uterus.

Brow Presentation and Mentoposterior Presentations

Brow presentations are rare. These are often transient in nature, and with good uterine contractions these often get rectified; however, failure to get them corrected leads to persistent brow presentations, which are best delivered by cesarean section. Mentoanterior presentations without any accompanying complications should be permitted vaginal delivery. Mentoposterior presentations should be delivered by cesarean section before it is too late and labor gets obstructed.

Shoulder Presentation

This is an uncommon obstetric complication which can come as a bolt from the blue. Anticipate this problem during delivery of a macrosomic fetus (diabetic patient) or postmaturity. Presence of a team of assistants trained in shoulder dystocia drill would be of great help during such an unexpected emergency. Suprapubic pressure or Robert's maneuver would help overcome the problem.

Cord Complications

These often present as emergency situations. Cord presentation diagnosed early in labor should be managed by emergency cesarean section. Management of cord prolapse occurring later in labor on should be dealt according to the stage of progress of labor at the time of diagnosis. If the cervix is fully dilated or a small rim of the cervix still present with the fetal head in the lower pelvic strait, consider the use of the obstetric forceps/ventouse to expedite delivery, but in cases remote from immediate delivery, reposit the cord, push up the presenting part manually, or fill the bladder with 500 ml of sterile saline to displace the head, and prepare for an immediate emergency cesarean delivery.

Antepartum Hemorrhage

Ultrasonography of the gravid uterus has simplified the diagnosis of placenta previa in clinical practice. The reported incidence varies from 1:200 to 1:327 pregnancies (Chauhan and Krishna, 2001). The reported incidence of abruption placenta varies from 1:50 to 1:500 (Ingle and Mehta, 2001) pregnancies. However, nonplacental causes (unclassified, polyp, ulcer, varicosity, neoplasm) account for 3–5% of all cases of antepartum bleeding. Apart from local speculum examination and sonography to determine the cause, most hemodynamically stable patients are advised expectant management to achieve a gestation maturity of about 37 weeks. Patients of placenta previa with major degrees of previa, posterior placenta overlying the sacral promontory, or presence of any other associated obstetric abnormality like breech presentation, transverse lie, or twin gestation are advised elective cesarean section. In patients with minor degrees of placenta previa, if the fetal head is overlying the pelvic brim, an amniotomy followed by oxytocin induction of labor often yields rewarding results. Many milder cases of accidental hemorrhage are treated conservatively with amniotomy and labor induction, but in cases of massive concealed hemorrhage, it is often wiser to terminate pregnancy by cesarean section rather than waiting until complications like coagulation disorder or renal shutdown sets in.

Operative Delivery

Some obstetric interventions require to be highlighted under the prevailing condition present in India. These are as follows.

Cervical OS Tightening (Incompetent Cervical OS)

Shirodkar, of Bombay, demonstrated convincingly the entity of incompetent cervix as a cause of repeated second trimester pregnancy loss and its effective treatment with cervical os tightening. McDonald's simplified technique of cerclage followed; it had been widely accepted globally and used effectively. Sonography has enabled us to establish the diagnosis of incompetent cervix more definitively. In exceptional circumstances, when an adequate length of the cervix is not available for performing cerclage operation by the vaginal route, successful os tightening has been accomplished by the abdominal route followed by a rewarding obstetric outcome (Tondare et al., 2001).

Obstetric Forceps and Vacuum Extraction

Extensive reviews on the subject of forceps delivery and vacuum extraction (ventouse) have appeared in Indian literature (Thakur et al., 1974; Swami and Soni, 1975; Moolgavkar et al., 1979; Goswami et al., 1981, Mitra et al., 1981; Sharma et al., 1989; Nargolkar et al., 2001; Tripathi, 2004)..

The present day views on instrumental vagina delivery may be summarized as follows:

- Both forceps and vacuum extraction are safe in experienced hands. Generally the two are often interchangeable.
- Operator experience and comfort should determine the choice of instrument.

- Vacuum extractor is associated with a higher incidence of cephalohematoma, retinal hemorrhage, and neonatal jaundice.
- Incidence of cephalohematoma increases with passage of time
- Midforceps delivery is safe and successful in experienced hands.
- The obstetric outcome worsens following failed attempts at vaginal instrumental delivery.
- Combination attempts at accomplishing delivery with help of both forceps and vacuum extraction carries higher risks of complications.
- Operative vaginal delivery should be attempted after careful consideration in cases of prolonged labor, suspected fetal macrosomia, and the possibility of encountering shoulder dystocia.
- Presence of neonatologist at the time of delivery is desirable.
- When in doubt, it is prudent to place the patient safety above all other considerations. A cesarean section is often the safer alternative.
- If there is any doubt about the capacity of the pelvis, or suspicion of presence of CPD, it is wiser to carry out trial of assisted vaginal instrumental delivery, with everything in readiness to opt out for the alternative of cesarean section as a safer choice, should the need arise.

Cesarean Section

There has been a steady increase in the rates of cesarean section globally. The last 30 years have witnessed the rise in incidence of cesarean section from 5–10% to the present day figures of 20–40%. This increase has been attributed to the following factors:

- Increase in numbers of patients with previous cesarean section
- Increase in the frequency of detecting fetal distress
- Increased employment of cesarean section for breech presentations
- More frequent use of cesarean section in maternal high-risk pregnancies like diabetes, elderly maternal age, prolonged previous infertility, severe pregnancy-induced hypertension, threatened HELLP syndrome, impending eclampsia, fetal malpresentations, bad obstetric history, HIV infection, active herpes genitalis, etc.
- Increased use of elective cesarean section in fetal interests (IUGR, placenta previa, premature rupture of membranes, postdatism, fetal macrosomia, multiple pregnancies, etc).
- To avoid medicolegal suit
- Patient insistence

The question uppermost in the minds of obstetricians today is that of the impact of the rising incidence of cesarean sections on the ultimate outcome of pregnancy. In an interesting study from Amritsar, Bedi et al. (1992) studied the maternal morbidity and perinatal outcome in 150 patients undergoing vaginal delivery and compared it with the obstetric outcome 150 patients delivered by cesarean section (Table 15-1).

Table 15-1. Comparison of maternal and perinatal outcome in vaginal and cesarean births

Parameter	Vaginal delivery		Cesarean delivery	
	Spontaneous	Complicated	Elective	Emergency
Maternal morbidity	9.3%	37.3%	10.7%	29.3%
Fetal morbidity	13.3%	38.9%	17.3%	36.0%
Perinatal morbidity	2.7%	8.6%	6.7%	12.0%

Table 15-1 shows that cesarean section has similar morbidity to vaginal delivery. However, the perinatal morbidity is somewhat higher following cesarean section, possibly because of the obstetric indications necessitating cesarean section. It is noteworthy that the perinatal morbidity was considerably higher in emergency cesarean sections when compared to that after complicated vaginal deliveries.

In a thought-provoking study from Baroda (Desai, 2005), reviewing obstetric practices over 20 years, it was observed that although the incidence of cesarean sections increased more than threefold from the earlier incidence of 5%, there was no significant impact on the obstetric outcome. In fact, the incidence of perinatal deaths from birth asphyxia and septicemia had increased. This study calls for caution and second thoughts on the hurry to alter our practices.

It may be concluded that we should continue to reassess our practices periodically and implement changes in our obstetric practices in light of our indigenous experiences and frank interchanges on the subject at our scientific fora, so that a rational national policy can be evolved for the country.

Obstetric hysterectomy may be required as an emergency lifesaving measure (uncontrolled bleeding or irreparable uterine rent in a case of rupture of the uterus) or as an elective procedure to safeguard against further morbidity, ill health, or future complications and sequelae. The incidence of obstetric hysterectomy ranges between 0.07 and 0.25% (Gupta et al., 2001; Kore et al., 2001; Sinha and Mishra, 2001; Mukherjee et al., 2002; Devi et al., 2004). The commonest indication for performing obstetric hysterectomy was uterine rupture (26.0–69.9%), the next common indication was intractable postpartum hemorrhage (5.0–33.0%). Morbidly adherent placenta (accreta) accounted for (5.1–26.9%). Traumatic postpartum bleeding accounted

for (3.1–5.0%) and secondary postpartum hemorrhage for (5.9%). Maternal mortality ranged between 6.1 and 12.2% (Gupta S et al., 2001; Kanwar et al., 2003). Septic abortions accounted for 29–46% of obstetric hysterectomies (Allahbadia and Vaidya, 1991; Devi et al., 2004).

IMPORTANT POINTS

1. Labor abnormalities are easily recognized by using the Friedman's curve. Their diagnosis in the absence of graphic analysis is possible but is imprecise and frequently in error.
2. Identification of labor abnormalities is only the first step in the analysis of this problem. The second step is to decide whether the labor abnormality originates in conditions affecting the "power" of the expulsive forces, the fetal "passenger," or the maternal "pelvis."
3. To precisely measure the "work" of the uterus it is necessary to use an IUPC.
4. Cephalopelvic disproportion, or CPD, also called "dystocia," is a common cause of labor abnormalities. CPD is an important cause of lack of progress in labor.
5. The diagnosis of CPD requires (a) documentation of adequate uterine work, (b) presence of clinical signs, (c) abnormal clinical pelvimetry, and (d) negative results of the Mueller-Hillis maneuver.
6. CPD is the cause of 20–50% of the cases of lack of progress in labor during the active phase of labor. Therefore the first thing to do after this diagnosis is to evaluate the fetal pelvic relationship.
7. Patients receiving epidural anesthesia during labor have more descent disorders and a higher incidence of operative vaginal deliveries than those without epidural blocks. These disadvantages are minimized by using a mixture of low-dose bupivacaine, fentanyl, and epinephrine for continuous epidural infusion.
8. External cephalic version is a reasonable alternative for patients with persistent breech presentations near term. The procedure reduces the number of cesarean sections secondary to breech presentations. External version is contraindicated in patients with conditions that require cesarean section.
9. The presence of an OP position of the fetal head should be suspected every time that a patient in labor has lack of progress in labor during the late part of the active phase and a persistent anterior rim of cervix. The diagnosis can be confirmed by pelvic and ultrasound examinations.
10. Operative vaginal delivery with forceps or vacuum is indicated when the second stage of labor in nulliparous patients reaches 3 hours with epidural or 2 hours without epidural anesthesia. In multiparas these limits are 2 hours with epidural and 1 hour without epidural.
11. The cardinal rule to avoid a poor outcome with operative vaginal delivery is to rigorously comply with the norms for outlet and low forceps applications.

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16

Hypertensive Disorders in Pregnancy

CHAPTER OUTLINE

Women with elevated blood pressure during pregnancy have a significantly increased maternal and fetal mortality and morbidity. Hypertension affects between 7 and 15% of all pregnancies and is associated with as much as 22% of all perinatal deaths and 30% of all maternal deaths in USA. There are multiple possible causes of elevated blood pressure during pregnancy but the overwhelming majority of cases can be included into five well-defined groups: chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome.

DEFINITIONS

Hypertension: According to the National High Blood Pressure Education Program Working Group (NHBPEP) and the American College of Obstetricians and Gynecologists (ACOG) hypertension in pregnancy is defined as a diastolic blood pressure of 90 mmHg or higher or a systolic blood pressure level of 140 mmHg or higher after 20 weeks of gestation in a woman with previously normal blood pressure (NHBPEP, 2000; ACOG, 2002). Diastolic blood pressure is determined as the disappearance of sound (Korotkoff phase V). The blood pressure level should be taken with an appropriate size cuff with the patient in an upright position after a 10-minute or longer rest period. For patients in the hospital the blood pressure can be taken whether the patient is sitting or in the left lateral recumbent position with the arm at the level of the heart (Box 16-1).

BOX 16-1

Guidelines for measuring blood pressure during pregnancy

1. *Patient conditions*
   - For measurements in the office the patient should be in the sitting position with her right arm supported in horizontal position at the level of the heart.
   - For measurements in the hospital the woman should be in semirecumbent position with the arm roughly at heart level.
2. *Equipment*
   - The cuff should encircle and cover two-thirds of the length of the arm. A large cuff should be used for obese patients.
   - Aneroid manometers should be calibrated every 6 months against a mercury manometer.
3. *Technique*
   - Inflate the cuff above the systolic pressure as recognized by disappearance of the radial pulse.
   - Use Korotkoff V (disappearance of the sound) to determine diastolic blood pressure. If the sound persists when the cuff is deflated, use Korotkoff IV (muffling of the sound).

Proteinuria: It is defined as the urinary excretion of 300 mg/L or more of protein in a 24-hour urine collection. This usually correlates with > 30 mg/dl (1+ by qualitative estimation using reagent strips). A diluted (<1010 sp.gr.) or concentrated (>1030 sp.gr.) urine or an alkaline specimen (pH > 8.0) may produce false results when tested with the reagent strips. The diagnosis should be based on a 24-hour urine sample if at all possible or on a "timed" collection if the former is not possible.

Chronic hypertension: It is defined as hypertension present before the 20th week of pregnancy or that present before pregnancy (ACOG, 2001). Hypertension should be documented on at least two occasions measured at least 4 hours apart (Sibai, 2002).

Chronic hypertension with superimposed preeclampsia: It is defined as proteinuria developing for first time during pregnancy in a woman with known chronic hypertension.

Gestational hypertension: Hypertension without proteinuria, developing after 20 weeks of gestation, during labor, or the puerperium in a previously normotensive nonproteinuric woman.

Preeclampsia: Hypertension associated with proteinuria, greater than 0.3 g/L in a 24-hour urine collection or 1+ by qualitative urine examination, after 20 weeks of gestation.

Eclampsia: Convulsions occurring in a patient with preeclampsia are known as eclampsia.

HELLP syndrome: Severe form of preeclampsia characterized by hemolysis (abnormal peripheral blood smear, bilirubin ≥ 1.2 mg/dl), thrombocytopenia (<100,000/mm^3), and elevated liver enzymes (AST > 70 U/L, LDH > 600 U/L).

GESTATIONAL HYPERTENSION

Gestational hypertension is the most frequent of the hypertensive conditions of pregnancy with a prevalence between 6 and 15% in nulliparas and 2–4% in multiparas (Hauth et al., 2000; Buchbinder et al., 2002). The condition is more frequent in obese women and in women with multiple gestations, diabetes, chronic hypertension, and with a history of preeclampsia. It is defined as the finding of hypertension (blood pressure at least 140 mmHg systolic and/or 90 mmHg diastolic) without proteinuria on at least two occasions at least 6 hours apart after the 20th week of gestation in women known to be normotensive before pregnancy and before 20 weeks of gestation (Sibai, 2003). The blood pressure recordings used to establish the diagnosis should not be more than 7 days apart. It should be noticed that the characteristic of this condition that differentiates it from preeclampsia is the absence of proteinuria. The characteristic that differentiates gestational hypertension from chronic hypertension is the onset of the problem after 20 weeks and the absence of hypertension before pregnancy.

Gestational hypertension used to be named "pregnancy-induced hypertension," or "PIH," and considered to be a relatively benign condition. The old name was a source of confusion because it was used to denominate all forms of hypertension during pregnancy. Also, the condition is not benign and pregnancy outcomes in gestational hypertension are worse than in mild preeclampsia (Buchbinder et al., 2002).

Classification

Gestational hypertension may be mild or severe. The condition is considered to be severe if there are sustained blood pressure elevations of systolic blood pressure to 160 mmHg or more and/or diastolic blood pressure to 110 mmHg or more. A rigorous definition of severe gestational hypertension requires that the elevated blood pressure should be observed for at least 6 hours. In practice this is not achieved because most obstetricians react immediately and give medications to lower the blood pressure, when it reaches the levels of the definition, without waiting for 6 hours to verify the diagnosis.

Pathophysiology

Similar to preeclampsia, the pathophysiology of gestational hypertension has not been clarified and there are multiple hypotheses to explain its occurrence. There is a strong possibility that, similarly to preeclampsia, there are two broad categories of gestational hypertension with different etiologies, pathophysiology, and maternal and perinatal consequences. The best clinical marker to recognize

these two forms of the condition is the gestational age at the time of its occurrence. Gestational hypertension before 30 weeks frequently is severe, advances to preeclampsia, and has a guarded perinatal prognosis. On the contrary, gestational hypertension after 34 weeks is usually a benign condition that rarely becomes severe, progresses to preeclampsia, and results in uniformly good perinatal outcome. Early gestational hypertension shares with preeclampsia a high incidence of poor placentation with histologic evidence of placental ischemia and hemodynamic changes characterized by vasoconstriction and decreased cardiac output (CO). Late gestational hypertension occurs more frequently in obese women and in multiple pregnancies, and the placentas do not show histologic changes consistent with ischemia. In late gestational hypertension the fundamental hemodynamic changes are increased plasma volume, increased CO, and normal peripheral vascular resistance (PVR). The fundamental problem behind early gestational hypertension is poor placentation, while late gestational hypertension corresponds to a poor maternal adaptation to the physiologic changes of pregnancy (Redman and Sargent, 2004). Later in this chapter, under preeclampsia, the potential mechanisms of disease that may be involved in the production of placental or maternal types of hypertension during pregnancy will be explained in more detail.

Maternal and Perinatal Outcome

Maternal and perinatal morbidity are increased in women with gestational hypertension. In the study of Gofton et al. (2001) induction of labor and cesarean section in women with gestational hypertension were almost double as those in the control group and were similar to preeclampsia and chronic hypertension. However, this study did not differentiate between mild and severe or between early and late gestational hypertension.

Barton et al. (2002) found differences in outcome depending on ethnicity with African-American women, exhibiting a higher incidence of placental abruption, stillbirth, and neonatal deaths than in White women. Also, women with mild gestational hypertension have an increased incidence of obstetrical interventions such as induction of labor and cesarean section. Women with severe gestational hypertension have a higher incidence of preterm birth and small-for-gestational-age newborns than in those with normal pregnancy and with mild preeclampsia (Buchbinder et al., 2002)

The most frequent complication of gestational hypertension is its progress to preeclampsia that is heralded by the development of proteinuria (300 or more mg of protein in a 24-hour urine collection or at least 30 mg/dl or 1+ in dipstick in at least two random urine samples collected at least 6 hours, but no more than 7 days apart). Approximately 15–25% of women with gestational hypertension develop preeclampsia and this risk varies with the gestational age. Saudan et al. (1998) analyzed retrospectively 460 and prospectively 112 women with gestational hypertension and found that the likelihood of progression to preeclampsia was 42, 36, 20, 16, and 7% for those diagnosed before 30, 30–31, 32–33, 34–35, and 36–37 weeks, respectively. Another finding was a strong association of progression to preeclampsia for women with gestational hypertension and a history of past miscarriage or a low serum albumin concentration. Barton et al. (2001) studied 748 women with gestational hypertension and found an overall progression to preeclampsia in 46% and to severe preeclampsia in 9.6% of the cases. The incidence of progression to preeclampsia was 52.1, 50.0, 49.3, and 37.3% at gestational ages of less than 30, 30–31, 32–33, and 34–35 weeks, respectively.

Approximately one-third of women with gestational hypertension present with a severe form of the condition. They have a substantial increase in poor maternal and perinatal outcome when compared with normotensive women. They have increased incidence of preterm delivery and small-for-gestational-age infants. They also have an increased incidence of abruptio placentae and admissions to the neonatal intensive care nursery (Buchbinder et al., 2002). Overall, their outcome is quite similar to that in women with severe preeclampsia.

Prediction

The value of uterine artery Doppler velocimetry in the prediction of gestational hypertension was studied by Valensise et al. (1993). These investigators found that an abnormal uterine artery resistance had better sensitivity for the prediction of preeclampsia (88%) than for the prediction of gestational hypertension (50%). Another study (Frusca et al., 2003) found that abnormal uterine artery velocimetry was a predictor of adverse perinatal outcome in women with gestational hypertension. Conde-Agudelo et al. (1993) investigated the predictive value of an elevated mean arterial pressure in the second half of pregnancy. They found that the sensitivity of this measurement to predict gestational hypertension was 72–92% while it was 39–48% in the prediction of preeclampsia.

Management

Initial evaluation

Women with elevated blood pressure (≥140 systolic or ≥90 diastolic) and no proteinuria by qualitative urine examination require an initial evaluation to determine whether or not they are at significant risk for a poor pregnancy outcome (Box 16-2). There are major and minor risk factors. The first and most important major risk factor to be considered in such evaluation is the degree of blood pressure

BOX 16-2

Criteria to identify high-risk women with gestational hypertension

- Blood pressure ≥ 150/100
- Gestational age less than 30 weeks
- Evidence of end-organ damage (elevated serum creatinine, liver enzymes, LDH, decreased platelet count)
- Oligohydramnios
- Fetal growth restriction
- Abnormal uterine and/or umbilical Doppler velocimetry

elevation. If the hypertension is severe (≥160 systolic or ≥110 diastolic) the patient has a risk similar to a severe preeclamptic and should be admitted to the hospital to complete her evaluation and start medical treatment. If the blood pressure is not in the severe range, the other components of the initial evaluation can be assessed on an outpatient basis. Another major risk factor is the gestational age at the onset of the disease, and the earlier the presentation, the greater the likelihood of complications and poor outcomes. From the fetal side, major risk factors for a poor outcome are the presence of fetal growth restriction and abnormal uterine and umbilical Doppler assessment. Minor factors include Black ethnicity, multiparity, decreased fluid volume, and significant changes in placental echographic morphology (grade III placenta, infarcts).

Gestational hypertension without risk factors

Women with gestational hypertension and no risk factors can be managed as outpatients. The objectives of their prenatal care are the early detection of preeclampsia and of progression of the condition to a severe form. They need to be instructed in the correct way to obtain their blood pressure at home and are asked to record their readings and bring this information to each office visit. They are given a blood pressure threshold, usually systolic ≥150 or diastolic ≥100, that requires office or hospital evaluation. They also need to be instructed in the correct way to perform qualitative examination of their urine for protein, using dipsticks, and are asked to test the first urine voided every morning and to call or come to the office or hospital if the result is ≥ 2+. These women need to be instructed about how to perform daily fetal movement counts. No dietary restrictions are necessary and normal activities are allowed; however, they should be excused from work if it involves strenuous physical activities, significant stress, or standing up for prolonged periods of time. They should have office visits every week. Performance of nonstress test (NST) is probably unnecessary if the fetal growth and the uterine, umbilical, and cerebral fetal Dopplers, as determined in the initial evaluation, are normal and there is no change in the weekly clinical assessment of the maternal and fetal condition.

The weekly assessment of patients with gestational hypertension and no risk factors must include a systematic review of the maternal and fetal status. From the maternal side the review includes the levels of blood pressure at home, the presence or absence of symptoms suggestive of end-organ damage (blurred vision, epigastric pain), and the presence of proteinuria. From the fetal side the review includes daily charting of fetal movements and measurement of the uterine fundal height. Proteinuria (≥2+) in a random urine sample is diagnostic of preeclampsia. When the proteinuria is trace or 1+ it is necessary to send the random sample to the lab for determination of the protein/creatinine and calcium/creatinine ratio. A protein/creatinine ratio > 0.30 is indicative of preeclampsia and a value less than 0.20 rules out significant proteinuria. Patients with preeclampsia have hypocalciuria and the finding of a calcium/creatinine ratio < 0.06 strongly suggests that this condition is present. The calcium/creatinine ratio in normotensive women is 0.44 ± 0.32, in chronic hypertension is 0.20 ± 0.18, and in preeclampsia is 0.03 ± 0.03. The development of proteinuria, elevation of the blood pressure above the threshold, decreased fetal movements, abnormal fundal growth, or development of maternal symptoms suggestive of end-organ damage require admission to the hospital for further evaluation and perhaps delivery. Patients with negative evaluations in their weekly assessment may continue with the pregnancy until they reach 38 weeks. At this time labor may be induced using cervical ripening agents when the cervix is not ripe.

Gestational hypertension with risk factors

Women with gestational hypertension and maternal or fetal risk factors, shown in Box 16-2, require admission to the hospital for further evaluation and treatment. The objectives of care are the pharmacologic control of their blood pressure and the early detection of preeclampsia, end-organ damage, and fetal decompensation. The initial evaluation includes a 24-hour urine collection for protein, platelet count, lactate dehydrogenase (LDH), and liver enzymes. PT (prothrombin time), PTT (partial thromboplastin time), and fibrinogen are unnecessary if the platelet count and the LDH are within normal limits (Barron et al., 1999). The laboratory evaluation is repeated once or twice per week. Fetal assessment includes NST, umbilical and cerebral Doppler, and fetal movement count. The blood pressure should be measured at intervals of no longer than 6 hours and the attending should be notified if it exceeds the 150/100 threshold.

The benefits of bed rest, in the hospital, for patients with severe gestational hypertension is a matter of discussion because there is no robust evidence indicating that this measure improves the outcome of pregnancy.

However, there are some studies suggesting benefit. Tuffnell et al. (1992) in a small trial randomized women to care in a day unit or conventional outpatient care. They found that outpatient care resulted in frequent hospital admissions for blood pressure control and had a higher rate of induction of labor and proteinuria than day unit care. In another study Crowther et al. (1992) randomized 218 women with gestational hypertension to ambulatory or hospital treatment. They found that multiparous women admitted to the hospital had a decreased incidence of severe preeclampsia. No improvement was noticed in fetal growth or neonatal morbidity. It is common to observe that the blood pressure decreases significantly and edema decreases or disappears after a few days in bed rest at the hospital. To avoid the possibility of venous thromboembolism the routine use of intermittent pneumatic compressions cuffs during the periods of bed rest is recommended.

Women with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg or mean arterial pressure ≥130 mmHg require treatment with antihypertensive agents. The objective of treatment is to avoid the potential complications (stroke, heart failure, pulmonary edema) associated with uncontrolled hypertension. Since the pathophysiology of gestational hypertension is one of significantly elevated CO with normal PVR (Bosio et al., 1999) treatment should be with beta-blockers and diuretics. Beta-blockers have been used extensively in pregnancy, are not associated with teratogenicity, and have found to be equivalent to methyldopa in several clinical trials. The most commonly used nonselective beta-blocker agent is labetalol, which can be used parenterally to treat severe hypertension and orally in less severe cases. Labetalol is rapidly metabolized by pregnant women and needs to be administered every 6–8 hours to optimize its effects. It is safe for both mother and fetus and the only reported neonatal effect is hypoglycemia, when used in high doses. The effective dose to reduce systolic blood

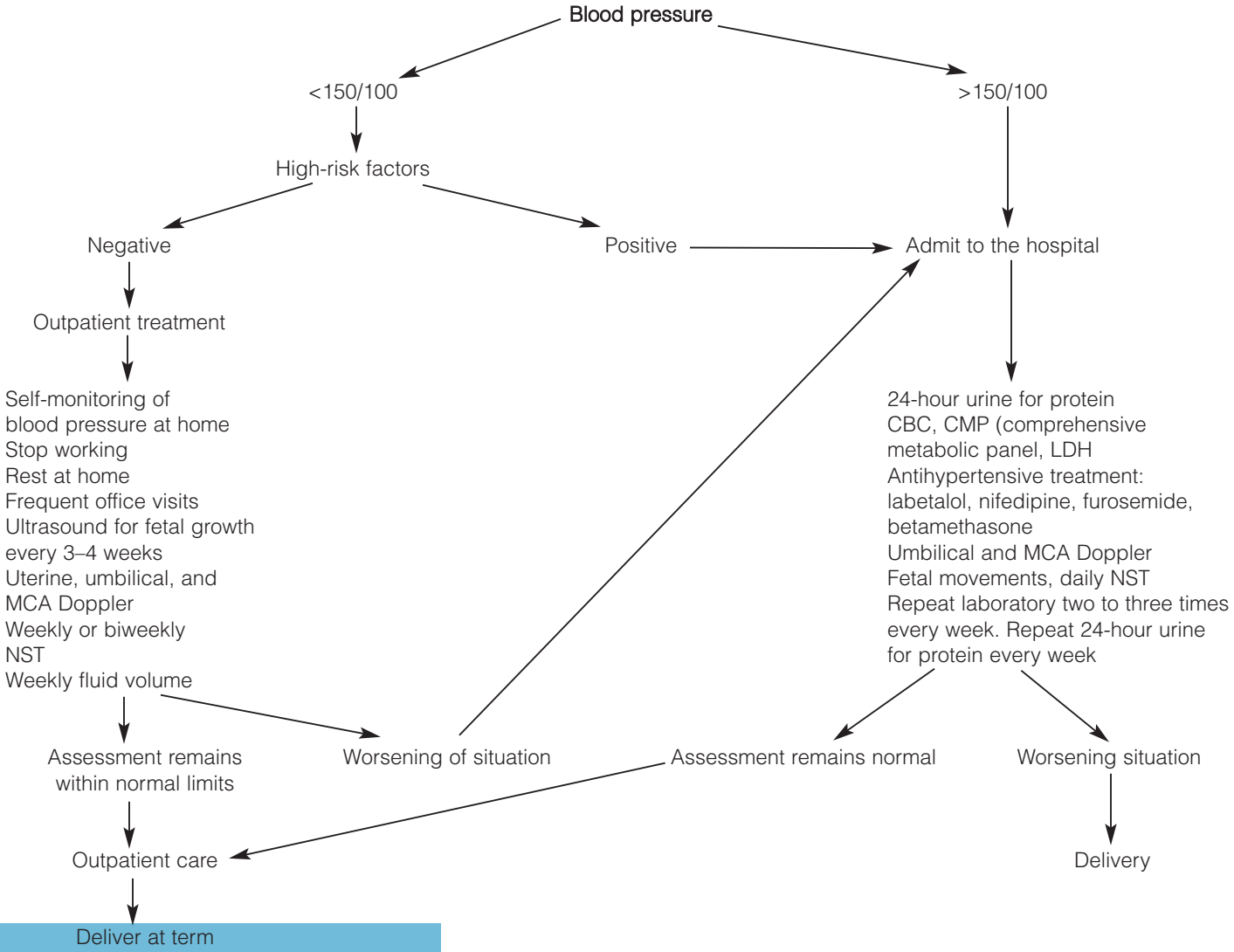

Figure 16-1. Management of gestational hypertension.

pressure to < 155 mmHg and < 105 diastolic varies from 600 to 2400 mg in 24 hours. Usually patients start taking 200 mg every 8–12 hours and the amount and frequency of medication is increased until the blood pressure reaches the desired level.

Diuretics should be given concurrently with beta-blockers. The reason for this is that the vasodilator effect of the beta-blocker or any other antihypertensive agent is compensated quickly by means of intravascular volume expansion, resulting in further blood pressure elevation. In addition, diuretics have an antihypertensive effect, initially by decreasing the preload (intravascular volume) and later by vasodilation of the capacitance vessels. The two diuretic agents most commonly used in pregnancy are furosemide and hydrochlorothiazide (HCTZ). Furosemide is a rapid-acting loop diuretic that has its peak of action within 1 hour of administration and a duration of effect of 6–8 hours. HCTZ inhibits sodium and potassium reabsorption in the distal tubule and has a more prolonged action. It peaks in about 4 hours and its effect lasts 8–12 hours. Furosemide can be given orally or intravenously in emergent situations. The oral dose is 20–40 mg every 6–12 hours. The dose of HCTZ is 25–50 mg daily.

Fetal surveillance is of the greatest importance in the expectant management of women with severe gestational hypertension. NST twice per week and weekly umbilical and cerebral Doppler are usually used for this purpose. In cases requiring prolonged hospitalization, ultrasound examinations to follow the fetal growth are performed every 3 weeks.

Expectant management is terminated when hypertension cannot be controlled or there is evidence of end-organ damage. Other indications for delivery are bleeding suggestive of abruptio placentae, arrest of fetal growth, worsening of Doppler evaluation with absent or reversed umbilical artery (UA) diastolic flow, and development of severe alterations in the fetal heart rate (FHR) monitoring.

Delivery

Gestational hypertension is not by itself an indication for cesarean section except in severe cases unresponsive to treatment or with fetal growth restriction before 32 weeks. Women with gestational hypertension who develop preeclampsia should be managed as described under preeclampsia. The route of delivery in women with severe gestational hypertension who require delivery depends on the results of the digital pelvic examination and on the cervical length by endovaginal ultrasound examination. If the cervix is unripe and the cervical length is ≥ 2.5 cm it is better to deliver by cesarean and avoid a prolonged induction. If the cervix is ripe vaginal delivery will be the best option. For women with mild gestational hypertension delivered after 37 weeks, induction of labor and vaginal delivery will be the first choice. Figure 16-1 summarizes the overall plan of management for women with gestational hypertension.

CHRONIC HYPERTENSION AND PREGNANCY

Chronic hypertension complicates between 1 and 3% of all pregnancies and corresponds to 25–50% of all cases of hypertension during pregnancy. According to ACOG, to establish a diagnosis of chronic hypertension during pregnancy it is necessary to document elevated blood pressure ≥140/90 mmHg (in repeated measurements several hours apart) before pregnancy, or prior to 20 weeks of gestation.

The main problem with this definition is that in many patients is not possible to document hypertension outside of pregnancy. Also, a significant number of women with undiagnosed chronic hypertension start their prenatal care after 20 weeks of gestation. To complicate the situation further, many women with chronic hypertension exhibit normal blood pressures during the second trimester of pregnancy and are erroneously classified as gestational hypertensives when their blood pressure increases in the third trimester.

Etiology

The majority of pregnant women with chronic hypertension have essential hypertension. Rarely, the hypertension results from chronic renal disease, renal artery stenosis, pheochromocytoma, hyperaldosteronism, or other causes (Box 16-3).

BOX 16-3

Etiology of chronic hypertension

1. Essential hypertension
2. Secondary hypertension
   - Renal
     - Renal parenchymal disease
     - Renovascular hypertension
   - Endocrine
     - Pheochromocytoma
     - Primary aldosteronism
     - Cushing syndrome
   - Neurogenic
     - Increased intracranial pressure
   - Vascular
     - Aortic coarctation
3. Systolic hypertension
   - Thyrotoxicosis
   - Hyperkinetic circulation

Pathophysiology

Normal pregnancy is characterized by increased plasma volume (preload), increased CO, and decreased PVR (Box 16-4). These changes result in a physiologic decrease in mean blood pressure during the second trimester. Chronic hypertension will modify the normal hemodynamic characteristics of pregnancy in different ways depending on the severity and duration of the hypertension.

The elevation of blood pressure in patients with chronic hypertension is a symptom resulting from an imbalance in the complex mechanisms that normally regulate blood pressure. The most important determinants of blood pressure are CO and PVR. These hemodynamic parameters are, in turn, the result of multiple influences. PVR is affected by humoral factors such as angiotensin and catecholamines, nervous sympathetic activity, and local factors such as endothelin and nitrous oxide. CO depends on cardiac contractility and the status of the intravascular volume. Elevated blood pressure may result from alterations in one or several of these factors.

For reasons unknown at present, essential hypertension starts with increased CO and normal PVR. This phase is followed by a gradual increase in PVR and fall in CO. The elevated blood pressure accelerates the progression of arteriosclerosis and through this mechanism produces damage to the heart, brain, kidneys, and other target organs. This process takes 30 or more years from beginning to end with the exception of a few patients who develop accelerated hypertension. A large majority of pregnant women with chronic essential hypertension are in the early stages of this process and usually have elevated CO and normal or mildly elevated PVR and rarely show evidence of end-organ damage. However, a normal PVR in the presence of elevated CO is abnormal because the physiologic response during pregnancy to the increase in CO is a decrease in PVR.

In the majority of women with chronic hypertension the decrease in PVR caused by the hormonal effects of pregnancy counterbalances the hypertensive effects of the increased CO, resulting in a decrease in blood pressure. However, this beneficial effect of pregnancy does not last too long. Pregnancy is associated with a significant increase in intravascular volume that causes an increase in CO that starts at the end of the first trimester and peaks at about 28–30 weeks' gestation. Women with chronic hypertension have a limited ability to counterbalance this increase in CO by further decreasing their PVR and maintain their blood pressure under normal limits. As a consequence, their blood pressure starts to rise. This aggravation of chronic hypertension during the third trimester of pregnancy differs from preeclampsia because of the absence of proteinuria or other end-organ injury.

BOX 16-4

Normal hemodynamic changes in pregnancy

	Nonpregnant	Pregnant
Cardiac output (L/minute)	4.3 ± 0.9	6.2 ± 1.0
Heart rate (bpm)	71 ± 10	83 ± 10
Systemic vascular resistance (dyne.cm/second^5)	1530 ± 520	1210 ± 266
Pulmonary vascular resistance (dyne.cm/second^5)	119 ± 47	78 ± 22
Mean arterial pressure (mmHg)	86.4 ± 7.5	90.3 ± 5.8
Pulmonary wedge pressure (mmHg)	6.3 ± 2.1	7.5 ± 1.8
Central venous pressure (mmHg)	3.7 ± 2.6	3.6 ± 2.5
Left ventricular stroke work index (g.m/m^2)	41 ± 8	48 ± 6

From Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989; 161: 1439–42.

Diagnosis

The diagnosis of chronic hypertension in pregnancy is established when an abnormal blood pressure (140/90 mmHg or above) is found before 20 weeks of gestation or when there is evidence of hypertension before pregnancy. In many cases these conditions are not fulfilled and the diagnosis cannot be made despite strong clinical suspicions.

It is possible to make false positive and false negative diagnosis of chronic hypertension in pregnancy as a result of inadequate techniques for blood pressure measuring. The most common error is to measure the blood pressure with a small cuff in obese patients. Another common source of error is variation in the use of Korotkoff sounds for determination of diastolic pressure. Although the use of Korotkoff V (point of disappearance of sounds) is recommended, it is common in pregnancy to hear sounds even with no pressure in the cuff. In these cases it is recommended to use Korotkoff IV (point of muffling of the sounds). Patient posture is also important and measurements of blood pressure during pregnancy should be obtained with the patient in the sitting position with the arm elevated at the level of the heart. When the patient lies on her left side and the blood pressure is taken on her right arm, the blood pressure is falsely low by as much as 15 mmHg. Some guidelines for measurement of blood pressure in pregnancy are shown in Box 16-1.

Maternal and Fetal Risks

The most important risks confronting pregnant patients with chronic hypertension are the development of severe hypertension, superimposed preeclampsia, fetal growth restriction, and abruptio placentae.

Severe hypertension

Some women with chronic hypertension, particularly of long duration, may develop severe nonproteinuric hypertension characterized by systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, at the end of the second or during the third trimester of pregnancy. In the majority of cases these women are asymptomatic, have been taking antihypertensive medications during the pregnancy, and the elevated blood pressure is a finding in one of their prenatal office visits.

The initial evaluation of these patients includes CBC (complete blood count), platelet count, metabolic panel, electrolytes, and 24-hour urine collection for protein. Fetal evaluation includes ultrasound for growth, fluid volume, and umbilical, uterine, and cerebral Doppler. Any evidence of end-organ damage worsens the prognosis and decreases the possibility of expectant management.

Severe hypertension is a medical emergency because these women are at high risk for stroke and abruptio placentae. They should be admitted to the hospital and treated aggressively with antihypertensive agents. An adequate response to treatment is an essential criterion for continuation of pregnancy. Otherwise delivery needs to be performed. Most patients respond to the continuous administration of IV labetalol in doses that vary from 20 to 60 mg/hour. When the blood pressure is not well controlled with labetalol, it is necessary to add nifedipine 10–30 mg orally every 6 hours. Furosemide is to be added to the treatment if there is evidence of excessive intravascular volume expansion. Once the blood pressure is stabilized in a range of 85–100 mmHg diastolic and 130–150 mmHg systolic, the IV labetalol is discontinued and oral administration (200–400 mg every 8–12 hours) is initiated.

Monitoring of the FHR is important during the treatment of the hypertensive crisis. A frequent complication of aggressive antihypertensive treatment and rapid decrease in blood pressure is the development of nonreassuring FHR monitoring patterns. Therefore it is not prudent to lower the diastolic blood pressure below 85 mmHg. This complication occurs more frequently in growth restricted fetuses with abnormal UA Doppler.

The course of women with severe hypertension is variable. Some of them show no evidence of end-organ damage, respond to treatment with antihypertensive agents, lose edema fluid and weight, and the fetal well-being tests are reassuring. After a short hospitalization they may be discharged and managed as outpatients. In some others the hypertension is difficult to control and they require multiple medications and soon they show fetal or end-organ alterations that demand delivery.

Superimposed preeclampsia

Patients with chronic hypertension and pregnancy have a 30% risk of developing superimposed preeclampsia. When this happens preeclampsia is usually severe, occurs early in pregnancy, and responds poorly to bed rest.

The differential diagnosis between superimposed preeclampsia and aggravation of chronic hypertension is based in the presence of proteinuria. The gold standard for the diagnosis of proteinuria is ≥ 300 mg of protein in a 24-hour urine collection. Although ≥ 2+ in a dipstick check correlates well with significant proteinuria, lesser values are not reliable and require confirmation with a timed urine collection. The problem with the 24-hour urine collection is the delay in establishing the diagnosis. This can be solved by determining the amount of protein in 8- or 12-hour urine samples and multiplying the result by 2 or 3, respectively. The correlation with the 24-hour results is excellent (Adelberg et al., 2001).

Another laboratory test that may be useful in the differential diagnosis between superimposed preeclampsia and aggravation of chronic hypertension is the determination of urinary calcium. Taufield et al. (1987) found that the mean urinary calcium excretion in patients with preeclampsia or with chronic hypertension with superimposed preeclampsia was lower (42 ± 29 and 78 ± 49 mg/24 hours, respectively) than in women with chronic hypertension alone (223 ± 41 mg/24 hours). Others have found that measurement of the calcium/creatinine ratio in a randomly obtained specimen of urine may be as useful as a 24-hour urine collection in the assessment of calciuria in patients with hypertension of pregnancy.

Fetal growth restriction

Poor fetal growth secondary to placental insufficiency affects 15–25% of pregnancies with chronic hypertension. For this reason it is necessary to assess the fetal growth by ultrasound examinations every 4 weeks. If the estimated fetal weight (EFW) by ultrasound falls below the 20th percentile, umbilical Doppler and FHR monitoring need to be performed frequently to assess the fetal well-being. Closer surveillance is necessary when the EFW falls or is below the 10th percentile. The perinatal prognosis is worse when growth restriction affects pregnant patients with chronic hypertension.

Abruptio placentae

Abruptio placentae occurs in approximately 5–9% of pregnant women with chronic hypertension. Abruption is an unpredictable event that occurs more frequently in women with superimposed preeclampsia or with severe chronic hypertension. It may present with severe abdominal pain, contractions or concealed bleeding, or bleeding may be the initial symptom of the condition. The perinatal outcome in patients with severe abruption is poor.

Management

Ideally, women with chronic hypertension should be seen for preconceptional counseling. Prepregnancy evaluation will permit the determination of the severity and the hemodynamic characteristics of the hypertension and allow for the collection of evidence to determine the presence of end-organ damage. Prepregnancy counseling will be useful to introduce lifestyle modifications that will improve pregnancy outcome. This is also a great opportunity for the prospective pregnant woman to become acquainted with the complications associated with her condition and the testing necessary to evaluate maternal and fetal well-being. Unfortunately, the majority of these patients are seen after conception.

The history and physical examination should be directed to determine the presence of signs or symptoms suggestive of secondary hypertension or end-organ damage. Also, patients with chronic hypertension frequently have undiagnosed medical problems such as renal disease, diabetes, or connective tissue disorders. Therefore the history should be meticulous and the physical examination should include measurement of blood pressure in both upper and lower extremities, auscultation of the flanks in search of a renal bruit, and examination of the optic fundi.

The majority of these women do not require extensive laboratory testing. Usually the work-up can be limited to an EKG, a serum biochemical profile, and a urine culture for the detection of asymptomatic bacteriuria. A creatinine clearance is ordered only if the serum creatinine concentration is above 0.8 mg/dl, the upper limit of normal for pregnancy. Quantitative urinary protein and analysis of the urinary sediment are done if the patient shows 2+ or more albumin on spot checks. ANA (antinuclear antibody) titers are important if the patient's history or examination suggests the possibility of autoimmune disease.

If the hypertension is severe or there are signs and symptoms suggesting secondary hypertension (Box 16-3), the patient may require determination of urinary vinyl mandelic acid and metanephrines, measurement of plasma renin activity, rapid-sequence IVP (intravenous pyelogram), chest x-ray, and renal arteriogram or renal biopsy.

Severity assessment

Assessment of severity is based on the magnitude of the blood pressure elevation. Traditionally, 160 mmHg systolic and 110 mmHg diastolic blood pressures have been accepted as the threshold to differentiate mild from severe hypertension.

Determination of the severity of the hypertension is important to establish a prognosis. Most clinicians and some data agree that the more severe the hypertension, the worse the prognosis and the greater the potential for complications. Severity assessment is also useful to determine the necessity for medications. If the patient is classified as severe, the need for treatment is clear. If the patient has mild disease, the need for antihypertensives will depend on the presence of high-risk factors.

BOX 16-5

Patients with mild chronic hypertension at high risk for complications and poor outcome

1. Diastolic blood pressure 85 mmHg or greater or mean arterial pressure 95 mmHg or greater in repeated observations at least 6 hours apart, after 14 weeks of gestation
2. History of severe hypertension in previous pregnancies
3. History of abruptio placentae
4. History of stillbirth or unexplained neonatal death
5. History of previous deliveries of small-for-gestational-age infants
6. Older than 35 years or more than 15 years of hypertension
7. Marked obesity
8. Secondary hypertension

The large majority of pregnant patients with chronic hypertension have mild disease and factors other than the level of the blood pressure should be taken into account to determine their prognosis. Patients with mild hypertension are at high risk for obstetrical complications if one or several of the conditions listed in Box 16-5 are present.

Self-monitoring of blood pressure

Self-monitoring of blood pressure is of importance in the management of the pregnant patient with chronic hypertension because office measurements every 2–4 weeks provide infrequent information about this dynamic process. Therefore, it is inadequate to determine the need for treatment or to assess the therapeutic response based solely on office evaluation. Also, it has been recognized for many years that the medical office setting can provoke anxiety, temporarily raising the patient's blood pressure. This phenomenon named "white coat hypertension," contributes to the inaccuracy of office blood pressure measurements and supports the use of self-monitoring in the management of blood pressure disorders. Self-monitoring of the blood pressure gives the obstetrician information on which better management decisions can be made. The method also supplies the patient with information that may enhance compliance.

Normally blood pressure has a circadian rhythm with a nadir between 2 and 4 am. This is followed by a rapid rise that reaches a peak between 6 and 8 am. The blood pressure remains stable during the day and falls progressively during the evening and night. This pattern is modified by multiple variables, especially stressful conditions. Therefore, several measurements throughout a 24-hour

period provide a better understanding of an individual need for or response to treatment.

Electronic and mechanical devices for self-monitoring of blood pressure are sold at most drug stores. These devices are reliable and because of their slow deflation rates (2 mm/second) the measurements obtained with them are often more accurate that those obtained by the clinician. The digital devices are also simple to use because they do not require a stethoscope.

All pregnant patients with chronic hypertension should obtain a digital device for daily blood pressure monitoring in the morning and the afternoon. They should bring their device to the obstetrician's office and be instructed in its correct use. They should maintain a daily record of their measurements as well. The majority of patients with chronic hypertension have lower blood pressure readings at home than at the office. The reverse situation is rare and when the blood pressure rises at home it will usually be elevated at the office.

Nonpharmacologic therapy

Bed rest

Bed rest has been used for many years as an adjunct in the management of pregnant patients with chronic hypertension. Blood pressure in the lateral recumbent position is approximately 10 mmHg lower than in the sitting or standing position. Bed rest increases the venous return that is impaired due to compression by the pregnant uterus and this permits mobilization of fluids, increases the urinary output, decreases peripheral edema, and improves placental perfusion.

There are no controlled, randomized studies comparing the efficacy of bed rest to other treatment modalities in pregnancy. However, Curet and Olson (1979) found that patients having 4 hours daily of bed rest had a decrease in perinatal mortality compared to prior pregnancies.

Despite the scarce scientific support, bed rest for the pregnant patient with chronic hypertension makes sense. These patients should be advised to rest 1 hour twice daily at the beginning of pregnancy. The bed rest periods should be increased to 2, 3, or 4 hours twice daily depending on the gestational age, the levels of blood pressure, and the accumulation of edema.

Salt restriction

The sodium content of the American diet is very high, 150–200 mEq/day (6–10 g of salt/day). A reduction in blood pressure of approximately 10 mmHg can be achieved in the nonpregnant status by lowering the sodium intake to 90 mEq/day (4 g of salt/day). This decrease in sodium intake is not dangerous to the pregnant woman or her fetus and it still provides enough sodium to allow adequate plasma volume expansion. Pregnant patients with chronic hypertension should be instructed to avoid processed foods, to minimize consumption of milk products, to scrutinize food labels for sodium content, and to resist adding salt to their food.

Weight gain and exercise

Excessive weight is frequently associated with hypertension particularly among Blacks, and weight reduction usually causes a decrease in blood pressure. However, obese hypertensive women should not lose weight during pregnancy. Rather, they should avoid a large weight gain by limiting caloric intake to only that necessary to cover their needs.

Exercise has a beneficial effect on blood pressure in nonpregnant patients. Pregnant hypertensive patients should avoid starting new exercise activities during pregnancy. However, they should continue any exercise program initiated prior to pregnancy.

Antihypertensive therapy

Pharmacologic treatment of chronic hypertension during pregnancy is indicated if it will decrease the frequency and severity of the associated complications. This stipulation is fulfilled in gravidas with severe hypertension and there is universal agreement that treatment of these patients decreases the frequency of maternal cardiac and cerebrovascular complications.

The controversy regarding pharmacologic treatment concerns patients with mild chronic hypertension. In these patients, the most common maternal complications are worsening of the hypertension, superimposed preeclampsia, and abruptio placentae. The fetus may be affected by growth restriction, antepartum and intrapartum hypoxia and acidosis. Proponents of universal treatment believe that the risk of accelerated hypertension, preeclampsia, and perinatal mortality and morbidity will be significantly reduced by treatment with antihypertensive drugs. Those who favor no treatment believe that most of these complications cannot be prevented by medication, that the risk of therapy is greater than the benefit, and that most of these patients have good perinatal outcome without treatment. Unfortunately, the results of controlled trials have given contradictory results (Abalos et al., 2001). The problem with these studies is that most of them have a small number of patients and a heterogenous population with respect to gestational age at the time of initiation of treatment, type of treatment, type of hypertension, and presence of high-risk factors.

Rather than adopting a universal policy of treatment or no treatment, it is better to individualize and use pharmacologic therapy for mild chronic hypertensive patients at high risk for maternal or fetal complications (Box 16-5).

BOX 16-6

Antihypertensive drugs that may be used during pregnancy

- Diuretics
  - Furosemide
  - Thiazides
- Vasodilators
  - Labetalol
  - Fenoldopam
  - Nicardipine
  - Nifedipine
  - Prazosin
  - Hydralazine
- Drugs that decrease the cardiac output
  - Beta-blocker agents
  - Propanolol
- Centrally acting drugs
  - Methyldopa

This approach is logical, avoids unnecessary treatment for many patients, and may prevent complications.

Treatment should be initiated as soon as the diagnosis and the indication for treatment have been established. An ideal antihypertensive drug should maintain the cardiac, renal, cerebral, and uteroplacental perfusion. It should not increase the heart rate or the plasma volume when the blood pressure drops, it should have no side effects, and it should be given once daily. This optimal medication does not exist. However, several medications are adequate for the treatment of chronic hypertension during pregnancy (Box 16-6). The largest experience has been with methyldopa. Recently, beta-blockers have surfaced as first line medications.

Beta-blockers

Beta-blockers may be the drugs of choice for the initial treatment of pregnant women with chronic hypertension. Our present understanding of the hemodynamics of mild chronic hypertension in pregnancy indicates that the majority of these patients have increased CO and hyperkinetic circulation. Propanolol reduces CO between 15 and 30% and suppresses renin production by 60%. After a few weeks of treatment there is also a drop in PVR. The effect on PVR is indirect and most probably is an autoregulatory response using vasodilatation to maintain adequate blood flow despite the drop in CO. These hemodynamic characteristics make therapy with beta-blockers ideal for the majority of patients with chronic hypertension and pregnancy. Also, beta-blockers are safe in pregnancy, and there is abundant literature documenting the excellent outcome of pregnant patients treated with these compounds.

Beta-blockers act upon blood pressure by competing with endogenous catecholamines for the beta-adrenergic receptors. They leave alpha-mediated vasoconstriction unopposed. Different compounds have different affinities for beta-receptors and are classified as cardioselective when they predominantly bind to beta-1 receptors or as noncardioselective when they bind to both beta-1 and beta-2 receptors. Atenolol is predominantly a beta-1 or cardioselective type of beta-blocker while propanolol is noncardioselective.

Propanolol is an effective drug for the treatment of chronic hypertension during pregnancy and has virtually no side effects. Several prospective studies have demonstrated the safety of its administration during pregnancy. Propanolol is metabolized by the liver and approximately 70% of the drug is removed in the first pass. It has a half-life of 3–6 hours but its effects are longer, and it can be given once or twice daily without problems. The medication lowers the blood pressure within hours, and the antihypertensive effect is not modified by changes in posture or activity. Treatment usually is initiated at a dosage of 40–60 mg twice daily. The initial dosage is adjusted according to the response and the side effects. The maximum dose is usually 480–640 mg/day, although higher doses rarely cause side effects.

Most of the side effects and contraindications for the use of propanolol are due to the nonspecific beta-1 and beta-2 blockade produced by the drug. Minor problems include fatigue, insomnia, and bad dreams. More serious side effects are bronchospasm and a blunted response to hypoglycemia, preventing its use in asthmatics and in brittle diabetics, respectively. Prolonged administration of propanolol may cause fluid retention.

Atenolol is a selective beta-1 adrenergic blocking agent that has significant advantages over propanolol because it does not cause bronchospasm and has a prolonged duration of action. Unfortunately it has been associated with an increased incidence of fetal growth restriction and is not used often during pregnancy.

Labetalol

Different from other beta-blockers, labetalol acts by decreasing PVR with little or no effect on CO. The drug has beta-1, beta-2, and alpha-1 blocking properties. The alpha to beta blockade ratio is 3:1 when given orally and 1:7 when given intravenously. One of the main obstetrical uses of labetalol is for hypertensive emergencies in patients with severe preeclampsia. Labetalol has replaced hydralazine for rapid reduction of blood pressure in preeclampsia, because it does not cause severe hypotension, headaches, tachycardia, and has no effect on uteroplacental blood flow. The drug is given intravenously, 20 mg initial dose, followed by 40–80 mg every 10 minutes, until the therapeutic response is achieved. It can also be given in IV drip, dissolving 250 mg in 250 ml of normal

saline and giving 20 ml/minute (20 mg/hour) and adjusting the rate up or down according to the patient's response.

Labetalol is also used orally for long-term treatment of chronic hypertension. Approximately 75% of the drug is inactivated in the first liver pass. The initial dose is 100 mg twice daily. This dose may be increased according to the patient's response. The maintenance dose is usually 200–400 mg twice daily.

Nifedipine

Nifedipine is a calcium channel blocker that impedes the influx of calcium into vascular smooth muscle cells, causing vascular relaxation and decreasing PVR. Nifedipine also relaxes the uterus and is frequently used as a tocolytic agent. Nifedipine can be used as a single agent or in combination with other antihypertensives in the treatment of chronic hypertension during pregnancy. The usual dose is 10–30 mg orally every 6 hours. It can be increased up to 20 mg every 4 hours. The medication is absorbed immediately and reaches a peak level serum concentration in 30 minutes. Biting the capsule before swallowing accelerates the absorption of the drug. Approximately 80% of nifedipine is eliminated by the kidney. The medication has no deleterious effects on uteroplacental blood flow. The most common side effects of nifedipine are facial flushing and headaches. In some patients it may cause constipation or exaggerated hypotension.

Methyldopa

Methyldopa has been the most widely used antihypertensive drug during pregnancy but lately is being replaced by beta-blockers as the first choice drug. The site of action of the medication is the central nervous system. Methyldopa induces the synthesis of alpha-methylnorepinephrine which stimulates alpha-receptors and decreases the sympathetic outflow from the central nervous system.

The effect of methyldopa is mainly on PVR, with little effect on CO. The medication causes dilation of both the arterial circulation and the capacitance vessels, thereby allowing expansion of the intravascular volume. Also, renal blood flow is maintained during treatment with methyldopa, and this property makes it the drug of choice in patients with actual or potential limitations in kidney function. Methyldopa reaches a maximum effect in 4–6 hours and has a total duration of action of about 8 hours. A single dose at bed time is usually effective for blood pressure control but to obtain maximum therapeutic efficacy, administration twice or three times daily is necessary. The drug is primarily excreted in the urine and may accumulate in patients with severe impairment of renal function.

Methyldopa is one antihypertensive medication that has been submitted to controlled trials during pregnancy and has been shown to have beneficial effects. The usual starting dose is 250 mg of methyldopa three times a day. This amount may be increased up to a total of 2 g/day according to the patient's response.

The most common side effect of methyldopa is postural hypotension, which subsides rather quickly with a decrease in the amount of medication. Excessive sedation and depression are occasionally seen. Positive Coombs and abnormal liver tests occur in approximately 10% of all patients. Hemolytic anemia is an uncommon complication.

In some patients, long-term administration of methyldopa causes salt and water retention. Apparently the kidneys of patients with chronic hypertension react to decreases in blood pressure caused by medications by fluid and sodium retention. This is clinically manifested by an increase in body weight beyond that expected for pregnancy alone, edema, and hemodilution. This situation may progress to a point at which "rebound" hypertension caused by the large intravascular volume expansion is observed. In these cases, a diuretic should be added to the treatment. The result will be increased urinary output, decreased edema, lowering of the blood pressure, and decrease in body weight.

Diuretics

Diuretics, particularly thiazides, have been used for more than 30 years and their efficacy and safety in nonpregnant patients with mild hypertension have been clearly demonstrated. In pregnant patients the situation is different and both the efficacy and the safety of diuretics have been questioned. The reason for conflicting recommendations about the use of diuretics is probably the heterogeneity of patients with chronic hypertension with respect to the expansion of their intravascular volume. Diuretics are useful in patients with expanded intravascular volume and may be detrimental in patients with decreased plasma volume. Their use in unselected populations will give mixed results.

Initially, diuretics decrease blood pressure by increasing urinary sodium excretion, decreasing the plasma volume and the extracellular fluid, and decreasing the CO. After 6–8 weeks of therapy the CO returns to prior level, the reduction in plasma volume and extracellular fluid is maintained, and the blood pressure remains low due to an effect on PVR.

The diuretic most commonly used during pregnancy is chlorothiazide. The usual dose is 25 mg every morning and may be increased to 50 mg daily, but larger doses usually have no greater antihypertensive effect. Another diuretic frequently used is furosemide. It may be given orally or parenterally. The time to onset and the total duration of action is relatively short and has minimal or no fetal or maternal side effects.

Side effects of thiazides and furosemide are mild and have little clinical significance. The most frequent biochemical changes are hypokalemia, hyperuricemia, and hyperglycemia but rarely these changes are severe enough to cause symptoms or require therapy.

Prazosin

Prazosin is a peripheral vasodilator that works by blocking postsynaptic alpha-receptors. The medication does not cause changes in CO but has a significant effect on capacitance vessels. Abrupt loss of venous tone with peripheral blood pooling has been invocated as the mechanism for the occasional occurrence of severe hypotension with the first dose of medication. On the positive side, the effect on the capacitance vessels combined with the effect on PVR are important advantages of the drug when used in chronic hypertensive patients who fail to adequately expand plasma volume during pregnancy. Prazosin in combination with a diuretic is highly effective for the treatment of severe hypertension refractory to other medications.

Prazosin reaches a peak plasma concentration approximately 3 hours after ingestion, is metabolized in the liver, and excreted in the bile and feces. Prazosin is a safe drug for pregnant patients. The initial dose should be 1.0 mg at bed time to avoid first-dose hypotension. The dose may be increased according to the patient's response but usually 2–4 mg twice daily is all that is necessary to achieve adequate blood pressure control. The main side effect of prazosin is postural hypotension which affects approximately 1% of the patients. Dizziness and lightheadedness are also frequent complaints.

Hydralazine

Hydralazine has been used for almost 40 years in the management of preeclampsia and is the prototype of peripherally acting antihypertensive drugs. It is a vasodilator that acts directly on the smooth muscle fibers of the arterial circulation. It has no effect on postcapillary capacitance vessels. The main obstetric use of hydralazine is to rapidly lower blood pressure, via intravenous injection, in patients with severe preeclampsia. The medication is unsuitable as a first choice antihypertensive for long term use during pregnancy.

Hydralazine increases CO and plasma volume by vasodilation and reflex stimulation of the renin angiotensin system. Consequently, resistance to treatment or treatment failures are common when the drug is used for prolonged periods. However, hydralazine may be useful when combined with diuretics and beta-blockers in patients not responding to single drug therapy.

The exact mechanism of action of hydralazine is unknown. It requires an intact endothelium and is probably mediated by prostaglandins. The onset of action occurs rapidly after intravenous injection. The drug is usually given in 5–10 mg intravenous doses that are repeated at 10–20 minutes intervals until the desired level of blood pressure is achieved. Orally, its action peaks in 3–4 hours and has a total duration of action of 6–12 hours. It is usually given twice daily in doses of 40–200 mg. Hydralazine is acetylated in the liver at a rate that is genetically determined. Slow acetylators respond to relatively small doses of medication with significant decreases in blood pressure, whereas fast acetylators are relatively resistant to the hypotensive effect of the drug.

Hydralazine can cause headaches, anxiety, nausea, vomiting, facial flushing, and epigastric pain. Most importantly, it causes decreased uteroplacental blood flow when the hypotensive effect is rapid or severe. In approximately 10% of the patients, hydralazine causes a reversible lupus-like syndrome. This lupus syndrome is limited to slow acetylators and usually responds to discontinuation of the medication. The appearance of positive ANA titers in pregnant patients treated with hydralazine is rare.

Selection of antihypertensive medications

Individualization of treatment is an important determinant of therapeutic success in pregnant patients with chronic hypertension. The patients should be classified into one of the three hemodynamic subtypes shown in Box 16-7. Most patients with mild chronic hypertension have increased CO and hyperdynamic circulation while the majority of those with severe forms of the disease have increased PVR.

BOX 16-7

Hemodynamic subtypes in patients with chronic hypertension and pregnancy

- *Increased cardiac output*
  White or Black, obese, diabetes, normal heart rate, increased plasma volume, normal peripheral vascular resistance
- *Hyperdynamic circulation*
  White, lean, young, migraines, cardiac awareness, increased cardiac output, increased plasma volume, decreased peripheral vascular resistance, predominant systolic hypertension, Korotkoff V sound zero
- *Increased vascular resistance*
  Black, lean, older, absence of physiologic murmur of pregnancy, no decrease in blood pressure or drop in hematocrit in the second trimester, no increase in plasma volume, minimally increased or normal cardiac output

The prototype of patients with increased CO and increased plasma volume is an obese patient with gestational diabetes. The first choice drug in these patients is a thiazide diuretic. Diuretics will have an immediate blood pressure lowering effect by decreasing the plasma volume. Continued administration will cause decreased PVR, and the intravascular volume will expand without causing elevation of the blood pressure. The administration of thiazides should be monitored with serial hematocrit determinations to evaluate their effect on plasma volume. If the expected physiologic increase in plasma volume does not occur, it may be necessary to add a vasodilator, such as prazosin or methyldopa, with effect on capacitance vessels or adjust the dose of diuretic to decrease urinary sodium losses.

The prototype of patients with hyperdynamic circulation is a young, lean, White female with tachycardia and a blood pressure with Korotkoff V sound at zero. The first choice drug in these patients is a beta-blocker, propanolol, or pindolol. The effect of the medication in these patients will be immediate and most of them will do well for a long time.

Patients with increased PVR are older, predominantly Black, have had chronic hypertension for many years, and show minimal or no decrease in blood pressure and no expansion of plasma volume in the second trimester of pregnancy. The drug of choice in these patients is a peripheral vasodilator such as a calcium channel blocker, labetalol, methyldopa, or prazosin. We prefer nifedipine although prazosin or methyldopa are also good choices because of their effect on the capacitance vessels.

General care during pregnancy

There is no substitute for frequent clinical observations in the antepartum care of pregnant patients with chronic hypertension. They should have prenatal office visits every 2 weeks until 32 or 34 weeks and then every week until the end of pregnancy. The critical variables to monitor during the prenatal visits are:

1. Blood pressure
2. Uterine growth
3. Preterm contractions
4. Fetal movements
5. Maternal weight

Blood pressure monitoring is of critical importance. The patients should measure her blood pressure at home twice daily and bring the written results at each office visit. Patients should be asked to call the doctor if the diastolic blood pressure is consistently above 100 mmHg or the systolic is above 150 mmHg. An initial evidence of intravascular volume expansion is the finding of a grade II systolic ejection murmur at about 12–14 weeks of gestation. Later on, if the diastolic blood pressure starts to decrease at the beginning of the second trimester, this is another indication of decreased PVR, expanded intravascular volume, and possibly a good outcome. Increased intravascular volume during pregnancy is necessary to ensure adequate placental blood flow. If the diastolic pressure remains above 80 mmHg well into the second trimester, and there is no systolic ejection murmur present, this is an indication of increased PVR and lack of intravascular volume expansion and perhaps an indication for initiation of therapy with vasodilator agents. The blood pressure measurements at home are also the best index to measure the patient's response to therapy. The goal is to keep the diastolic blood pressure below 90 mmHg and the systolic blood pressure below 140 mmHg.

Monitoring maternal weight is also important in the prenatal follow-up of patients with chronic hypertension. Too much or too little weight gain is of concern but preoccupation with the latter should be greater. In fact, the pregnant patient with chronic hypertension who does not gain weight during pregnancy is at high risk for fetal growth restriction. In contrast, too much weight gain may be normal and predictive of the birth of a large baby. Excessive weight gain may also be the consequence of unopposed methyldopa action or the first sign of superimposed preeclampsia.

Fetal growth restriction is a frequent complication in women with chronic hypertension and pregnancy. Clinical evaluation of the fetal growth is imprecise and ultrasound measurements should be obtained every 3 or 4 weeks. This evaluation is necessary even in patients with mild or well-controlled chronic hypertension.

It is customary to initiate fetal well-being testing with NST or BPP (biophysical profile) in women with chronic hypertension and pregnancy when they reach 34 weeks and earlier if fetal growth restriction or maternal complications develop. However, it will be unusual to find monitoring signs of fetal hypoxia and acidosis in patients with mild or well-controlled chronic hypertension and normal fetal growth in serial ultrasound examinations. If there is any alteration in fetal growth or if the hypertension is inadequately controlled, it is necessary to evaluate closely the fetal well-being. A relatively simple and accurate way to assess fetal well-being in these patients is by means of the modified biophysical profile (MBPP), which consists of an NST with vibroacoustic stimulation plus an ultrasonic determination of fluid volume. The MBPP is performed weekly after 34 weeks or earlier if there are clinical or ultrasound suggestions of impaired fetal growth, sudden deterioration of the maternal status, or decreased fetal movements.

Doppler studies of the uteroplacental and fetal–placental circulation are important in the care of the pregnant woman with chronic hypertension. Uterine artery Doppler at 24 weeks is important to determine the risk of

fetal growth restriction and that of developing preeclampsia. Normal uterine artery waveforms will be reassuring of the integrity of the uteroplacental circulation while the presence of early bilateral diastolic notching increases the probabilities of growth restriction and preeclampsia. Doppler waveform analysis of the UA is an excellent test to evaluate fetuses with inadequate growth. Umbilical Doppler reflects downstream vascular impedance and is affected by conditions that compromise the placental vascular tree at the level of the tertiary villi. This type of placental compromise frequently occurs in patients with chronic hypertension and fetal growth restriction. The prognosis for fetuses with normal umbilical and uterine Doppler is good. In contrast, an abnormal umbilical or uterine Doppler suggests that there is placental compromise and the potential for fetal hypoxia is significant. However, an abnormal umbilical Doppler should not be used as indication for delivery except when exhibiting absent or reversed diastolic flow. An abnormal Doppler has only prognostic value and indicates the need for closer fetal surveillance.

Laboratory evaluation of patients with chronic hypertension and pregnancy is simple. An important test is the hematocrit/hemoglobin, which is used to determine if plasma volume expansion occurs. There is no need for monthly or periodical creatinine clearance tests and quantitative urinary protein determinations unless the serum creatinine level is larger than 0.8 mg/dl or there is 1+ or more protein in qualitative examination of a random urine specimen.

Assessment of fetal pulmonary maturity is occasionally necessary in patients with chronic hypertension. However, in the majority of cases early delivery is a consequence of either fetal or maternal deterioration, and determination of fetal lung maturity adds little to the plan of management.

Delivery

The large majority of patients who remain stable during the prenatal period will develop spontaneous labor and deliver at term or near term. In these patients cesarean section is usually necessary only for obstetric indications or for FHR monitoring suggestive of fetal compromise. Patients with moderate or severe hypertension and those with mild hypertension and high-risk factors may require preterm delivery because of maternal or fetal compromise.

Chronic hypertension by itself is not an indication for cesarean delivery. However, the incidence of cesarean is high because of the development of complications and the need to deliver prematurely. Figure 16-2 summarizes the plan of management for women with chronic hypertension during pregnancy.

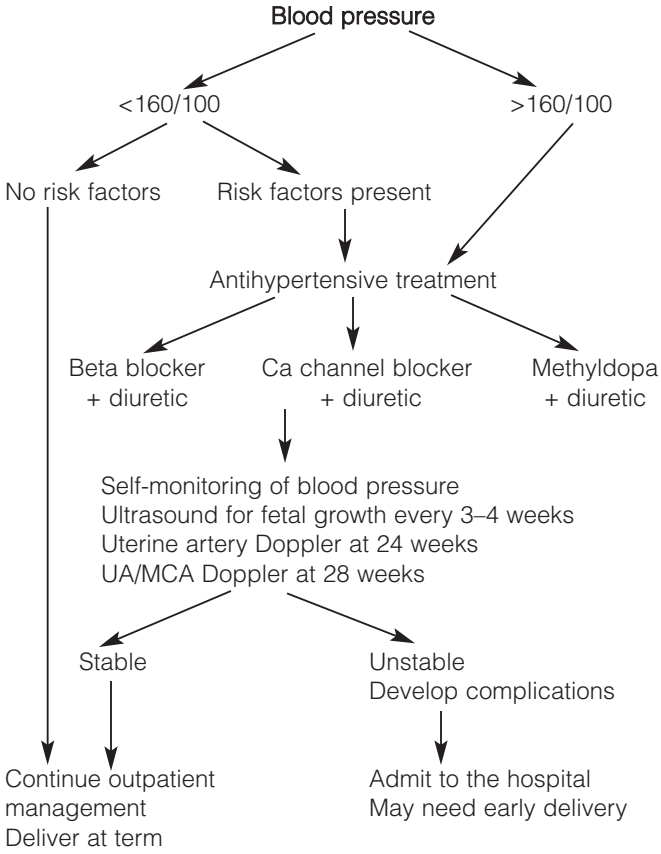

Figure 16-2. Management of chronic hypertension during pregnancy.

PREECLAMPSIA

Pathophysiology

The exact nature of the primary event causing preeclampsia is not known. However, evidence accumulated in the past 20 years indicates that in a large number of these women abnormal placentation is one of the initial events. Some of the main features of abnormal placentation are inadequate trophoblastic invasion of the maternal spiral arterioles and accelerated apoptosis of the trophoblast with abundant release of fetal DNA into the maternal circulation. In normal pregnancy the wall of the spiral arteries is invaded by trophoblastic cells and transformed into large, tortuous channels that carry a large amount of blood to the intervillous space and are resistant to the effects of vasomotor agents. These physiologic changes are incomplete in patients with preeclampsia and the trophoblastic invasion affects only some of the spiral arteries and does not progress into the myometrial portion of the arteries. This deficiency results in decreased uteroplacental perfusion. The anatomic and physiologic disruption of normal placentation is thought to lead to the synthesis of products that

affect angiogenesis and to abnormal lipid peroxidation. With the advance in gestation, these products will affect the endothelial system with the production of signs and symptoms of multiple organ compromise.

Not all women with preeclampsia exhibit abnormal placentation and not all cases of abnormal placentation result in preeclampsia. Abnormal placentation is a condition that is also found in fetal growth restriction, premature labor, and premature rupture of the membranes. Also, some women with preeclampsia, particularly those who are obese, diabetic, with chronic hypertensive, and with multifetal pregnancies may have placentas of normal or large size without the characteristic features of abnormal placentation (Zhang et al., 2006). Thus, some investigators have suggested the term "placental preeclampsia" to denominate those cases of preeclampsia with evidence of abnormal placentation and "maternal preeclampsia" to identify those cases where the placenta is normal but there is an underlying chronic maternal condition associated to the preeclampsia (Redman and Sargent, 2004). In "placental preeclampsia" the root of the disorder and the trigger of the pathophysiologic changes is the abnormal anatomy and function of the placenta. In "maternal preeclampsia" the normal adaptative inflammatory response that occurs with pregnancy is aggravated by maternal medical conditions such as diabetes, hypertension, autoimmune disorders, etc., to a point of decompensation that will manifest clinically as preeclampsia. Irrespective of the etiology and the mechanism of disease there are several important pathophysiologic changes in preeclampsia. These changes include but are not limited to hemodynamic changes due to alterations in blood volume and PVR, alterations of the hemostatic system, and abnormal renal function.

Hemodynamic changes

Hemodynamic studies in preeclampsia are confusing and difficult to interpret because of variations in the severity of the disease, mix of treated and untreated patients, invasive and noninvasive methods of evaluation, and small sample size. The predominant concept that emerges after reviewing the literature is that an increase in maternal CO rather than increased PVR is the most common hemodynamic feature in mild preeclampsia. However, once preeclampsia becomes severe, there is a switch to normal or decreased CO and elevated PVR (Hibbard et al., 2004). Bosio et al. (1999) using noninvasive Doppler techniques studied 400 women, 24 of which developed gestational hypertension and 20 developed preeclampsia. They found that women with preeclampsia initially have increased CO and normal PVR. However, with worsening of the disease there was a hemodynamic crossover to low CO and elevated PVR.

Changes in intravascular volume

Women with gestational hypertension and mild preeclampsia have normal expansion of intravascular volume. However, the increase in intravascular volume that normally occurs during pregnancy is minimal or completely absent in patients with severe preeclampsia. This limited blood volume expansion is probably the result of generalized constriction of the capacitance vessels but it is also possible that the decrease in capacitance may be the result rather than the cause of the decreased intravascular volume. The reduced plasma volume results in hemoconcentration as the disease progresses. After delivery, the plasma volume increases and the hemoglobin and hematocrit values decrease because of decreased vasospasm, excessive blood loss during delivery, and mobilization of extracellular fluids into the intravascular compartment.

Changes in PVR

The changes in PVR that occur with preeclampsia are clearly demonstrated by the vascular response that preeclamptic patients exhibit to the pressor effects of vasoconstrictive substances. Women who remain normotensive during pregnancy show a progressive resistance to the pressor effect of angiotensin II and catecholamines throughout gestation. In contrast, patients destined to develop preeclampsia show a progressive loss of resistance to the pressor effects of these agents. For example, at 24–26 weeks' gestation women who will remain normotensive require 12–14 ng/kg/minute of angiotensin II to raise the diastolic pressure by 20 mmHg. At the same gestational age, patients destined to develop preeclampsia will need less than 8–9 ng/kg/minute to have a similar pressure response. A pattern of decreased vascular resistance to the pressor effects of angiotensin II also exists in patients with chronic hypertension destined to develop superimposed preeclampsia.

Hemostatic abnormalities

Overt coagulation abnormalities exist in only a minority of patients with severe preeclampsia. The most common is mild thrombocytopenia, which affects less than 10% of the cases. The most serious hematologic complication of preeclampsia is the HELLP syndrome that is a form of severe preeclampsia which presents with hemolytic anemia, thrombocytopenia, hemolytic anemia, and elevated liver enzymes. As it will be seen later, the prognosis of this complicated form of preeclampsia is guarded, and these patients would be best cared for in tertiary centers.

The association between thrombophilic factors (factor V Leiden mutation, prothrombin 20210 promoter mutation, methylenetetrahydrofolate reductase (MTHFR) mutation, protein S, plasminogen activator inhibitor 1

4G/4G mutation, and antiphospholipid antibodies) and preeclampsia has been a subject of multiple investigations resulting in conflicting information. A recent large population study and meta-analysis (Morrison et al., 2002) suggests the existence of an association between severe preeclampsia and thrombophilia, particularly factor V Leiden and to a lesser extent MTHFR C677T mutations. This systematic review did not find an association between thrombophilia and mild preeclampsia or gestational hypertension. It seems that women who develop severe preeclampsia before 32 weeks will benefit from a thrombophilia evaluation because a positive finding may be useful for the prevention of recurrence in a future pregnancy.

Renal changes

Since proteinuria is one of the cardinal elements of preeclampsia, it is not surprising that the kidney has been extensively studied in this condition. The distinctive renal lesion in preeclampsia has been called "glomerular endotheliosis." This lesion is evident by electron microscopy and consists of swelling, vacuolization, and deposits of osmophilic material causing enlargement of the cytoplasm of the endothelial cells, which impinge and appear to obliterate the capillary lumen. There is no change in the epithelial cells or foot processes, no proliferation of intercapillary cells, and no alteration in the architecture of the renal medulla. The nature of the osmiophilic deposits has been elucidated with the help of immunofluorescent techniques. It has been found that these deposits correspond to a material that reacts with antibodies against fibrinogen and fibrin. A similar material is found in immunofluorescent studies of liver biopsies from patients with preeclampsia (Arias and Mancilla-Jimenez, 1986).

When nulliparous patients with hypertension during pregnancy are submitted to kidney biopsy studies, 75% of them show glomerular endotheliosis, 16.3% have chronic renal lesions, and 7.6% of them have both preeclampsia and chronic renal disease. When the same study is carried out in multiparous patients with hypertension in pregnancy, the characteristic histologic lesion of preeclampsia is found in only 23%, chronic renal disease will be present in 51%, renal lesion plus preeclampsia will be found in 13%, and normal histology in 11% (Fisher et al., 1981). This research suggests that chronic renal disease must be strongly considered in the differential diagnosis of multiparous women developing preeclampsia.

The difficulties and complications associated with kidney biopsy during pregnancy and the lack of therapeutic or prognostic value make the performance of this procedure difficult to justify. Recently Stevens et al. (2003) performed kidney biopsies in 12 normotensive pregnant women and in 36 with hypertension and pregnancy. They found glomerular endotheliosis in all the women with hypertension and in 5 of the normal pregnant control cases. There was a progressive increase in severity of lesions from normotensive to gestational hypertension to preeclampsia. These findings suggest that preeclampsia may be an extreme of the physiologic adaptation to pregnancy rather than a separate pathological condition.

Prediction

Several tests have been proposed to identify women at risk of developing preeclampsia. Some of these tests such as the cold pressor test, the isometric hand grip exercise, and the roll-over test depend on the pathophysiologic changes that occur in preeclampsia. Other tests, such as the measurement of urinary calcium or plasma fibronectin, are based on the presence of biochemical alterations peculiar to this disease.

Angiotensin sensitivity test

The abnormal vascular reactivity of patients destined to develop preeclampsia may be detected several weeks before the development of clinical signs and symptoms, and the degree of sensitivity to angiotensin II may be used as a screening test to identify the patients at risk. Unfortunately, this test is labor intensive and has a high incidence of false negative and false positive results. Also, angiotensin II preparations for human use are not available in USA.

Roll-over test

The roll-over test was originally described as a noninvasive office procedure having an excellent correlation with the angiotensin sensitivity test and serving as an excellent predictor of the development of preeclampsia. A positive test is an elevation of 20 mmHg or more in blood pressure when the patient rolls over from the lateral decubitus to the supine position. Unfortunately, the test has poor sensitivity and poor specificity and is of limited clinical value.

Mean blood pressure in the second trimester

Mean arterial pressure (systolic + 2(diastolic)/3) (MAP) in the second trimester of pregnancy was proposed long time ago as a predictor of preeclampsia. However, an analysis of 39,876 patients with preeclampsia and 207 patients with eclampsia indicated low sensitivity and low positive predictive values for this test. A recent systematic review (Conde-Agudelo et al., 1993) suggests that MAP in the second trimester is a better predictor of gestational hypertension than of preeclampsia.

Urinary calcium

Several studies have demonstrated that preeclampsia is associated with hypocalciuria. A urinary calcium concentration equal to or less than 12 mg/dl in a 24-hour collection has positive and negative predictive values of 85 and 91%, respectively, for the diagnosis of preeclampsia. Determination of the calcium/creatinine ratio in a randomly obtained urine sample seems to be as accurate as 24-hour collections. In normotensive pregnancies this ratio is 0.44 ± 0.32. In cases of chronic hypertension the ratio is lower 0.20 ± 0.18, but in preeclampsia is much lower (0.03 ± 0.03). There are suggestions that hypocalciuria occurs early and persists throughout gestation in women with preeclampsia, being potentially useful for the early identification of patients at risk.

Fibronectin

Patients with preeclampsia have elevated levels of plasma fibronectin—a glycoprotein that has an important role in all cellular adhesions and is a component of connective tissue and basement membranes. There are studies indicating that increased plasma levels of endothelium-originated fibronectin precede the clinical signs of preeclampsia and may be useful for prediction of the disease.

Uterine artery Doppler

Several investigations have suggested that uterine artery Doppler velocimetry at 22–24 weeks is useful to identify women destined to develop preeclampsia. The largest study included 7851 women with singleton pregnancies who had transvaginal color Doppler assessment of the uterine arteries at 23 weeks (Papageorghiou et al., 2001). Early diastolic notches were present in both uterine arteries in 9.3% of the cases. The sensitivity of a pulsatility index above the 95th percentile or the presence of bilateral notching in detecting women destined to develop preeclampsia and fetal growth restriction was 69% and preeclampsia without fetal growth restriction was 24%. The sensitivity increased to 93 and 80%, respectively, for women developing severe forms of these complications requiring delivery before 32 weeks. The positive and negative likelihood ratios of uterine artery Doppler screening are 6.61 and 0.55, respectively. It seems that, although not a perfect screening tool, uterine artery Doppler ultrasound is the best available test for the early detection of preeclampsia of placental origin.

Diagnosis

Blood pressure elevation

Hypertension is the most important sign of preeclampsia because it reflects the severity of the disease. Unfortunately, mistakes are frequently made due to lack of consistency in the measurement of the blood pressure (Box 16-1). One common error is taking the blood pressure in an obese patient with a regular-size cuff. This causes abnormally high readings. Another common error is not using the same maternal position in repeated measurements. When an abnormally high reading is obtained, it is common practice to repeat the measurement with the patient in the lateral recumbent position and to disregard the initial measure if the second is lower. This is an inappropriate technique because in the pregnant woman the lateral recumbent values are always lower than those in the sitting position, and to ignore the initial high blood pressure value will delay proper diagnosis and treatment. To avoid these errors the blood pressure at each prenatal visit should be taken with the patient in the sitting position. A third error is the use of different end points to measure the diastolic blood pressure. The official recommendation of the NHBPEP and the ACOG is to use the Korotkoff V sound, the point of disappearance of the sound, as the marker of diastolic pressure.

Proteinuria

Proteinuria is a sign of preeclampsia which is defined as ≥300 mg of protein in a 24-hour urine collection. This usually correlates with 30 mg/dl or a 1+ reading in dipstick in a random urine specimen. Proteinuria is also valuable as a sign of severity and a value ≥5 g in 24 hours is one of the criteria to classify preeclampsia as severe.

The 24-hour urine collection for protein is the gold standard in the diagnosis of preeclampsia. To avoid the time consumed in the collection of 24-hour urine specimens, efforts have been made to develop faster methods to determine the concentration of urinary protein. One of these methods is the dipstick that has a good, although not perfect, correlation with the protein concentration in the urine. The correlation of the dipstick with the 24-hour excretion of protein was studied by Meyer et al. (1994). A 1+ dipstick has a 92% positive predictive value to predict > 300 mg of protein. However a negative to trace dipstick result does not rule out proteinuria and up to 66% of these patients will have ≥ 300 mg of protein in a 24-hour urine collection. If the dipstick is 3+ or 4+, significant proteinuria (≥300 mg/24-hour) is almost uniformly present, but this result should not be used to classify preeclampsia as severe. A second rapid method for evaluation of proteinuria is the protein/creatinine ratio that, in the nonpregnant status, correlates well with the 24-hour collection. A protein/creatinine ratio of 0.3 has a positive predictive value of 85.5% and a sensitivity of 81.0% for significant proteinuria in the 24-hour collection (Durnwald and

Mercer, 2003). Unfortunately, a negative result (<0.3) has a negative predictive value of 47.5%, meaning that about half of the women with a negative result will have significant proteinuria in the 24-hour collection specimen. In a small series of patients when the cutoff is lowered to > 0.19 the sensitivity and specificity were 85 and 73% and the positive and negative predictive values of the test were 46 and 95%, respectively (Ragip et al., 2004). In summary a protein/creatinine ratio ≥ 0.3 almost always indicates significant proteinuria and a ratio ≤ 0.2 almost always indicates absent or nonsignificant proteinuria. Intermediate values have elevated percentages of false negative and false positive results.

The proteinuria of preeclampsia is "nonselective," meaning that it is a mixture of several proteins of different molecular weights. Proteinuria in preeclampsia characteristically occurs in the absence of either a nephritic (red cells, red cell casts) or a nephrotic (birefringent lipids, wax casts) urinary sediment. The urinary sediment in preeclampsia is usually unrevealing and in most cases shows an abundance of fine and coarse granular casts. The presence of a nephritic or nephrotic type of sediment must alert the clinician to the possibility of an underlying renal disease.

Vasoconstriction

Clinical evidence of vasoconstriction may be obtained by ophthalmologic examination. The most common findings in patients with severe preeclampsia are an increase in the vein to artery ratio and segmental vasospasm. Patients with mild preeclampsia usually have a normal funduscopic examination. Papilledema is not a common finding in preeclampsia, and it suggests the possibility of a brain tumor, causing increases in intracranial pressure and secondary hypertension. The presence of microaneurysms will indicate diabetes.

Examination of the optic fundi in patients with gestational hypertension without proteinuria is also important because it may suggest the presence of chronic hypertensive disease independent of pregnancy. The presence of hemorrhages, exudates, or extensive arteriolar changes suggests chronic hypertension.

Excessive weight gain and edema

Excessive weight gain and edema are no longer considered signs of preeclampsia. Large increases in body weight as well as edema of hands, face, or both are common in normal pregnancy and the incidence of preeclampsia is similar in patients with or without generalized edema. There is no evidence to indicate that measures limiting weight gain during pregnancy, such as the use of low-salt diet or diuretics, prevent the development of preeclampsia.

Other signs and symptoms

Headaches are usually present in severe forms of preeclampsia. They may also appear before other indications of overt disease. The pain may be frontal or occipital, may be pulsatile or dull, may occur simultaneously with visual symptoms, and may frequently be intense, especially when preceding the onset of convulsions. Intracranial Doppler ultrasound measurements suggest that headaches in preeclampsia are secondary to increase vascular pressure.

Epigastric or right upper quadrant pain is also common in patients with severe forms of the disease, particularly HELLP syndrome, but may also occur before the onset of obvious signs or symptoms of preeclampsia. This complaint is frequently attributed to indigestion or to gallbladder disease and is treated with antacids and antispasmodics. When such pain appears in patients with severe hypertension, it is frequently a harbinger of convulsions and is often accompanied by marked alterations in AST (aspartate aminotransferase), ALT (alanine aminotransferase), and LDH values.

The most common visual symptom appearing in patients who are going to develop preeclampsia is scotomata, a transient perception of bright or black spots. This may progress to a sudden inability to focus, blurred vision, and in severe cases, complete blindness. In most patients who complain of visual symptoms, ophthalmologic examination reveals only vasospasm. This indicates that the abnormality originates in the occipital cortex rather than in the retina. Patients with severe preeclampsia may suffer from cortical blindness, and it is amazing how fast their vision recovers following delivery.

Brisk deep tendon reflexes are also common and result from central nervous system irritability. In some cases, clonus and twitching of digits may also occur. It is unusual for preeclamptic patients to have seizures without first showing signs of nervous system irritability.

Laboratory findings

Laboratory tests are usually unrevealing in cases of mild preeclampsia, but there are multiple findings in severe forms of the disease. The laboratory changes reflect the effects of the disease on the kidney, liver, fetoplacental unit and, in some cases, the hematologic system.

Altered renal function

In severe preeclampsia, there are elevations in serum creatinine, blood urea nitrogen (BUN), and uric acid levels as well as proteinuria, decreases in creatinine clearance, and changes in the urinary sediment. The serum creatinine almost never exceeds 1.2 mg/dl (the upper limit of normal during pregnancy is 0.8 mg/dl) and the BUN rarely exceeds 20–25 mg/dl (the upper limit of normal in pregnancy is 15

mg/dl) unless there are unusual complications. The creatinine clearance is usually at the nonpregnant level. It should be noted that a creatinine clearance of 100 ml/minute is abnormal during gestation when the lower limit of normal is 130 ml/minute.

Some investigators have postulated that an elevated serum uric acid is a specific laboratory finding in preeclampsia. However, there is a high degree of overlap among the values found in normal pregnancy, mild preeclampsia, severe preeclampsia, and eclampsia. Serum uric acid levels normally decrease at the beginning of pregnancy, remain low during the second trimester, and slowly increase during the third trimester, nearly reaching nonpregnant levels at term. In most cases of mild or moderate preeclampsia, serum uric levels are indistinguishable from those obtained in normotensive patients at term. Marked elevation of uric acid, BUN, and creatinine only occur with severe preeclampsia.

Changes in liver function tests

Patients with mild preeclampsia show little or no alteration in hepatic enzyme levels, but in severe preeclampsia increases in AST, ALT, and LDH are occasionally found. The elevated LDH is usually the result of an increase in the hepatic isoenzyme. When hemolytic anemia is present, the elevated LDH is also a reflection of the elevation of erythrocytic isoenzymes. After delivery, AST and ALT levels decrease rapidly and, in most cases, reach normal levels by the 5th postpartum day. LDH falls more slowly, and normal values are reached by postpartum day 8–10.

Hematologic abnormalities

The only hematologic change that may be observed in patients with mild preeclampsia is an elevation of hemoglobin and hematocrit caused by decrease in plasma volume. With more severe disease other hematologic abnormalities, commonly mild thrombocytopenia, may be present. The plasma fibrinogen concentration is usually increased, and it is unusual to find a fibrinogen level below 200 mg/dl unless preeclampsia is complicated by abruptio placentae.

Abnormal fetal growth

A common finding in women with moderate or severe preeclampsia is fetal measurements 2–4 weeks less than expected for the gestational age, suggesting the presence of fetal growth restriction. The head to abdomen and femur to abdomen ratios frequently are abnormally elevated in these cases, suggesting asymmetric growth restriction of placental origin. The finding of abnormal fetal biometry in women with preeclampsia demands evaluation with uterine, umbilical, and middle cerebral artery (MCA) Doppler.

The uterine artery Doppler will provide assessment of the uteroplacental circulation. An abnormal uterine Doppler (increased systolic to diastolic (S/D) ratio, bilateral diastolic notching) indicates abnormal impedance or resistance to the blood flow in the maternal side of the placental circulation, while a normal result suggests integrity of the maternal supply line. The uterine artery Doppler is a part of the initial evaluation of the woman with preeclampsia but has no value in the follow-up of these cases. Its value is as indicator of the presence of placental damage and as prognostic index of poor pregnancy outcome.

The UA Doppler provides an assessment of the placental-umbilical circulation. As explained in Chapter 1, there are four possible results with the UA Doppler. It may be normal or may show an elevated S/D ratio, absent diastolic flow, or reversed diastolic flow. A normal UA S/D ratio is indicative of a normal blood flow in the fetal side of the placenta and when it is associated with a normal uterine artery Doppler, it rules out significant placental pathology and suggests a benign form of preeclampsia. An abnormally elevated UA S/D ratio, absent diastolic flow, and reversed diastolic flow are increasingly worsening indicators of resistance to blood flow in the fetal side of the placental circulation.

When the UA S/D ratio is elevated but diastolic flow is still preserved it is necessary to perform Doppler of the MCA to correctly evaluate the significance of this abnormality. When UA S/D ratio is larger than the MCA S/D ratio (UA/MCA > 1.0) the placenta still has adequate reserves and the fetus is not under significant hypoxemia or acidosis. An UA/MCA ratio < 1.0 indicates that the placental insufficiency has reached such a degree of severity that the fetus is increasing the blood flow to the brain and decreasing the blood flow to other organs (centralization of flow or brain sparing effect). However, centralization of blood flow as demonstrated by an UA/MCA ratio < 1.0 is not an indication for immediate delivery in pregnancies of less than 34 weeks. This mechanism of fetal compensation to placental insufficiency may continue for several days before decompensation occurs, making it possible to administer steroids before delivery.

Absent UA diastolic flow indicates a worsening of the fetal situation and the beginning of acid/base changes. A good number of fetuses with absent diastolic flow show mild acidosis at the time of delivery. These fetuses should be delivered before they reach a more advanced state of acidosis, manifested by reversed UA diastolic flow or by severe alterations of the FHR monitoring. Reversed UA diastolic flow reflects the latest state of the fetal response to hypoxia. Fetal death usually occurs within a few hours following this finding, which is an indication for immediate delivery. In the majority of cases the baby will be acidotic at birth.

The NST and the MBPP (NST plus ultrasound assessment of the amniotic fluid volume) are the most useful tests to periodically assess fetal well-being in patients with preeclampsia and increased UA S/D ratio. Since preeclampsia is a progressive condition, the test should be performed twice every week. Doppler evaluation of the UA and MCA waveforms is performed weekly.

Classification

Preeclampsia may be mild or severe and one of the first tasks in the initial evaluation of these patients is to determine the severity of the disease. The classification depends on the level of blood pressure elevation and the presence of symptoms or signs of end-organ damage.

Preeclampsia is mild if the systolic blood pressure is less than 160 mmHg and the diastolic blood pressure is less than 110 mmHg and the patient does not have any of the signs and symptoms associated with severe preeclampsia shown in Box 16-8.

Management

Once the diagnosis of preeclampsia is established, the patient must be admitted to the hospital. After careful initial evaluation most patients with preeclampsia need to remain in the hospital until delivery.

Mild preeclampsia

Initial evaluation

The first step in the management of women with mild preeclampsia is an assessment of gestational age.

Gestational age ≥ 37 weeks

If the pregnancy is 37 weeks or more, the patient should be delivered. There is no benefit in continuing the pregnancy when infant and mother have nearly a 100% chance of a good outcome if delivery is accomplished. However, if the pregnancy is at less than 37 weeks, the chances for a good perinatal outcome decrease in direct relation to the prematurity because of the rising incidence of respiratory distress syndrome (RDS) and other neonatal conditions associated with early gestational age.

BOX 16-8

Criteria for the diagnosis of severe preeclampsia

1. Systolic blood pressure of 160 mmHg or higher or diastolic 110 mmHg or higher on two occasions at least 6 hours apart while the patient is in bed rest
2. Proteinuria of 5 g or higher in a 24-hour urine specimen or 3+ or greater on two random urine samples collected at least 4 hours apart
3. Oliguria of less than 500 ml in 24 hours
4. Cerebral or visual disturbances
5. Pulmonary edema or cyanosis
6. Epigastric or right upper quadrant pain
7. Impaired liver function
8. Thrombocytopenia
9. Fetal growth restriction

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Gestational age between 32 and 36 weeks

Management of the patient with mild preeclampsia between 32 and 36 weeks depends on clinical and laboratory observations during the initial evaluation. This period of observation is best handled in an intensive care area such as labor and delivery. Ultrasound examination needs to be performed to determine EFW, amniotic fluid volume, and uterine, umbilical, and middle cerebral arteries Doppler. Maternal laboratory evaluation includes serum creatinine, BUN, uric acid, AST, ALT, LDH, platelet count, and a timed urine collection for proteinuria. The presence of persistently elevated blood pressure ≥ 150/100, thrombocytopenia (<200,000/mm^3), elevated liver enzymes, oligohydramnios, fetal growth restriction, abnormally elevated S/D ratio in UA Doppler, and proteinuria greater than 1 g/24-hour indicates that the potential for complications is high and the patient needs to remain in the hospital until delivery (Box 16-9). The presence of severe headaches, persistent visual symptoms, and severe epigastric or right upper quadrant pain is also indication for in-hospital management. Another indication for in-hospital care is if the patient is unreliable and possibly unable to comply with outpatient treatment.

If the initial evaluation is negative, the next decision is whether or not the patient should remain in the hospital or be treated on an outpatient basis. In-hospital management has the advantage of continuous clinical and laboratory observation, making possible the early detection and prompt treatment of complications. The disadvantages associated with a prolonged hospital stay are increased cost, disruption of family life, boredom, exogenous depression, and the monotony of hospital food. Unfortunately, there are no randomized clinical trials indicating that one is better than the other, and in the majority of cases the decision to keep a patient in the hospital

BOX 16-9

Women with mild preeclampsia before 37 weeks who require in-hospital management

- Gestational age 32 weeks or less
- Unreliable patients
- Proteinuria ≥ 1 g/24 hour
- Labile hypertension with occasional readings ≥ 150 mmHg systolic or ≥ 100 mmHg diastolic
- Platelet count < 200,000

or manage her as outpatient is a decision based in the "gut feelings" of the obstetrician. We prefer to keep all women with mild preeclampsia in the hospital because even if the probability of a poor outcome with outpatient management is small, the consequences for the mother and fetus may be severe.

Gestational age < 32 weeks

Preeclampsia before 32 weeks of gestation has a significant potential for severe complications and in-hospital care is mandatory.

General measures

The management of women of less than 37 weeks with mild preeclampsia should be the same irrespective of being outpatients or inpatients. The only difference is that inpatients will be observed on daily basis while outpatients will be seen on weekly basis. The general measures with these patients are as follows:

1. Measurement of blood pressure at least four times per day
2. Measurement of body weight every other day
3. Daily urinary dipstick evaluation for protein in the first urine voided every morning
4. Proteinuria in a 24-hour specimen every week
5. CBC with platelet count, LDH, AST, ALT twice per week
6. Questioning in each contact about fetal movements, development of scotomas or headaches, and presence of epigastric or right upper quadrant pain

Fetal monitoring consists of the following:

1. Fetal biometry every 3 weeks
2. Daily FHR monitoring for 1 hour
3. Daily fetal movement count
4. Umbilical and cerebral Doppler every week

During expectant management the patient should not receive medications other than vitamin and iron supplements. If the blood pressure of a preeclamptic patient during expectant management rises to a point at which treatment is necessary (≥160/110), the patient needs to be delivered.

There should be no dietary sodium restriction. Patients should eat regular food. Strict bed rest is unnecessary. In-hospital activity is significantly less than outpatient activity, and most patients will spend a majority of their time resting. To avoid deep vein thrombosis secondary to prolonged bed rest external pneumatic compression (EPC) cuffs or pressure hoses need to be used when the patient is in bed.

Most women admitted with mild preeclampsia at less than 36 weeks quickly improve with hospital bed rest and the diastolic blood pressure decreases to the mild range of 90–100 mmHg. Improvement is usually heralded by an increase in urinary output. Despite this apparent improvement, these patients need continuous monitoring for signs and symptoms of aggravation of the disease.

Diuretics

For many years the use of diuretics in women with preeclampsia has been discouraged on the basis that they could further affect an already depleted intravascular volume and worsen uteroplacental perfusion. This is true in women with severe preeclampsia, but the large majority of women with mild preeclampsia have expanded intravascular volume and the placental perfusion will not be affected by diuretics. The initial effect of diuretics is to decrease the blood pressure by decreasing the plasma volume but after some time they also decrease PVR and have a vasodilator effect in capacitance vessels. It is because of these properties that they are a good symptomatic treatment in women with mild preeclampsia. The problem is to determine if the intravascular volume is expanded before initiating the treatment and to assess the degree of volume contraction that occurs with the treatment. The hemoglobin/hematocrit (H/H) may be useful in this respect. Preeclamptic women with low H/H values are volume expanded unless they are anemic—a problem that can be ruled out to a large extent by observing the mean corpuscular volume and the mean corpuscular hemoglobin concentration. The most common type of anemia during pregnancy is caused by an iron deficiency and results in a decrease in these indices. Also, the finding of a serum creatinine < 0.8 mg/dl tends to corroborate the presence of hemodilution.

The diuretics most commonly used in the treatment of preeclampsia are the thiazides and furosemide. Furosemide can be given IV or orally, acts quickly, has a relatively short duration of action, and has minimal maternal or fetal side effects. Thiazide is an oral medication, with a long duration of action, and its use has been associated with neonatal thrombocytopenia. However, this association is far from proven because infants born to women with severe preeclampsia may have thrombocytopenia in the absence of thiazide treatment.

Antihypertensive treatment

Antihypertensive treatment is frequently used in women with mild preeclampsia in a plan of expectant management at home or at the hospital. The benefits or disadvantages of this intervention have not been elucidated by adequate clinical trials. For many there is a fear that antihypertensive treatment may mask the most important sign of the condition and result in inappropriate delays. Others believe that deterioration of the situation cannot be masked by antihypertensive agents and that

they help to keep blood pressure under control and avoid or delay the onset of severe hypertension. The antihypertensive of choice in this situation is labetalol. It may be given orally in doses of 100–400 mg every 8–12 hours.

Persistent elevation of the blood pressure to the severe range (>160/110) is the most common indication for delivery in women with mild preeclampsia. When this happens, antihypertensive medications should not be given in an attempt to further prolong the pregnancy. Antihypertensives need to be given when the blood pressure reaches the severe range simultaneously with magnesium sulfate to prevent seizures while preparing for delivery. Trying to deal with a deteriorating condition using antihypertensive drugs and avoiding delivery is an invitation for disaster. Proteinuria (>5 g in a 24-hour specimen) is an important sign of deteriorating renal function and is second only to hypertension as an index of worsening of the disease and as indication for delivery. Excessive weight gain, elevation of BUN, creatinine, or uric acid levels, and decreased creatinine clearance are not indications for delivery unless they occur simultaneously with an elevated blood pressure.

Delivery

Induction of labor and vaginal delivery should be attempted in women with mild preeclampsia, once delivery is indicated or the pregnancy reaches 36 weeks. However, the majority of these women are primigravidas with an unripe cervix due to their early gestational age and, as a consequence, the incidence of cesarean births is high. Spinal anesthesia is the procedure of choice in cases of cesarean delivery.

The benefit of intrapartum and postpartum administration of magnesium sulfate for the prevention of seizures in women with mild preeclampsia was clearly shown in the Magpie Trial (2002). In this study close to 10,000 women, the majority (74%) with mild preeclampsia, were randomized between magnesium sulfate and placebo. There was a significantly lower risk of eclampsia, lower maternal mortality, and lower risk of abruption in women receiving magnesium sulfate. The lower risk of eclampsia was apparent for both severe and mild preeclampsia. The incidence of eclampsia in women with mild preeclampsia in the placebo group was 1.5% (59/3710) and 0.6% (25/3758) in the magnesium sulfate group. The Magpie Trial clearly indicates that administration of magnesium sulfate to women with mild preeclampsia decreases the incidence of eclampsia 2.5 times. However, because of the low incidence of eclampsia, it is necessary to expose approximately 100 women to the toxic effects of magnesium sulfate to avoid one case of eclampsia. Another randomized clinical trial (Livingston et al., 2003) compared

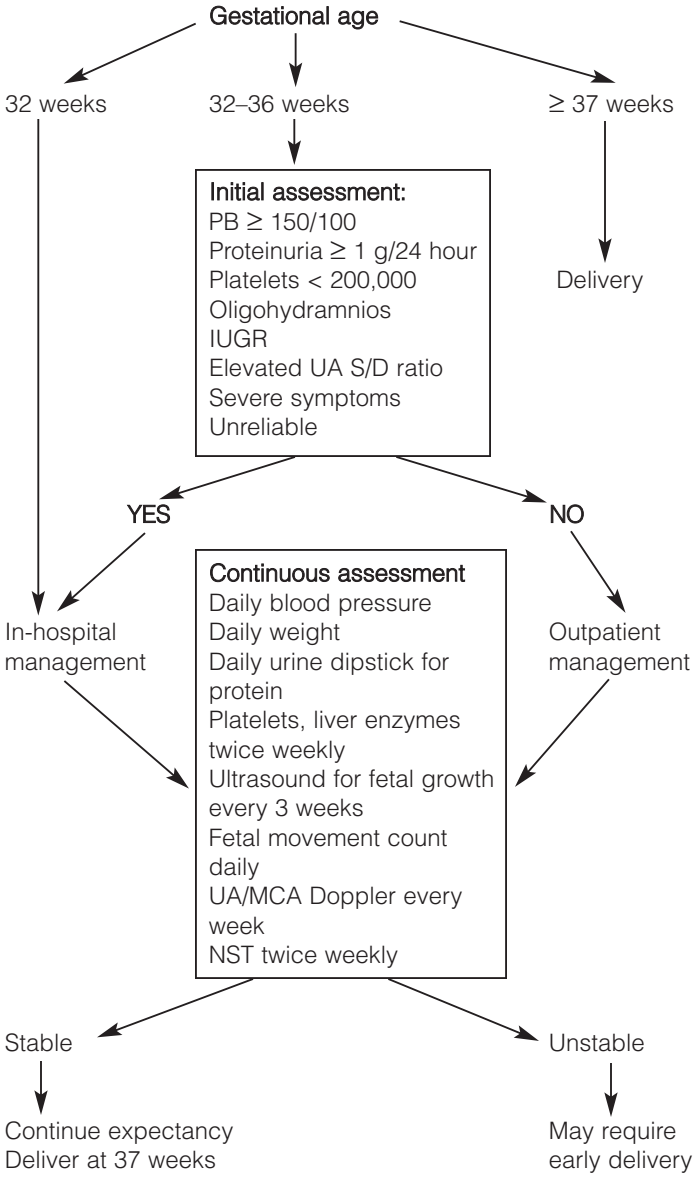

Figure 16-3. Management of mild preeclampsia.

magnesium against placebo in women with mild preeclampsia. No significant differences between the groups were found in the number of patients who developed eclampsia. However, the number of patients included in this trial (222) was too small to give validity to this finding.

In summary, the current trend is not to give magnesium sulfate to women with mild preeclampsia. However, a careful, systematic assessment of these patients at frequent intervals is necessary to identify those showing subtle signs of disease severity, making necessary to manage them as severe preeclamptic. A summary of the overall plan of management for patients with mild preeclampsia is shown in Figure 16-3.

Severe preeclampsia

If the patient has severe preeclampsia (Box 16-8), the management will depend on the gestational age at the time of diagnosis.

Gestational age ≥ 34 weeks

If the gestational age is ≥ 34 weeks the best approach is to treat with magnesium sulfate for the prevention of seizures, give antihypertensives to control the blood pressure, and deliver by cesarean section or by induction of labor if the cervix is ripe.

Prevention of seizures

Magnesium sulfate: Magnesium sulfate is the medication most commonly used in USA for the prevention and treatment of seizure activity in patients with preeclampsia and eclampsia. The mechanism of seizure control by magnesium sulfate is controversial. For some investigators, the effect of magnesium sulfate on the central nervous system does not account for its anticonvulsive effect. They argue that the cerebrospinal fluid Mg++ concentration is independent of and significantly higher (2.4 mEq/L) than the plasma concentration and increases very slowly despite therapeutic plasma levels. Accordingly, they believe that Mg++ is a peripheral anticonvulsant because of its ability to block neuromuscular transmission by decreasing the acetylcholine release in response to nerve action potentials. This hypothesis is reinforced by investigations showing abnormal electroencephalographic patterns in women with preeclampsia and eclampsia despite therapeutic magnesium levels (Sibai et al., 1984). Other investigators argue that the magnesium levels reached during treatment of eclamptic seizures are never high enough to cause peripheral muscular paralysis and, therefore, the anticonvulsant action of the medication should be explained through a central effect. Belfort and Moise (1992) studied the pulsatility index of the maternal MCA in preeclamptic women and found that magnesium has a vasodilator effect in the cerebral vessels, suggesting that the medication may prevent seizures by avoiding vasospasm and tissue ischemia.

There is robust evidence indicating the effectiveness of magnesium sulfate in the prevention of seizures in women with severe preeclampsia. In the study by Coetzee et al. (1998), involving 699 women with severe preeclampsia, the incidence of eclampsia was 3.2% in women in the placebo group and 0.3% for women in the magnesium sulfate group. In the Magpie Trial (2002) 26% of the 10,110 participants had severe preeclampsia. The incidence of eclampsia was 37/1345 (2.7%) in the placebo group versus 15/1297 (1.1%) in the magnesium sulfate group, a significant difference (RR 0.42 (0.23–0.76)). In another large study by Belfort et al. (2003) 1650 women with severe preeclampsia were randomized to receive nimodipine or magnesium sulfate. They found an incidence of eclampsia of 2.6 in women receiving nimodipine and 0.8% in women receiving magnesium.

BOX 16-10

Guidelines for intravenous magnesium sulfate administration

Loading dose

- Give 30 ml of 20% magnesium sulfate (6 g) in 100 ml of Normal saline over 15–20 minutes.

Maintenance dose

- Add 20 g of magnesium sulfate (four 10 ml amps of 50% solution) to 1000 ml of Normal saline solution and give intravenously piggyback at a rate of 100 ml/hour (2 g/hour).

Monitoring for magnesium toxicity

- Urine output should be at least 30 ml/hour.
- Deep tendon reflexes should be present.
- Respiration rate should be > 14 breaths/minute.
- Pulse oximetry should be ≥ 96%.
- Any change in these indices makes it necessary to reevaluate the rate of administration.

The most common way to administer magnesium sulfate is by continuous intravenous infusion (Box 16-10). A loading dose of 6 g of magnesium sulfate given over approximately 20 minutes causes an immediate elevation of the normal Mg++ level to 5–9 mg/dl. Intracellular transfer of the ion and elimination by the kidney will cause a drop in plasma concentration to 4–5 mg/dl 1 hour after injection. When the loading dose is followed with a continuous infusion of 2 g/hour, the maintenance levels of magnesium will be between 4 and 8 mg/dl (Sibai, 1990). At this elevated plasma level, about one-third of the Mg++ is protein bound, and its renal clearance is very similar to the glomerular filtration rate.

Magnesium sulfate is not an innocuous drug, and it is necessary to carefully monitor patients who are receiving the medication to prevent serious side effects. The medication may cause maternal death from overdose and its use is associated with decreased myometrial activity, slow cervical dilatation, increase blood loss at delivery, decreased vital capacity, and pulmonary edema. In order to prevent or timely detect these complications, it is necessary to carefully monitor the urinary output, patellar reflex, respiratory rate, and pulse oximetry. Since Mg++ is eliminated by the kidneys, monitoring of the urine output is extremely important. The urine output is frequently decreased in patients with severe preeclampsia. This may lead to an abnormally high serum Mg++ concentration, resulting in respiratory or cardiac arrest. A urine output of at least 30 ml/hour is necessary for the continuous administration of magnesium sulfate. Administration of diuretics to a preeclamptic patient with impaired renal function does not prevent Mg++ accumulation to toxic levels despite the increase in urine output. Disappearance

of the patellar reflex is important because it is the first sign of impending toxicity. The patellar reflex is usually lost when plasma Mg++ concentration reaches 8–10 mEq/L. In this case, the drug must be discontinued until the patellar reflex is present. Otherwise, the plasma level will continue to increase until a level is reached, usually more than 12 mEq/L, where respiratory depression and respiratory paralysis may ensue.

An excellent marker of magnesium toxicity is pulse oximetry. The oxygen saturation usually starts to drop before there is evidence of respiratory distress. The treatment of respiratory depression induced by hypermagnesemia is intravenous calcium gluconate, 10 ml of a 10% solution, given over 3 minutes. Ca++ antagonizes the effect of magnesium by increasing the amount of acetylcholine liberated by the action potentials at the neuromuscular junction. In many cases decreased oxygen saturation and respiratory distress in severe preeclamptic patients receiving magnesium sulfate are not signs of magnesium toxicity, but initial manifestations of pulmonary edema. In these cases the medication of choice is furosemide and the intravenous administration of 20–40 mg of furosemide is usually followed by profuse urination and improvement of the respiratory distress.

Magnesium sulfate may be harmful to the fetus. Maternal levels rapidly equilibrate with fetal plasma, and the concentration in both compartments is similar. Respiratory depression and hyporeflexia have been observed in newborns delivered to mothers undergoing intravenous magnesium sulfate therapy.

Magnesium sulfate decreases FHR variability. This is a frequent reason to misinterpret as normal FHR tracings indicating fetal compromise. In general, decreased or absent FHR variability in patients with preeclampsia who are receiving magnesium sulfate should not be attributed to the treatment unless other signs of fetal well-being such as accelerations with contractions or with scalp stimulation are present.

Magnesium sulfate acts synergistically with the muscle relaxants used for general anesthesia. Obstetrical anesthesiologists are aware of this fact and prescribe a smaller dosage of such medications when giving general anesthetics to patients on magnesium sulfate therapy.

Phenytoin: Phenytoin has been successfully used for the treatment and prophylaxis of eclamptic seizures. The medication is well tolerated and has few side effects. Phenytoin acts by inhibiting the spread of abnormal activity from the seizure foci to the motor cortex. The superiority of magnesium sulfate over phenytoin in the prevention of eclamptic seizures was demonstrated in a large randomized clinical trial involving more than 2000 subjects (Lucas et al., 1995). Twenty-three percent of the subjects in this population had severe preeclampsia. Ten of the women assigned to phenytoin had eclamptic seizures compared with none of the women assigned to magnesium sulfate.

For the treatment of eclampsia, the loading dosage of phenytoin is 10–15 mg/kg. The medication should be given slowly intravenously, never exceeding a rate of 50 mg/minute. This will avoid cardiovascular toxicity and central nervous system depression. The loading dose should be followed by maintenance doses of 100 mg IV every 6–8 hours.

For prophylaxis, phenytoin should be given in 100 mg doses IV or IM every 4 hours. Oral administration should continue for several days during the postpartum period.

Antihypertensive treatment

The objective of antihypertensive treatment is to prevent intracranial bleeding and left ventricular failure. Also, there is evidence suggesting that antihypertensive treatment may be useful for the prevention of eclamptic seizures. Antihypertensives would prevent seizures by lowering the perfusion pressure and preventing vasogenic edema or by inhibiting the cerebral arterial vasospasm that causes tissue ischemia and pericapillary bleeding. This topic will be discussed more extensively in the section about eclampsia.

Labetalol: Labetalol is the medication of choice for the treatment of acute severe hypertension in pregnancy and for maintenance treatment of hypertensive disorders during pregnancy. The reasons for being the first choice drug are its effectiveness, the low incidence of side effects, and the availability of oral and parenteral preparations. Labetalol is a combined alpha- and beta-adrenergic blocker. The ratio of alpha- to beta-blockade is approximately 1:3 for the oral form and 1:7 for the intravenous form. Labetalol is effective in the treatment of severe hypertension and can be given by continuous or intermittent intravenous infusion. For continuous IV use, 500 mg (100 ml) of labetalol are added to 400 ml of normal saline solution (1 mg/ml) and administered at an initial rate of 20 mg/hour (20 ml/hour). If the blood pressure does not fall into the expected range (diastolic 80–95 mmHg, systolic < 160 mmHg) in 20 minutes, the dose is doubled and continued to be doubled every 20 minutes until the expected range is obtained or a maximum dose of 220 mg/hour is given. The effective dose range is between 50 and 200 mg/hour. For intermittent dosing, 20 mg should be given over a 2-minute period. Additional doses of 40–80 mg may be given at 20-minute intervals. It is recommended not to exceed 220 mg/hour. The maximum effect of IV labetalol is usually reached 5 minutes after injection. For oral treatment labetalol needs to be given at shorter intervals than those recommended for nonpregnant subjects. The dose varies from patient to patient but usually is between 100–400 mg every 6–12 hours.

Hydralazine: Hydralazine is commonly used for the treatment of elevated blood pressure in obstetrics. Hydralazine acts directly on arteriolar smooth muscle to reduce PVR. The blood pressure response is almost immediate although it is less dramatic than that with diazoxide. Hydralazine is administered in intravenous boluses, starting at 5 mg and increasing by 5 mg every 20 minutes up to 20 mg. The most frequent side effects of hydralazine administration are decreased uteroplacental perfusion and hyperdynamic circulation. The first is indicated by late decelerations in patients who previously had a normal FHR tracing. Recovery from this abnormal pattern can be seen after the drug is discontinued, and the blood pressure rises. This complication occurs more often if there is a precipitous drop in the diastolic pressure, usually below 80 mmHg. For this reason, electronic fetal monitoring is mandatory when hydralazine is used. The amount and frequency of repeated hydralazine doses must be based on both the maternal and the fetal response. Hyperdynamic circulation after hydralazine administration is a result of its positive inotropic effect and is manifested by maternal tachycardia. A meta-analysis of randomized clinical trials using hydralazine for the treatment of severe hypertension in pregnancy concluded that the evidence does not support the use of this agent as first line drug when compared with labetalol and nifedipine (Magee et al., 2003).

Nifedipine: Nifedipine is a calcium channel blocker used for the treatment of chronic hypertension. The medication is an excellent peripheral vasodilator and a good tocolytic agent. Nifedipine lowers the blood pressure by inhibiting the intracellular influx of calcium into cardiac and vascular smooth muscles and by decreasing PVR. The medication is rapidly absorbed after oral administration and reaches peak levels 30 minutes after ingestion. The plasma half-life of nifedipine is approximately 2 hours. The initial dose of nifedipine is 10–30 mg orally. If there are no side effects, the medication may be given in 10–30-mg doses every 4–6 hours according to the blood pressure response. Doses above 120 mg/day are rarely necessary.

Nifedipine is usually well tolerated. The most frequent side effect is headaches that may confuse the clinical picture in women with preeclampsia. Sudden and severe drops of blood pressure are almost exclusively seen when the capsule is perforated and the medication is applied sublingually. The drug is not absorbed through the buccal mucosa but is rapidly absorbed from the gastrointestinal tract when the capsule is broken and when the medication is given in a liquid form.

Other antihypertensive agents: There are several antihypertensive agents that are not used frequently in the treatment of severe preeclampsia because of a variety of reasons. Methyldopa is used frequently in women with chronic hypertension and pregnancy but is not used in preeclampsia because of its delayed onset of action. Reserpine may cause nasal stuffiness in newborns, which is a rather serious problem because of their obligatory nasal breathing. Diazoxide may cause a rapid, dramatic hypotensive response and at least one maternal death has been reported in a preeclamptic patient who developed irreversible shock after diazoxide administration. Diazoxide may also cause fetal and maternal hyperglycemia, inhibition of uterine contractions, and sodium and water retention. Sodium nitroprusside is an excellent medication to gradually decrease elevated blood pressure. However, cyanide is a product of its metabolic degradation and there is a possibility of significant fetal toxicity with prolonged administration.

Gestational age 28–33 weeks

In this gestational age group delivery may be postponed for 24–48 hours to administer steroids to the mother for their protective effect against neonatal hyaline membrane disease and intracranial bleeding. All the measures described for the management of severely preeclamptic women of more than 34 weeks apply in this situation and the only difference is the administration of steroids, 12 mg of betamethasone IM every 24 hours for two doses. Delivery will be accomplished 12–24 hours after the second steroid dose.

Gestational age 24–28 weeks

Traditionally, severe preeclampsia has been an indication for delivery of the fetus irrespective of the gestational age. In severe preeclampsia, the maternal risks associated with prolongation of pregnancy are so frequent and severe that they overrule fetal considerations. However, the fetal consequences of early delivery are also severe, and some investigators have looked at the possibility of prolongation of pregnancy to achieve better perinatal outcomes.

Expectant management

Expectant management may have a role in selected patients with severe preeclampsia between 24 and 34 weeks. However, it is important to remember that expectant management of severe preeclampsia has no maternal advantages and exposes the mother to significant risks. The largest published series on this subject is by Haddad et al. (2004). These investigators expectantly managed 239 severely preeclamptic women between 24 and 33 weeks. They found a median pregnancy prolongation of 5 days (range 2–35). The perinatal mortality was 5.4% and, worrisome, the incidence of maternal HELLP syndrome was 14.2%. These data beg the question of the advantages of accepting all the maternal risks associated with expectancy for a median prolongation of pregnancy of 5 days.

Strict patients' selection criteria and adequate patient and neonatal care facilities are essential to avoid a major

BOX 16-11

Guidelines for the expectant management of severe preeclampsia less than 34 weeks

- Bed rest (EPC cuffs)
- Daily weight
- Daily input and output
- Antihypertensive treatment (Aldomet, labetalol, nifedipine)
- Betamethasone (two 12 mg doses 24 hours apart)
- Laboratory every other day or more frequently if needed: AST, ALT, LDH, platelet count, H/H, creatinine, bilirubin, 12-hour urinary protein
- Daily NST
- Daily fetal movement count
- Umbilical and middle cerebral Doppler twice every week
- Amniotic fluid volume twice every week
- Ultrasound for fetal growth every 2 weeks

BOX 16-12

Criteria to interrupt expectant management and deliver women with severe preeclampsia

- Blood pressure persistently 160/100 or greater despite treatment
- Urine output < 400 ml in 24 hours
- Platelet count < 50,000/mm^3
- Progressive increase in serum creatinine
- Progressive increase in AST and ALT
- LDH > 600 U/L
- Minimal or no fetal growth by ultrasound estimation
- Absent or reversed umbilical artery Doppler
- Oligohydramnios (AFI < 5 cm)
- Repetitive variable or late decelerations with poor variability
- Severe headache, epigastric or upper right quadrant pain
- Persistent visual symptoms

disaster when women with severe preeclampsia are managed expectantly. Prior to initiation of expectant management these patients should remain in labor and delivery and be carefully evaluated for a minimum of 24 hours. Women not requiring immediate delivery may be transferred to a high-risk antepartum area for intensive fetal and maternal monitoring. The main aspects of expectant management are shown in Box 16-11.

An important point is the use and interpretation of fetal well-being tests in these patients. Acceleration of the heart rate with movement or in response to vibroacoustic stimulation, which is the main criterion to determine "reactivity" in the NST, is usually not present in the second trimester fetus. Therefore, the elements to assess fetal health in the FHR tracing will be the presence of variability and the absence of decelerations. With respect to the BPP, only fetal movement, fetal tone, and amount of fluid can be assessed regularly because the NST is usually nonreactive and respiratory movements may not be present in the second trimester fetus.

Patients with severe preeclampsia managed expectantly need meticulous attention and the desirability of expectancy versus the need to deliver should be determined daily. The criteria to interrupt expectant management and move to delivery are shown in Box 16-12. The obstetrician should always remember that immediate delivery is the only measure that interrupts the progression of this disease. In a study (Hibbard, 1983) reluctance in interrupting the pregnancy, usually because of prematurity, was one of the most common errors resulting in maternal mortality. This study also found the following other common errors in the management of preeclampsia:

1. Underestimation of the severity of the disease
2. Masking of symptoms with medications
3. Failure to aggressively use antihypertensive drugs to combat extreme elevations of blood pressure

There is literature suggesting that administration of plasma volume expanders such as dextran or albumin may be valuable in preeclampsia. This treatment attempts to correct the deficit in intravascular volume, which is an important part of the multiorgan perfusion defect exhibited by these patients. This therapy should be avoided because there is no evidence of effectiveness and because patients with severe preeclampsia or eclampsia may have large capillary leaks allowing large molecular weight molecules to pass into the pulmonary interstitial space, increasing the possibility of pulmonary edema.

Gestational age < 24 weeks

Sibai et al. (1985) reported on 60 patients with severe preeclampsia between 18 and 27 weeks managed conservatively. They found serious maternal complications including eclampsia in 16.7%, HELLP syndrome in 16.7%, acute tubular necrosis (ATN) in 5.0%, and individual cases of hypertensive encephalopathy, intracerebral hemorrhage, and liver hematoma. The overall perinatal mortality was 87%. They found that when severe preeclampsia had its onset before 25 weeks, 23/31 or 74% of the pregnancies ended in fetal death, in contrast with an incidence of 28% when the onset of the disease was after 25 weeks. Odendaal et al. (1987) confirmed these observations and reported a perinatal mortality with expectant management of 100 and 75% for preeclamptic women delivering infants with birth weights less than 750 and less than 1000 g, respectively. The accumulated evidence indicates that conservative management for severe preeclampsia developing before 25 weeks is not adequate. Maternal morbidity is severe and perinatal survival is less than 10%. Therefore, these patients should be delivered to reduce maternal risk and avoid severe maternal morbidity and prolonged hospitalization.

Delivery

In most cases of severe preeclampsia before 34 weeks, induction of labor is unsuccessful and approximately 80% of these women will end up having a cesarean delivery (Blackwell et al., 2001). If the fetus is growth restricted the incidence of abnormal FHR monitoring patterns during labor is high. The high probability of operative delivery must be discussed with the mother, and many of them will opt for cesarean to avoid prolonged and usually unsuccessful inductions.

Hemorrhage is poorly tolerated in the severe preeclamptic patient due to the constricted intravascular volume. A blood loss of 1000 ml during a cesarean section corresponds to approximately 35–40% of the blood volume of a pregnant woman with severe preeclampsia.

Regional anesthesia is the anesthesia of choice in patients with severe preeclampsia, and in the hands of a competent obstetric anesthesiologist spinal and epidural anesthesia are safe for the preeclamptic patient. The main contraindication to regional anesthesia in these patients is thrombocytopenia. In some cases the sympathetic blockade associated with regional anesthesia causes venous dilatation, significant blood pooling, and a reduced preload. These hemodynamic effects may be avoided by administration of intravenous fluids, elevating the lower extremities, and assumption of the lateral decubitus position to improve venous return.

BOX 16-13

Useful guidelines for the management of patients with severe preeclampsia

- *Do not attempt to normalize blood pressure.*
  Rapidly lowering the blood pressure is associated with significant maternal and fetal/neonatal morbidity. These patients have a rightward shift of the renal, cerebral, coronary, and placental pressure/flow autoregulation, and a rapid decrease in blood pressure will cause a marked decrease in blood flow to these organs.
- *Do not give diuretics before delivery.*
  The majority of these patients are vasoconstricted and intravascular volume depleted, and diuretics will aggravate organ perfusion.
- *Give diuretics after delivery.*
  Administration of crystalloids during delivery, autotransfusion with blood from the uterus, postpartum mobilization of interstitial fluid to the intravascular space, and renal dysfunction are factors that predispose to postpartum pulmonary edema which may be avoided, stimulating diuresis.
- *Do not give diazepam to stop an eclamptic seizure.*
  Seizures are self-limited and rarely last more than 1–2 minutes. Rapid administration of diazepam may produce apnea and facilitate aspiration. The management of the seizure consists in giving oxygen, avoiding trauma to the tongue and other organs, and waiting for spontaneous resolution.
- *Do not push the padded tongue blade to the back of the throat.*
  The padded tongue blade is to avoid that the patient bites her tongue during the seizure. If it is pushed to the back of the throat, it will stimulate the gag reflex and vomit with increased danger of aspiration.

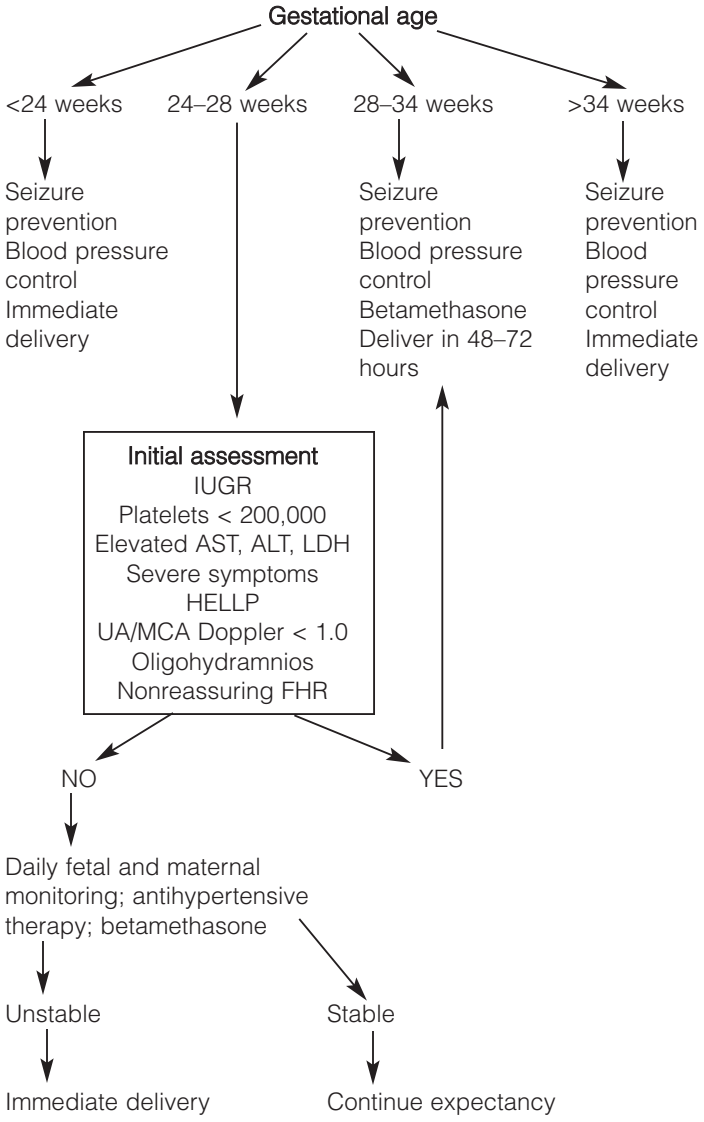

Figure 16-4. Management of severe preeclampsia.

The management of severe preeclampsia based on seizure prophylaxis, antihypertensive treatment, and timed delivery involves adherence to some basic rules shown in Box 16-13. An overall management plan for severe preeclampsia is summarized in Figure 16-4.

ECLAMPSIA

Eclampsia is an extremely severe form of preeclampsia characterized by the sudden onset of generalized tonic-clonic seizures. This condition affects between 1 in 2000 and 1 in 4000 deliveries in the Western world but the

incidence may be several times higher in underdeveloped countries. Eclampsia occurs antepartum in 35–45%, intrapartum in 15–20%, and postpartum in 35–45% of the cases.

Pathophysiology

The pathophysiology of eclampsia is controversial. Autopsy studies have shown edema, cortical and white matter microinfarcts, pericapillary and parenchymal bleeding, and vascular lesions predominantly in the occipital and watershed areas. The dominant finding in MRI is subcortical white matter edema involving the posterior portions of the cerebral hemispheres bilaterally. Additional findings are areas of petechial hemorrhage and ischemia particularly in the occipital and parietal-occipital regions. One likely explanation for the posterior predominance of the brain lesions is that the anterior circulation of the brain is much better supplied with sympathetic innervation and therefore better protected against the effects of elevated blood pressure than the posterior part of the brain. The MRI findings in eclampsia are similar to those found in nonpregnant patients with hypertensive encephalopathy (Schwarts et al., 2000). In these cases vasogenic edema is the result of forced leakage of serum through the capillary walls due to increased perfusion pressure that is mainly a result of the systemic arterial blood pressure. However, there are clinical observations that are inconsistent with a model of increased perfusion pressure to explain eclamptic seizures. One of them is that seizures frequently occur in women who have mild hypertension or no hypertension at the time of the seizure. Another argument against this theory is that systolic and diastolic blood pressures were not different among preeclamptic women with and without brain edema in the MRI study of Schwartz et al. (2000).

An explanation for the onset of seizures in women with normal brain perfusion pressure is that in these cases seizures are the result of an abnormal autoregulatory response consisting of severe arterial vasospasm with rupture of the vascular endothelium and pericapillary hemorrhages with development of foci of abnormal electrical discharges that generalize and cause convulsions. If this is the case, the mechanism of seizures is different in preeclamptic women who have severe hypertension than in those with mild hypertension. In the severely hypertensive women the normal autoregulatory response to increased blood pressure is vasoconstriction, but once the upper limit of autoregulation is exceeded, vasodilation occurs with hyperperfusion, causing endothelial capillary damage and interstitial vasogenic edema. The level of cerebral perfusion pressure required to cause barotrauma and seizures varies between individuals. In preeclamptic women with mild hypertension or with normal blood pressure the mechanism of seizures will be abnormal autoregulation with exaggerated vasoconstriction and ischemic changes. The practical implication of these ideas is that an agent that decreases perfusion pressure will be the ideal seizure prophylactic agent for women with severe preeclampsia and a vasodilator the best for women with mild preeclampsia.

Investigations using intracranial Doppler have demonstrated that the majority of preeclamptic women, both mild and severe, when compared with normotensive pregnant women have elevated perfusion pressure and lower vascular resistance in the cerebral circulation (Riskin-Mashiah and Belfort, 2005). Similar results have been obtained using phase-contrast MRI (Morris et al., 1997).

Intracranial Doppler has also been used to assess the effect of medications used to prevent eclamptic seizures on cerebral perfusion pressure. Belfort et al. (1999) demonstrated that magnesium sulfate and nimodipine cause brain vasodilation but nimodipine increases while magnesium sulfate decreases cerebral perfusion pressure. According to these observations nimodipine will be an ideal agent for patients with ischemia secondary to severe vasoconstriction. Labetalol, on the other hand, decreases cerebral perfusion pressure and may be an effective agent in the prevention of seizures in women with excessive perfusion pressure. These observations increase the need for randomized clinical trials of medications for the prevention of seizures in preeclamptic women, classified according to their intracranial perfusion pressure.

Maternal and Perinatal Outcome

Eclampsia is associated with elevated maternal and fetal morbidity and mortality. Preeclampsia and eclampsia are the cause of approximately 20% of all maternal deaths in USA and approximately one-half of them are associated with eclampsia (MacKay et al., 2001). The most common causes of maternal death are intracranial bleeding and acute renal failure secondary to abruptio placentae. The greatest risk of death is when eclampsia develops before 28 weeks of gestation. Perinatal mortality occurs in 5–12% of the cases. The most common causes of fetal death are prematurity and fetal asphyxia and acidosis. Perinatal morbidity is substantial and correlates strongly with preterm birth, abruptio placentae, and fetal growth restriction. Eclampsia is a major obstetric emergency that requires mobilization of efforts and adequate management to avoid catastrophic events.

Diagnosis

The diagnosis of eclampsia is usually clear when women present with seizures, hypertension and proteinuria. Unfortunately, in approximately 15% of the cases hypertension and proteinuria are not present. However, when seizures develop in a pregnant woman without a his-

tory of seizure disorder, eclampsia should be the diagnosis until proven otherwise. The presence of hemoconcentration, elevated liver enzymes, elevated LDH, and thrombocytopenia help to establish the correct diagnosis when high blood pressure and proteinuria are not present. Twenty-six percent of eclamptic patients have platelet counts below 150,000 and the LDH is elevated in 74% of these patients. Also, in the majority of cases, the onset of convulsions is preceded by persistent headaches, throbbing in nature, occipital or frontal, and by visual symptoms.

Management

Seizure treatment

The first step in the management of women with eclampsia is the treatment of the seizure (Box 16-14). To decrease the risk of aspiration the patient should be placed in the lateral decubitus position. The bedside rails should be elevated to avoid maternal injury. Protection from severe tongue bite should be established by inserting a padded tongue blade between the patient's teeth. Supplemental oxygen by mask should be started at 8–10 L/minute. The seizure usually lasts only 1–2 minutes and oxygenation is not seriously compromised. However, if the patient has an IV line, a 6 g loading dose of magnesium sulfate should be given over 20 minutes, to be followed by a maintenance dose of 2 g/hour. If another seizure occurs when the patient is on maintenance dose of magnesium sulfate, an additional 2-g bolus of magnesium sulfate should be given over 5 minutes. If another seizure occurs, give phenobarbital 300 mg IV over 5 minutes.

In the majority of cases it is unnecessary to monitor magnesium plasma levels. However, this is indicated when the patient requires additional loading doses of the medication, the urinary output is less than 50 ml/hour, the serum creatinine is 1 mg/dl or greater, or there are signs of magnesium toxicity such as slurred speech or somnolence. The therapeutic level of magnesium is 4–8 mg/dl. When magnesium toxicity is suspected an effective antidote is 10% calcium gluconate, 10 ml given IV over 5 minutes. Treatment with magnesium sulfate should continue for at least 24 hours after delivery in order to avoid postpartum eclampsia. The superiority of magnesium sulfate as an anticonvulsant in preeclampsia when compared with diazepam and phenytoin was determined in a randomized clinical trial (Collaborative Eclampsia Trial, 1995).

A useful medication in the management of the eclamptic patient is nimodipine, a calcium channel blocker with selective vasodilation effects in the brain vasculature. Nimodipine is particularly of benefit when the mechanism of seizure is severe cerebral vasoconstriction—a phenomenon that seems to occur predominantly in eclamptic women with normal or mildly elevated systemic blood pressure. Nimodipine is given in doses of 60 mg orally every 4–6 hours. The medication has a remarkable effect on the neurologic symptoms, and women who are barely conscious become widely awake and capable of lucidly interacting with the care providers.

BOX 16-14

Treatment of eclamptic seizures

- Do not try to stop seizure
- Place patient in lateral decubitus
- Insert padded tongue blade, avoiding gag reflex
- Suction oral secretions
- Give oxygen by mask at 8–10 L/minute
- Elevate bedside rails and pad them to avoid injury
- Use physical restrains if necessary
- Pulse oximetry
- Once the seizure ends, start IV fluids (LR at 125 ml/hour)
- Give loading dose (6 g) of magnesium sulfate over 15–20 minutes followed by a maintenance dose of 2 g/hour as a continuous IV infusion
- If blood pressure is ≥ 150/100, give IV boluses of labetalol, 20 mg initially, then 40 mg, and then 80 mg at 15-minute intervals until blood pressure is in the desired range
- If blood pressure is normal or only mildly elevated, give nimodipine, 60 mg po every 4 hours

Treatment of hypertension

Treatment of elevated blood pressure is of the largest importance in eclamptic patients. As mentioned before, the antihypertensive treatment is not only useful to lower the blood pressure but may also have an important role in the treatment and prevention of seizures. The first line antihypertensive drug is labetalol. When the hypertension is severe (≥160/110) the initial dose should be an IV bolus of 20 mg. If the blood pressure does not decrease to the expected range (80–110 diastolic) in 10 minutes, a second IV bolus of 40 mg is given. Rarely a third IV bolus of 80 mg is necessary 10 minutes after the second dose until a total of 300 mg labetalol has been injected. Once the blood pressure is in adequate range, oral labetalol 200–400 mg every 12 hours is started. For continuous IV administration, one 40-ml vial containing 200 mg labetalol is added to 160 ml of lactated Ringers solution. The resultant solution will contain 1 mg/ml. The initial dose is 20 mg/hour. This dose can be doubled every 20 minutes up to a maximum of 200 mg/hour. The therapeutic range is usually between 50 and 200 mg/hour. Once the blood pressure reaches the desired level, the IV solution is discontinued and the patient started in oral labetalol, 100–400 mg every 6–12 hours.

It is uncommon to not be able to control the blood pressure of eclamptic patients with IV labetalol. In these cases hydralazine should be given in 5–10 mg IV boluses that may be repeated every 20 minutes. In the exceptional situation when the blood pressure remains elevated after IV

labetalol and three or four boluses of hydralazine, our personal choice is to puncture a 10-mg capsule of nifedipine and squeeze the content of the capsule under the patient's tongue. This can be repeated every 10–20 minutes for up to three doses. This usually causes a significant drop in blood pressure and the medication may be continued at doses of 20–30 mg orally every 4–6 hours.

Diuretics

Diuretics are not to be given before delivery to eclamptic women with the exception of those with concomitant pulmonary edema. However, they should be an integral part of the postpartum care. Furosemide, 20–40 mg IV every 6–12 hours should be initiated shortly after vaginal or cesarean delivery and continued orally for several days after the patient is able to tolerate oral intake. Women with severe preeclampsia and eclampsia usually have an acute expansion of intravascular volume during delivery due to the substantial amount of IV fluids that they receive. The autotransfusion that follows the contraction of the uterus during delivery adds additional volume to the intravascular space. Finally, following delivery large amounts of fluid accumulated in the interstitial space start to mobilize toward the intravascular space. This is a perfect set-up for congestive heart failure and pulmonary edema, particularly in women with renal function impairment. There is one randomized clinical trial indicating that aggressive postpartum stimulation of diuresis with furosemide enhances and speeds the recovery of preeclamptic women (Ascarelli et al., 2005).

Fetal response to maternal seizures

During a seizure there are no maternal respirations for 1 or 2 minutes, there is a transient build up of lactic acid, and a prolonged strong uterine contraction is present. These factors combine to cause fetal bradycardia, loss of FHR variability, and late decelerations. Fortunately, in the majority of cases this situation is transient and the FHR returns to a normal or to a compensatory tachycardia pattern shortly after the seizure is over. Occasionally the tetanic uterine contraction is severe enough to cause an abruption and the abnormal FHR pattern continues until the fetus dies. In general, if there is no evidence of improvement and the ominous FHR pattern continues for more than 5 minutes after the end of the seizure and despite the administration of oxygen to the mother, abruption should be suspected and emergency cesarean performed. In these cases the maternal and the fetal prognosis is poor.

Delivery

In current obstetrical practice the large majority of eclamptic women are delivered by cesarean section. Many of those cesareans are indicated because of the presence of associated abnormalities such as unripe cervix, gestational age < 30 weeks, fetal growth restriction, inadequate blood pressure control, and poor progress in labor. In other cases the indication is not clear and the cesarean is performed to avoid the maternal and fetal effects of pregnancy continuation. The most common exceptions to cesarean delivery are women with a fetal demise and the rare ones are those with a very ripe cervix.

The anesthesia of choice for eclamptic patients is regional, spinal, or epidural. The only contraindication to regional block anesthesia is a platelet count < 50,000/mm^3. When general anesthesia is necessary, administration of labetalol before endotracheal intubation is important to avoid the significant elevation of blood pressure which may result from this procedure.

Postpartum care

Magnesium sulfate should be continued for a minimum of 24 hours following delivery. As mentioned previously, administration of furosemide and aggressive diuresis should be initiated immediately following delivery and maintained for several days after the patient is discharged from the hospital. Oral administration of antihypertensive agents (labetalol, calcium channel blockers) should continue in the postpartum period until complete normalization of the blood pressure is demonstrated.

Prevention

Sibai et al. (1986) demonstrated that in 31.3% of cases eclampsia is not preventable despite adequate prenatal care and admission to the hospital. However, 69.7% of the cases are preventable. The most common problems affecting the efficacy of preventative measures are physician errors in 36.3% and inadequate administration of magnesium sulfate in 12.8% of the cases.

Long-Term Prognosis

The seizures characteristic of eclampsia are acute and transient and long-term neurologic deficits are rare in patients adequately treated. However, approximately 35% of patients who develop eclampsia will have preeclampsia in a subsequent pregnancy.

HELLP SYNDROME

The development of thrombocytopenia (<100,000/mm^3) in a patient with preeclampsia demands an examination of the blood smear for evidence of red cell fragmentation and determination of serum haptoglobin and liver enzymes. If fragmented erythrocytes are seen in the smear, the haptoglobin is absent or markedly decreased, and the

liver enzymes are elevated, the patient has preeclampsia with hematologic complications. Hemolysis in these cases results from cell passage through small vessels partially obliterated with fibrin deposits (microangiopathic hemolytic anemia). This complication of preeclampsia is recognized by the acronym HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome.

Diagnosis

The criteria for the diagnosis of HELLP syndrome are shown in Box 16-15. In most cases the diagnosis of HELLP syndrome is straightforward. Patients usually present with nausea and vomiting and epigastric pain. Seventy-five per-cent have severe hypertension and 85% have significant proteinuria. Rarely there are differential diagnostic difficulties with fatty liver of pregnancy, disseminated herpes, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura. The obstetrician should always keep in mind that HELLP is relatively frequent, while the other possible diagnoses are rare and patients with hemolysis, thrombocytopenia, and elevated liver enzymes have HELLP unless proven otherwise.

The hallmark for the diagnosis of HELLP is the presence of hemolysis. This requires a blood smear, positive for burr cells, schistocytes, and polychromasia or a bilirubin concentration of 1.2 mg/dl or more. Another indicator of hemolysis is markedly decreased or absent plasma haptoglobin. The elevated liver enzymes include AST and ALT ≥ 72 U/L and LDH ≥ 600 U/L. Total LDH concentration is the result of the combined activity of several isozymes of hepatic and red cell origin and represents both altered liver function and hemolysis. Finally, the platelet count should be ≤ 100,000/mm^3.

Approximately 70% of the cases of HELLP occur in the antepartum period with the rest occurring postpartum. The majority of cases (70%) occur between 28 and 36 weeks of gestation, 20% occur after 37 weeks, and 10% before 26 weeks. The large majority (80%) of the postpartum cases occur within 48 hours of delivery.

BOX 16-15

Criteria for the diagnosis of HELLP syndrome

Hemolysis
- Burr cells, schistocytes in the blood smear
- Bilirubin ≥1.2 mg/dl
- Absent plasma haptoglobin

Elevated liver enzymes
- AST ≥ 72 IU/L
- LDH > 600 IU/L

Low platelet count
- Platelets < 100,000/mm^3

Maternal and Perinatal Outcomes

HELLP is associated with 1% risk of maternal death. Most of these deaths are the consequence of abruptio placentae with disseminated intravascular coagulation, acute renal failure, and pulmonary edema. Maternal morbidity is frequent and severe (Box 16-16). Perinatal mortality and morbidity are also significantly increased in women with HELLP syndrome. The perinatal mortality changes with the gestational age and may vary between 7 and 20%. The rate of preterm birth is as high as 70% and as many as 15% occur before 28 weeks. With this high incidence of prematurity the frequency of RDS, intracranial bleeding, necrotizing enterocolitis, and bronchopulmonary dysplasia is equally high.

Hepatic rupture is a severe complication of women with HELLP syndrome. It may occur antepartum or postpartum, and in both cases the signs and symptoms are those of profound circulatory collapse. The signs of peritoneal irritation and the progressive hypovolemia will point to intraabdominal bleeding as the cause of the problem. If the patient has not delivered, the pregnancy must be terminated immediately. At the time of the laparotomy, the laceration is almost always found on the diaphragmatic aspect of the right lobe of the liver. It frequently coexists with subcapsular petechiae and subcapsular hematomas. The prognosis for preeclamptic patients with liver rupture is ominous. Attempts at surgical repair or excision are usually followed by extension of the laceration, more bleeding, consumption coagulopathy, and ultimately death. In these cases, the least manipulation of the hepatic tissue will be rewarded with the best results. The bleeding hepatic surface should be covered with Avitene, Oxycel, or Gelfoam and then packed with surgical sponges placed above the hemostatic agent. One of the sponges is brought outside the abdominal incision to facilitate removal on the 2nd or 3rd postoperative day.

Management

The diagnosis of HELLP syndrome is an indication for immediate delivery if the pregnancy is ≥ 34 weeks or at any gestational age if pulmonary edema, renal failure, placental abruption, severe liver dysfunction or bleeding, nonreassuring fetal status, or uncontrollable hypertension

BOX 16-16

Maternal morbidity associated with HELLP syndrome

Abruptio placentae	10–15%
Disseminated intravascular coagulation	10–15%
Pulmonary edema	6–8%
Acute renal failure	5–8%
Adult RDS	1–2%
Death	1%

is present. All other cases require administration of magnesium sulfate, steroids for the prevention of IVH (intraventricular bleeding) and RDS, and delivery within 24 hours after the second steroid dose. Delivery should not be delayed further even if there is some apparent improvement in the patient situation during the time required for steroid administration.

The clinical course of HELLP is one of progressive deterioration of the maternal and fetal conditions, and the selection of cases to delay delivery and administer steroids should be rigorous. In this situation is better to err by delivering patients without the benefit of steroids than to risk serious maternal and fetal complications associated with prolongation of pregnancy. Women selected for steroid treatment should receive betamethasone 12 mg IM, two doses 24 hours apart or dexamethasone 6 mg IV, four doses every 6 hours. Delivery should be accomplished within 24 hours following the last dose of steroids. There is no evidence that giving betamethasone every 12 hours instead of every 24 hours or giving dexamethasone in two 12-mg doses every 12 hours improves the outcome of these patients.

There are multiple indications for cesarean delivery in women with HELLP syndrome. Vaginal delivery is a consideration if the cervix is ripe, the gestational age is ≥ 32 weeks, the FHR is reactive, and there are no indications for cesarean delivery. Labor should proceed rapidly and cervical changes should be seen shortly after initiation of induction. If vaginal delivery is not foreseen within 12 hours after the onset of induction, it is better to perform cesarean section.

Platelets (1 unit single donor or 10 units pooled donors) are given when the platelet count is below 50,000/mm^3 and particularly if the patient shows signs of altered hemostasis. If a platelet transfusion is necessary, each unit of pooled platelets will raise the count by about 10,000/mm^3. The survival time of the transfused platelets in a presumably nonimmunized recipient will depend on the severity of the disease. After delivery the platelet count will reach a nadir in 24–48 hours but will rapidly increase after the 3rd postpartum day. Platelet counts greater than 600,000/mm^3 are not uncommon by the 7th or 8th day. An upward trend in platelet count and a downward trend in LDH should be apparent by the 4th postpartum day in patients recovering without complications. For those patients who follow a relentless course of deterioration despite conventional therapy, plasmapheresis may be a lifesaving measure. Plasmapheresis has a dramatic effect on the course of the disease and accelerates the recovery period. The main risk of plasmapheresis is the potential for viral hepatitis.

The large majority of women with HELLP do not require central venous pressure lines or Swan-Ganz catheters to monitor their hemodynamics. Careful monitoring of their input/output, pulse oximetry, and periodic auscultation of their lungs is all that is necessary to assess their pulmonary and renal situation.

The use of dexamethasone to improve the clinical course and accelerate the recovery of women with HELLP has been recommended on the basis of uncontrolled observations and clinical trials without adequate power. A recent double-blind, placebo-controlled clinical trial with adequate number of subjects (Fonseca et al., 2006) demonstrated that dexamethasone treatment does not improve the outcome in women with HELLP. In the same study an unplanned subgroup analysis suggested a beneficial effect in platelet count recovery in women with severe HELLP (platelet count < 50,000/mm^3), opening the opportunity for further research in this area.

SEVERE COMPLICATIONS OF PREECLAMPSIA

Pulmonary Edema

Pulmonary edema is a rather common complication of severe preeclampsia and eclampsia, affecting approximately 3% of these patients. Most cases are the result of aggressive use of crystalloid solutions for intravascular volume expansion. Pulmonary edema usually occurs in the postpartum period and is characterized by profound respiratory distress, severe hypoxemia, and diffuse rales on auscultation.

There are clinical differences between the pulmonary edema of organic heart disease and that of preeclampsia. In the majority of preeclamptic patients pulmonary edema results from fluid overload and left ventricular failure. Most cases occur in young women without a previous history of heart disease, with normal electrocardiogram, and without cardiomegaly on chest x-ray or echocardiogram.

Respiratory distress, a drop in oxygen saturation, and bilateral rales on auscultation of the lungs are typical findings in preeclamptic women with pulmonary edema. This usually is associated with the administration of large amounts of intravenous crystalloids and with oliguria. The response to aggressive administration of furosemide is usually dramatic with profuse diuresis and improvement of the respiratory symptoms.

The use of central hemodynamic monitoring (central venous pressure or Swan-Ganz catheters) is unnecessary in the majority of cases and should be limited to the rare patients who do not respond to IV furosemide. Treatment consists of administering oxygen by nasal prongs or a rebreathing mask, restriction of intravenous and oral fluids, and furosemide 20–40 mg IV every 6 hours.

Acute Renal Failure

Oliguria is not uncommon in patients with severe preeclampsia. Oliguria in women with severe preeclampsia

most of the time is prerenal in origin and may be the result of different mechanisms. The majority of women with severe preeclampsia who develop oliguria are volume depleted and they usually respond to an increase in the rate of intravenous fluid administration. Occasionally some patients do not respond to the fluid challenge and it is necessary to make a rapid assessment of the pathophysiology of the process. Severely hypertensive women with increased H/H reflecting hemoconcentration need aggressive treatment with vasodilators to effect afterload reduction and decrease renal artery vasospasm. Normotensive or mildly hypertensive women with low H/H values have expanded intravascular volume and need aggressive diuresis.

In some patients, usually older and obese, there is a large increase in plasma volume with normal or decreased CO. These women are at significant risk of pulmonary edema and require fluid restriction and aggressive preload reduction with diuretics. In other patients there is a contracted intravascular volume due to low plasma oncotic pressure and endothelial cell damage with leaking of serum into the interstitial space. These women usually respond to interruption of pregnancy and expansion of intravascular volume.

In some other cases the oliguria is the result of severe renal vasoconstriction. These cases respond well to interruption of the pregnancy and administration of fenoldopam. This medication is a dopamine agonist that increases renal blood flow and sodium excretion. Fenoldopam is 10 times more potent than dopamine as a renal vasodilator. The onset of action is within 5 minutes and the duration of action is short between 30 and 60 minutes. Two 1 ml amps containing 10 mg/ml are dissolved in 500 ml of normal saline to obtain a solution containing 40 µg/ml. The recommended initial dose is 0.1 µg/kg/minute (9 ml/hour for a 60-kg woman) and it may be increased by 0.1 µg/kg/minute every 15 minutes to a maximum dose of 1.6 µg/kg/minute. The medication is used until the urine output shows steady improvement. Its use is limited to hypertensive crisis with oliguria and usually is not extended more than 48 hours.

In rare cases oliguria is renal in origin. Most of these are cases of ATN that occur in the setting of preeclampsia complicated with severe abruption and disseminated intravascular coagulation. Most of these patients require dialysis but recovery is the rule. The remote prognosis of properly managed ATN in patients with preeclampsia is good and most patients had normal renal function on long-term follow-up.

Establishment of adequate urinary output is an important priority because the longer the low urinary output persists, the greater the possibility that the patient will develop severe or irreversible renal damage. Hence, if vaginal delivery cannot be anticipated to occur in a few hours it is better to perform a cesarean section. In many occasions delivery is followed by disappearance of the renal vasospasm and brisk diuresis.

Abruptio Placentae

About 7% of all patients with eclampsia will have premature separation of the placenta. Abruption is often an unexpected finding at the time of delivery. The management of abruptio placentae in preeclamptic patients is no different than under other circumstances and is described in Chapter 9. The management of the patient with abruptio placentae and anuria is identical to that of the obstetric patient in acute renal failure, as described in Chapter 19.

Intracranial Bleeding

Intracranial bleeding is the leading cause of death in preeclampsia. Underestimation of the severity of the disease, extended outpatient treatment, failure to use antihypertensive drugs to treat extreme elevations of blood pressure, and discharge from the hospital before obtaining adequate control of the hypertension are the most frequent errors found in the analysis of those deaths. An important clinical observation from the analysis of 28 women who sustained a stroke in association with preeclampsia and eclampsia was that the main correlation of this event was the systolic, not the diastolic blood pressure (Martin et al., 2005). This suggests that antihypertensive therapy may be indicated when the systolic blood pressure reaches 150, not 160, in preeclamptic women.

In the majority of cases, the preeclamptic with intracranial bleeding is admitted to the hospital in a coma following the onset of headaches and convulsions at home. The diagnosis is suggested by a deepening stupor and sensorimotor deficits and becomes highly probable if focal neurologic signs, such as unilateral pupil dilation, are present. The diagnosis is confirmed by CAT scan or MRI. The prognosis is very poor, and recovery is the exception rather than the rule. In most cases, coma becomes more profound, respiratory paralysis appears, and finally, the electroencephalogram shows loss of electrical activity.

Severe occipital and temporal headaches are important symptoms in pregnant patients because they are frequently harbingers of convulsions. These headaches are usually secondary to inadequate blood pressure control and they are an indication for aggressive treatment with hypotensive agents.

Visual Disorders

Blindness may occur in patients with severe preeclampsia and eclampsia and may persist for several days, although quick recovery after delivery is the rule. In most cases,

examination of the optic fundi does not show severe retinopathy, since the problem is usually caused by multiple microhemorrhages and microinfarcts occurring in the occipital lobe. Cortical blindness is equivalent to a seizure, and patients with this symptom should be treated as having eclampsia.

The funduscopic examination of patients with preeclampsia usually does not reveal more than focal or generalized vasospasm and, in some cases, retinal edema, which frequently is missed in the examination because it begins in the periphery of the retina. Papilledema in preeclampsia is highly unusual and demands a reevaluation to rule out the possibility of an intracranial tumor or bleeding. Diplopia is a symptom that may occur, and it is caused by functional impairment of the sixth cranial nerve pair. In some rare cases, it is possible to find sixth nerve paralysis. This finding requires a CAT scan to rule out a tumor in the brainstem area. Like most lesions caused by preeclampsia, sixth nerve paralysis improves after delivery and eventually disappears several weeks later.

LONG-TERM PROGNOSIS OF PREECLAMPSIA AND ECLAMPSIA

When counseling women who have preeclampsia or eclampsia, the main questions about long-term prognosis are the possibilities of recurrence in a future pregnancy and the possibility of chronic hypertension later on in life. Since preeclampsia is typically a disease of the first pregnancy, the obstetrician commonly is reassuring and tells the patients that preeclampsia rarely recurs in future gestations. This is incorrect. In fact, the probability of recurrence of preeclampsia is approximately 30% and this probability increases in inverse relationship to the gestational age at which the patient developed the disease. If the patient had preeclampsia at term, the chance of recurrence in a future pregnancy will be 25%. If the onset was between 30 and 37 weeks, the recurrence rate is 40%, but if preeclampsia developed before 30 weeks of gestation, the chances of recurrence are approximately 70%. Women who develop preeclampsia as multiparas have a 50% chance of developing hypertension in later pregnancies. Persistent hypertension for more than 10 days in the immediate postpartum period, maternal obesity, early gestational age at the onset of symptoms, and severity of the hypertension are factors significantly associated with the probability of developing recurrent preeclampsia.

Women who develop preeclampsia are also at high risk for chronic hypertension later in life. A cohort study in Scotland (Wilson et al., 2003) indicated that women who develop gestational hypertension and preeclampsia are at higher risk of developing chronic hypertension and dying from stroke than those who remain normotensive during pregnancy. However, women who develop preeclampsia are not at high risk of developing hypertension when using oral contraception (Pritchard and Pritchard, 1977).

When a pregnancy is complicated by eclampsia, the risk of developing mild preeclampsia in a second pregnancy is 19.5%, the chances of developing severe preeclampsia are 25.9%, and the risk of recurrence of eclampsia is 1.4%. In a classical study, Chesley (1978) periodically reexamined women with eclampsia for periods up to 44 years and compared their subsequent reproductive performance and their development of chronic hypertension with control women matched by race and age. He found that 33.8% of 151 women having eclampsia as nulliparas developed hypertension in later pregnancies. In about 40% of these cases, hypertension was mild. Multiparous women who have eclampsia have a higher incidence of hypertension, annual death rate, and cardiovascular deaths later in life than normotensive controls.

PREVENTION OF PREECLAMPSIA

As stated by Dekker and Sibai (2001) prevention of preeclampsia can be theoretically achieved at primary, secondary, or tertiary levels. Primary prevention is equivalent to avoiding the occurrence of the disease—a task that is impossible at this time because of our limited knowledge about the etiology and initial mechanisms of the disease—and tertiary prevention is synonymous with treatment to avoid complications of the disease. For these reasons, efforts to prevent preeclampsia have been focused in secondary prevention that consists of correcting the pathophysiology of the process to avoid the onset of clinical signs and symptoms.

Secondary prevention requires knowledge of the pathophysiology of preeclampsia, adequate tests to detect the disease before the onset of clinical symptoms, and effective interventions to correct the abnormal changes. Unfortunately, there are serious deficiencies in all of these areas. The pathophysiology of preeclampsia is understood only partially, there are no accurate methods to detect the disease before the onset of clinical symptoms and signs, and the available interventions to modify the pathophysiologic changes are few, have the potential to alter other metabolic pathways, and cause fetal or maternal damage.

Efforts toward secondary prevention of preeclampsia require development of accurate tests to predict the development of the condition. Uterine artery Doppler at 24 weeks and unexplained elevated maternal serum alpha-fetoprotein and human chorionic gonadotropin in genetic screening tests have the highest sensitivity and positive predictive value among different predictors of the disease. However, they are not perfect tests and are not universally recommended for screening. Further studies of

the accuracy of sFlt-1 and PGF (placental growth factor) to predict preeclampsia may change the present situation. The three preventative strategies more carefully studied during the last 15 years have been low-dose aspirin administration, calcium supplementation, and antioxidant administration.

Low-Dose Aspirin

There is substantial evidence indicating that an imbalance in the production of thromboxane A2 and prostacyclin is an essential feature in the pathophysiology of preeclampsia. Thromboxane A2 is produced primarily by the platelets and is a powerful vasoconstrictor and promotor of platelet aggregation. Prostacyclin is produced in the vascular endothelium, is a powerful vasodilator, and inhibits platelet aggregation. In preeclamptic patients prostacyclin synthesis is decreased and thromboxane production is increased, leading to vasoconstriction and platelet aggregation.

Prostacyclin and thromboxane are products of the metabolism of arachidonic acid by the enzyme cyclooxygenase, which is irreversibly inhibited by aspirin. Selective inhibition of platelet cyclooxygenase should decrease thromboxane production and restore the balance between these antagonic substances. Platelets cannot synthesize proteins "de novo" and restoration of their cyclooxygenase activity after treatment with aspirin requires the production of new cells by the bone marrow. In contrast, endothelial cells can rapidly regenerate cyclooxygenase activity after aspirin treatment. Therefore, the net effect of low-dose aspirin is a selective inhibition of platelet thromboxane production. This mechanism is the basis for attempts to prevent the development of preeclampsia with low-dose aspirin.

A recent systematic review of 33,439 women enrolled in 43 trials (Duley et al., 2003) found that the use of aspirin was associated with a 19% decrease in the risk of preeclampsia, 7% decrease in the risk of delivery before 37 completed weeks, 8% reduction in the risk of small-for-gestational-age babies, and a 16% reduction in fetal and neonatal deaths. In the overall population the confidence intervals indicate that the reduction of risk could be as much as 25% and as little as 12%. There was a greater reduction of risk of preeclampsia to 27% in women at high risk than in women at moderate risk (15%). There was a greater reduction of risk observed in 19 trials of 4965 women who received more than 75 mg/day of aspirin, and it seems that the dose of aspirin is important and that a better protection is obtained when doses higher than 75 mg/day are used; furthermore, it seems that the protective effect is greater when the treatment is started early in gestation.

The evidence from systematic reviews indicates that aspirin has a moderate effect in the prevention of preeclampsia and its use in patients at high risk is justified. The fact that the effect of aspirin is not larger indicates that the imbalance of thromboxane/prostacyclin is not a major mechanism of disease. The use of aspirin in higher doses than it is commonly used (81 mg/day) may have additional anti-inflammatory effects increasing its effectiveness, but this is a question that needs to be solved by randomized clinical trials.

Fish oil supplementation has been another attempt to modify the thromboxane/prostacyclin balance and decrease the incidence of preeclampsia. The rationale is that the eicosapentaenoic and docosahexaenoic *n*-3 fatty acids abundant in fish oil will act as competitive inhibitors of arachidonic acid as substrate for cyclo-oxygenase, inhibiting the production of thromboxane by the platelets. However, several controlled trials have failed in demonstrating the benefits of fish oil supplementation in decreasing the incidence of preeclampsia or the incidence of poor pregnancy outcomes.

Calcium

The possibility that calcium may prevent preeclampsia was borne of epidemiologic observations of a low incidence of this condition in populations with high calcium intake. Calcium may prevent preeclampsia by decreasing the release of parathormone and consequently the intracellular calcium concentration resulting in decreased smooth muscle contractility. This mechanism of action has no experimental support. The literature about dietary calcium supplementation in the prevention of preeclampsia is contradictory and confusing. A large randomized trial in USA (Levine et al., 1997) did not find any difference in the incidence of preeclampsia between women randomized to calcium and women taking placebo. In contrast, a systematic review of 11 randomized clinical trials (Atallah et al., 2002) found a significant decrease in the risk of hypertension in general and also in the risk of preeclampsia. The decrease in risk was greater in women at high risk for developing hypertension and in women with a diet deficient in calcium. The systematic review also demonstrated smaller effects in the larger trials and no overall improvement in perinatal outcome or in risk of preterm delivery. This heterogeneity of results added to the weakness of the pathophysiologic explanation for the effect of calcium in preventing preeclampsia generates doubts regarding the value of this intervention.

Antioxidants

Some investigators consider preeclampsia as a two-stage disorder: the first one being abnormal placentation and the second one a maternal syndrome resulting from endothelial dysfunction (Roberts and Speer, 2004). The same theory explains the linkage between these two stages

by the production by the diseased placenta of oxidative stress mediators that will be released into the maternal circulation and injure the vascular endothelium. An obvious consequence of this theory is the possibility of preventing the stage of clinical expression of the disease by means of antioxidant substances. A small randomized clinical trial (Chappell et al., 1999) using vitamins C and E in women at high risk, selected on the bases of uterine Doppler studies at 20 weeks, demonstrated a significant decrease in the incidence of preeclampsia in the treated group. A second study again using a small number of cases and assuming a high efficacy of the prevention intervention (Beazley et al., 2005) did not find a significant difference between women taking vitamins C and E and those taking placebo in the incidence of preeclampsia. Prevention of preeclampsia using antioxidants needs to be studied in a large population to better assess the potential benefits and the safety of this treatment.

INDIAN EXPERIENCE OF HYPERTENSIVE DISORDERS IN PREGNANCY

Management begins by attempting to identify women who will be prone to develop hypertension during the course of their pregnancy. To meet this goal, predictive tests have been evaluated. Some important Indian contributions have been briefly reviewed below.

Predictive Tests

1. Evaluation of the isometric exercise (Handgrip test) as predictor of early PIH. Kaur et al., (2003) from Amritsar evaluated this in their antenatal department and concluded that this test has a sensitivity of 51.5%, positive predictive value of 70.8%, and negative predictive value of 92.54% for predicting risk of developing PIH.
2. Role of calcium:creatinine ratio in first morning urine in the midtrimester of pregnancy for predicting risk of PIH has been evaluated by Kar et al., (2002) of Gorakhpur and Desai et al. (2001) from Baroda. They confirmed that a ratio < 0.04 is predictive of increased risk for PIH. A ratio > 0.04 predicted a 96% chance of not developing PIH.
3. Estimation of serum calcium and magnesium levels by Sawhney et al., (2001) and Desai et al., (2001) were not very helpful in predicting the risks of PIH. These were comparable in both hypertensive and normotensive pregnant patients. Perhaps estimation of intracellular levels of calcium and magnesium may be more meaningful.
4. Satyanarayan et al., (2001) from Chandigarh studied the association between second trimester maternal serum quantitative beta-hCG and predictive risks for PIH. The mean beta-hCG values were higher in normotensive women as compared to women developing PIH. In the latter group, values were higher in proteinuric women as compared to nonproteinuric women, however there was a great deal of overlap—hence the test had limited value.
5. Joshi-Kale and Sapre (2004) from Gwalior noted that thrombocytopenia had a close relation with PIH, a count of less than 1 lakh/ml was strongly indicative of high risk of developing HELLP syndrome. Kaur et al., (2003) from Amritsar noted that estimation of platelet counts and liver enzymes was important in prognosis of cases of PIH. Elevated liver enzymes and dropping platelet counts were each of bad prognostic significance independently; if both the tests were abnormal, the prognosis worsened. In their experience, the perinatal mortality rate (PNMR) was 66.7% in HELLP syndrome when both parameters were abnormal, but PNMR was 32.4% when only one parameter was abnormal.
6. Antioxidants play an important role in combating oxidative stress during pregnancy. Estimation of enzymes superoxide desmutase, catalase, RBC glutathione, and vitamin E are known to fall in women with PIH indicating increasing peroxidation (Anandan and Shanmugasunderam, 2001; Desai et al., 2003; Kharb et al., 2000).
7. Desai and Rao (2002) from Baroda studied the role of midtrimester serum quantitative assays of beta-hCG as a predictive marker for PIH. In his assessment 68.9% of women who had developed serum beta-hCG values > 2 MoM (multiples of the mean) manifested PIH.
8. Chhabra and Gandhi et al., (2001) of Wardha, studied the predictive value of presence of midtrimester microalbuminuria and the risk of PIH. In their study of 200 women, 60% of women with positive microalbuminuria and 20% with negative microalbuminuria developed PIH.
9. Blood flow studies using color Doppler has been extensively used to assess fetal well-being during pregnancy. Notching of the uterine artery during the midtrimester has been widely accepted as a predictor for PIH. Saxena et al., (2002) from Aligarh assessed the blood flow in five arteries—both maternal uterine arteries, fetal middle cerebral artery, umbilical artery, and the aorta in normotensive and PIH patients. In their experience, they reported that in the normotensive group of patients, 78.2% delivered babies that were appropriate for gestational age (AGA), with a mean birth weight of 2.88 kg and no perinatal loss. As against the PIH group of patients, in whom 66% delivered AGA babies, with the mean birth weight of 2.44 kg and one perinatal death.

10. Gupta et al., (2001) of Lucknow demonstrated the value of MRI and renography in doubtful cases of eclampsia. They demonstrated hypersensitivity in the parietal lobes (66.6%), occipital lobe (53%), and frontal lobes (50%) and narrowing of the renal arteries on renography (49.6%).

Clinical Aspects of Pregnancy-Induced Hypertension

1. Kumar Majhi et al., (2000) reporting from a referral hospital in Calcutta reported that the incidence of eclampsia was 2.79% and primiparae accounted for 88.7% (58% of these patients were under the age of 20 years). Intrapartum eclampsia accounted for almost 44.6% cases. The caesarean section rate was 10.5% and maternal mortality rate was 11.28% for PIH of these 48.7% was due to eclampsia. The perinatal mortality rate was 39.9% and the incidence of low birth weight and maternal outcome was better in the actively managed cases.
2. Khanna and Prabhakar (2002) from Varanasi reported on the maternal and fetal outcome with low dose aspirin (50 mg) and controls in PIH cases. Prophylactic use of aspirin was not associated with any significant effect on major pregnancy outcome. However, the cases of severe PIH decreased in the aspirin treated group.
3. Devi and Uday (2001) from Bangalore drew attention to some of the unusual accompaniments of PIH. In their study, the incidence of PIH was 11.7%, ascites was observed in 2.8%, pleural effusion in 1.2%, HELLP syndrome in 0.8%, cortical venous thrombosis in 2.8%, and duodenal perforation in one patient who was on prophylactic aspirin. All these additional features worsen the pregnancy outcome and require to be watched for meticulously. Ching Ling et al., (2002) from Mumbai described a case of HELLP syndrome with liver tears which required exploration and suturing to control internal bleeding.
4. Girija et al., (2001) reported some unusual accompaniments of PIH like pleural effusion in 1.8%, ascites in 2.8%, HELLP in 1.2%, cortical venous thrombosis in 2.8%, and duodenal ulcer perforation following aspirin administration in one case.
5. Gokhroo et al., (2001) from Ajmer reported meconium staining of the liquor amnii in 9.37% of 1450 live-born deliveries, of these 24% had meconium aspiration. In this group 13.8% were primigravidae. Fetal distress was reported in 448 cases. The incidence of meconium staining in PIH cases was higher at 13.18% and 3.34% in eclamptic patients.
6. Kaur et al., (2003) from Amritsar reported an incidence of PIH. Of these 4.0% developed HELLP syndrome, 67.5% of these had elevated liver enzymes, 24.3% had lowered platelet count, and 8.2% had both elevated liver enzymes and lowered platelet counts. The perinatal mortality was 66.7% in HELLP syndrome, 3.0% in cases of moderate PIH, and 21.33% in severe PIH cases.
7. A report on maternal and perinatal outcome associated with HELLP syndrome in PIH and eclampsia from Bangalore (Jophy et al., 2004) stated that the incidence of severe PIH was 5.18%. Of these 63.3% were primigravidae and 36.7% were multiparae. HELLP syndrome developed in 19.32% of primiparae and 28.98% of multiparae. Maternal mortality rate (MMR) was 13/1000 for PIH, but the MMR for HELLP syndrome was 69.7%. In cases of abruptio placenta, the incidence of HELLP syndrome was 39.5%, DIC was reported in 60%, and acute renal failure occurred in 25%. Of these 63% required hemodialysis. Postpartum bleeding occurred in 13.9% and perinatal mortality was reported in 42.2%.
8. The role of low dose aspirin in the prevention of PIH was investigated in a randomized controlled trial by Sehgal and Sood (Delhi, 2001). The control trial consisted of two groups. Group-1 consisted of patients at high risk for developing PIH and Group-2 consisted of normal controls. The authors concluded that the aspirin was more effective than placebo in preventing PIH, preterm births, and intrauterine fetal deaths.
9. Banerjee-Basu et al., (2002) conducted a randomized controlled clinical trial comparing 54 cases of PIH treated with nimodipine with the outcome in 57 patients treated wit alpha-methyldopa. The fall in blood pressure was faster and the platelet count increased quicker with nimodipine as compare to alpha methyldopa, however the obstetric outcome was comparable in both groups.
10. In the treatment of eclampsia, Hangarga and Pragya of Hubli compared the results of treatment with phenytoin sodium, magnesium sulfate (magsulf) therapy, and Menon's regime. They observed the following: (a) phenytoin sodium—fit recurrence 6.26% and PNMR 31%, (b) magsulf therapy—fit recurrence 8.8% and PNMR 41%, and (c) Menon's regime—fit recurrence 52.94% and PNMR 58%. They therefore endorsed the phenytoin sodium regime for the management of eclampsia. Datta et al., (2002) from Jamshedpur reported on a series of 100 cases of eclampsia, comparing the obstetric outcome following use of diazepam and the magsulf regime. Their results have been summarized below in Table 16-1.

Table 16.1. Comparison of the obstetric outcome in case of diazepam and magsulf regime

Parameter	Diazepam regime	Magsulf regime
Recurrence of fits	16%	2.0%
Ventilatory support	8%	2.0%
Maternal mortality rate (MMR)	38%	14.0%
Perinatal mortality rate (PNMR)	30%	15.0%
Rate of caesarean births (LSCS)	62%	55.0%

INDIAN EXPERIENCE WITH CHRONIC HYPERTENSION AND PREGNANCY

Chronic hypertension complicates between 1 and 3% of all pregnancies. The diagnosis is based on documenting elevated blood pressure of 140/90 mmHg or above on repeated occasions before the onset of pregnancy, or prior to 20 weeks of gestation, or demonstrating its persistence after the puerperium. About 25–50% of pregnant hypertensive patients fall in this group. In rural India, women often report for antenatal care only in the latter half of pregnancy, hence their earlier blood pressure status is often not known.

The majority of reports state that hemorrhage, hypertensive disorders in pregnancy, and sepsis are the chief indications for admission for critical care obstetric practice (Tripathi et al., 2000). Complicated hypertensive disorders in pregnancy account for over 20% of these admissions. Intensive care units account for 5% of patients in hospitals and account for 20–28% of total hospital costs (Batra et al., 1991).

In a comparative study of the obstetric outcome of normotensive women with those with hypertension complicating pregnancy from Aligarh, it was observed that whereas almost 80% of normotensive women gave birth to infants that were appropriate for gestational age (AGA), this figure was 66.6% in the hypertensive patients. The average birth weight in the hypertensive group was 2.0 kg as against 2.44 kg in the control group. The incidence of preterm births, birth asphyxia, and low Apgar scores was higher in the hypertensive group. The PNMR was 3% in the affected group and nil in the normal controls. Color Doppler studies of the uterine artery at 20 weeks of gestation demonstrated notching in about a third of the hypertensive patients. Later in pregnancy, the middle cerebral artery blood flow was a good indicator of fetal compromise (Saxena et al., 2001).

In an interesting study of abruptio placenta from Calcutta, the authors reported an incidence of 1:215 pregnancies. Obstetric outcome is adverse in many patients. In the authors experience the maternal mortality in hypertensive pregnant women suffering from abruptio placenta was 9.9% and the perinatal mortality was 71% (Mukherjee et al., 2003).

IMPORTANT POINTS

1. Hypertension in pregnancy is defined as diastolic blood pressure of 90 mmHg or more or systolic blood pressure of 140 mmHg or more, after 20 weeks of gestation, in a woman with previously normal blood pressure.
2. Korotkoff V sound, the point of disappearance of sound, should be used to determine diastolic blood pressure during pregnancy. Measurements should be taken with the woman sitting with the right arm supported on a table or desk in a roughly horizontal position at heart level.
3. The exact nature of the primary event causing preeclampsia is not known. However, evidence indicates that in a large number of cases, particularly when preeclampsia is severe and develops before 32 weeks, the condition is associated with deficient trophoblastic invasion of the spiral arteries (abnormal placentation).
4. Chronic hypertension complicates approximately 1–3% of all pregnancies. To establish this diagnosis it is necessary to document the presence of hypertension before pregnancy or before 20 weeks of gestation.
5. The overwhelming majority of pregnant women with chronic hypertension have essential hypertension. Rarely the hypertension is secondary to renal artery stenosis, chronic renal disease, pheochromocytoma, or other causes.
6. Chronic hypertension usually starts with a phase of increased CO and normal PVR. After several years there is a gradual increase in PVR and fall in CO. The elevated blood pressure causes accelerated arteriosclerosis and results in damage to the heart, brain, kidney, and other organs. Most pregnant women with chronic hypertension are in the earlier phases of this disease and have no evidence of end-organ damage.
7. The most common maternal risks for patients with chronic hypertension during pregnancy are the development of uncontrolled hypertension, superimposed preeclampsia, and abruptio placentae. The most common fetal risks are fetal growth restriction, preterm birth, and hypoxia and acidosis.
8. Severe hypertension is defined as a diastolic blood pressure of 110 mmHg or greater or systolic blood pressure of 160 mmHg or greater. Most pregnant patients have mild hypertension.
9. In pregnant patients with mild chronic hypertension, factors other than the elevation of blood pressure should be taken into consideration to determine if they are at risk for complications and in the need for antihypertensive therapy.

10. The hemodynamic characteristics of patients with chronic hypertension during pregnancy are different. The majority have increased CO and normal PVR. Others have hyperkinetic circulation. Those at higher risk have elevated PVR and normal CO.
11. Self-monitoring of blood pressure is important in the management of patients with chronic hypertension and pregnancy. The frequent occurrence of "white coat hypertension" makes occasional office measurements unreliable in monitoring these patients.
12. Antihypertensive drugs should be a part of the treatment of patients with severe hypertension and patients with mild hypertension and risk factors for poor outcome.
13. Diuretics lower blood pressure initially by decreasing the plasma volume and after a few weeks by decreasing PVR. They are useful for hypertensive patients with expanded intravascular volume and increased CO.
14. Contrary to other beta-blockers, labetalol acts by decreasing PVR with little change in CO. The main indication for the use of labetalol is to rapidly reduce blood pressure in patients with severe preeclampsia.
15. Prazosin is a peripheral vasodilator with a significant effect on capacitance vessels. The combination of prazosin and a diuretic is extremely effective for hypertension resistant to other drugs.
16. The association between beta-blockers and fetal growth restriction has not been rigorously demonstrated.
17. Fetal growth should be assessed by periodic ultrasound measurements in all patients with chronic hypertension. There is no need for repeated creatinine clearance and quantitative protein determinations unless the serum creatinine is greater than 0.8 mg/dl or more than 2+ protein is found by examination of a random urine specimen.
18. An increase in maternal CO rather than an increased PVR is the most frequent hemodynamic finding in preeclampsia. The elevation in CO in patients with preeclampsia may start as early as 11 weeks and remain in the puerperium despite resolution of the hypertension.
19. Glomerular endotheliosis is a characteristic, not pathognomonic, renal lesion in preeclampsia.
20. Recent investigations suggest that in preeclampsia there is excessive trophoblastic production of sFlt-1 that binds and inhibits PGF and vascular endothelial growth factor. Placental peroxidation products and sFlt-1 affect endothelial cell function.
21. Labetalol and nifedipine are useful antihypertensive agents for the treatment of patients with preeclampsia.
22. Maternal morbidity is severe and perinatal mortality is greater than 90% when conservative management is adopted for patients with severe preeclampsia developing before 24 weeks. In these patients expectancy is not justified and delivery is the treatment of choice.
23. In selected patients with severe preeclampsia between 24 and 34 weeks delivery may be postponed for 48–72 hours for the purpose of giving the mother steroids and to prevent neonatal RDS and IVH. Additional prolongation of pregnancy is dangerous for the mother and should be undertaken exclusively in tertiary centers.
24. FHR monitoring in the second trimester is difficult. The NST usually is nonreactive and fetal breathing movements are not present. Fetal health is demonstrated by the presence of variability and absence of decelerations. Usually the maximum possible biophysical profile score is 6.
25. Eclampsia is associated with elevated maternal and fetal mortality and morbidity. The most common causes of maternal death are intracranial bleeding and acute renal failure. The most common causes of fetal death are prematurity and fetal asphyxia.
26. Eclampsia is not preventable by adequate prenatal care in more than 30% of the cases.
27. Plasmapheresis may be lifesaving for women with HELLP syndrome who follow a relentless course of deterioration following delivery.
28. Pulse oximetry is valuable in the monitoring of preeclamptic patients with oliguria receiving large amounts of IV fluids because it may detect changes in oxygen saturation that occur before the development of overt pulmonary edema.
29. Invasive hemodynamic monitoring is rarely needed in the management of women with eclampsia, HELLP syndrome, or severe preeclampsia.
30. Intracranial bleeding is the leading cause of maternal death in preeclampsia. Underestimation of the severity of the disease, extended outpatient treatment, failure to use antihypertensive drugs, and discharge from the hospital before obtaining adequate control of the hypertension are frequent errors in the management of these patients.
31. Prevention of preeclampsia is disappointing. The only medication with some preventative effect in a selective subgroup of patients is low-dose aspirin.

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17

Diabetes and Pregnancy

CHAPTER OUTLINE

Abnormalities of carbohydrate metabolism occur frequently during pregnancy and between 3 and 5% of all pregnant patients will show glucose intolerance. Approximately 90% of these women have gestational diabetes. Women with gestational diabetes are individuals with a genetic or metabolic predisposition toward diabetes who are incapable of adequately compensating for the diabetogenic effects of pregnancy. Approximately 50% of women with gestational diabetes will develop type II diabetes later in life. A smaller group is formed by women with pregestational diabetes type I or type II diagnosed before they became pregnant.

CARBOHYDRATE METABOLISM DURING PREGNANCY

The most important reason why pregnancy exacerbates the diabetic tendency of asymptomatic women is the progressive increase in insulin resistance that occurs during gestation. Other reasons for this diabetogenic tendency are the increased lipolysis and the alterations in gluconeogenesis which normally occur during gestation (Box 17-1).

During the first and early part of the midtrimester there is increased sensitivity to insulin and diabetic patients have a tendency towards hypoglycemia. This enhanced insulin sensitivity is probably due to the high levels of estrogen. The opposite occurs in the third trimester when

BOX 17-1

Diabetogenic effects of pregnancy

Insulin resistance
- Production of human placental lactogen
- Increased production of cortisol, estriol, and progesterone
- Increased insulin destruction by kidney and placenta

Increased lipolysis
- The mother utilizes fat for her caloric needs and saves glucose for fetal needs

Changes in gluconeogenesis
- The fetus preferentially utilizes alanine and other amino acids, depriving the mother of a major neoglucogenic source

a given dose of insulin has a decreased hypoglycemic effect. This increased insulin resistance stems mainly from the antagonistic effect of human placental lactogen. Accelerated insulin catabolism by renal and placental insulinases and the anti-insulin effects of other hormones (cortisol, estriol, progesterone) produced in large amounts during pregnancy also contribute to insulin resistance. The increased insulin resistance in the third trimester explains why gestational diabetes is more common after 26 weeks. It also explains the increased risk for ketoacidosis in pregnant women with type I diabetes. As a result of the physiologic changes of pregnancy, the normal fasting blood sugar is 65 ± 9 mg/dl. The mean nonfasting blood sugar level is 80 ± 10 mg/dl. Postprandial elevations normally never exceed 140 mg/dl (Cousins et al., 1980).

EFFECTS OF DIABETES ON PREGNANCY

The great majority of women with carbohydrate intolerance during pregnancy do not have signs or symptoms. Unfortunately, carbohydrate intolerance during pregnancy causes significant increases in fetal and maternal morbidity. The maternal consequences of diabetes in pregnancy are important (Box 17-2). These women have a greater incidence of preeclampsia, infection, postpartum bleeding, and cesarean deliveries (Cousins, 1987). The incidence of preeclampsia is approximately 15% and it is associated with poor glycemic control and end-organ damage (Siddiqui et al., 1991). The consequences to the fetus are more serious than those to the mother (Box 17-3). Among the fetal effects, the frequency of congenital abnormalities is increased in women with poorly controlled type I diabetes and the incidence of fetal macrosomia is increased in women with gestational and type II diabetes. Fetal growth restriction is common in women with type I diabetes and end-organ damage.

BOX 17-2

Effects of diabetes on the mother

Preeclampsia
- Affects 10–25% of all pregnant diabetics

Infection
- High incidence of chorioamnionitis and postpartum endometritis

Postpartum bleeding
- High incidence due to exaggerated uterine distention

Cesarean section
- High incidence of pregnant diabetics

BOX 17-3

Effects of diabetes on the fetus

- Congenital abnormalities
- Hypoglycemia
- Hyperviscosity syndrome
- Hyaline membrane disease
- Macrosomia
- Hypocalcemia
- Apnea and bradycardia
- Traumatic delivery

EFFECTS OF PREGNANCY ON DIABETES

Pregnancy imposes a heavy burden on the patient with diabetes (Box 17-4). These patients have a tendency toward metabolic instability and will need frequent blood glucose monitoring, continuous adjustments in therapy, and a highly regulated lifestyle. For diabetic patients who already have organ damage, pregnancy may accelerate end-organ disease, requiring intensive testing and therapeutic procedures. The complex interaction between abnormal carbohydrate metabolism and pregnancy should be clearly explained to each patient immediately after the diagnosis is made, and prior to pregnancy when the patient has overt diabetes.

BOX 17-4

Effects of pregnancy on diabetes

- More insulin is necessary to achieve metabolic control
- Progression of diabetic retinopathy
- Worsening of diabetic nephropathy
- Increased risk of death for patients with diabetic cardiomyopathy

DIAGNOSIS

The large majority of women with diabetes during pregnancy are affected by gestational diabetes, which is defined as carbohydrate intolerance of varied severity with onset or first recognition during the present pregnancy. Unfortunately, gestational diabetes presents no reliable signs or symptoms and it is necessary to screen the entire obstetrical population, or at least the pregnant women at high risk, to identify those who need to have a definitive test to determine the presence of the condition.

Screening for Gestational Diabetes

There are several conditions that should be fulfilled in order to adopt a generalized screening method during pregnancy:

1. The condition to be screened for should have a significant impact on maternal and fetal health.
2. The screening method should have high sensitivity and specificity.
3. An effective method should be available to treat the condition and reduce its impact on the outcome of pregnancy.

As mentioned before, gestational diabetes is associated with an increased risk of preeclampsia, polyhydramnios,

and cesarean delivery and is a precursor of type II diabetes in almost 50% of women with this diagnosis. From the fetal viewpoint gestational diabetes is associated with fetal macrosomia, birth trauma, and neonatal complications such as hypoglycemia, hyperbilirubinemia, and hyperviscosity syndrome. Perinatal mortality is rare. In answer to the first question about screening, it appears that the maternal and neonatal complications merit generalized screening.

Screening for gestational diabetes is performed by orally administering 50 g of glucose and measuring the venous plasma glucose 1 hour later. It is not necessary to follow a special diet before the test and it is not necessary to be in a fasting state. Plasma glucose values should not be substituted with capillary reflectance meter glucose values. The sensitivity of the test is related to the threshold used for diagnosis and with the prevalence of the condition in the population. When 130 mg/dl is used as the threshold, the test will have a sensitivity of 90%, which decreases to 80% when the threshold is 140 mg/dl. However, the use of the lower threshold implies testing of 20–25% of the overall obstetrical population while the upper threshold limits the testing to 14–18% of the population. Since the incidence of gestational diabetes is on the average between 2 and 5% the number of unnecessary screening tests (false positives) will be much higher with the 130 mg/dl threshold. Some communities may have a prevalence of gestational diabetes as high as 14% and in this case the number of false positive will be small even if the lower threshold is adopted for screening.

With respect to the third condition to accept a screening test, the Cochrane database (Tuffnell et al., 2003) suggests that there is no conclusive evidence of improvement in perinatal outcomes following the diagnosis of gestational diabetes. However, this analysis did not include recent studies demonstrating significant differences in perinatal outcomes among treated and untreated women with gestational diabetes. In a study by Langer et al. (2005) 555 gravidas with untreated gestational diabetes diagnosed after 37 weeks were matched with 1110 women with treated gestational diabetes and 1110 women without gestational diabetes. A composite adverse outcome was 59% for untreated, 18% for treated, and 11% for nondiabetic subjects. In an Australian study (Crowther et al., 2005) 1000 women with gestational diabetes were randomized to an intervention group and a routine care group. The intervention group had dietary instructions, self-monitoring of blood glucose, and insulin therapy if the capillary blood glucose (CBG) exceeded certain limits. They found that the rate of serious perinatal complications was significantly lower among the newborns of women in the intervention group. They also found a higher rate of induction of labor and admission to the neonatal intensive care unit in women assigned to the intervention group. These investigations are strong evidence indicating not only that gestational diabetes carries significant perinatal morbidity but also that available treatment of the condition substantially improves outcomes.

BOX 17-5

Women at low risk for gestational diabetes

- Age younger than 25 years
- Not a member of an ethnic group at high risk for the development of type II diabetes (Hispanic, African, Native American, South or East Asian, or Pacific Islands ancestry)
- Body mass index of 25 or less
- No previous history of abnormal glucose tolerance
- No previous history of adverse obstetric outcomes usually associated with gestational diabetes (macrosomia, neonatal hypoglycemia, etc.)
- No known diabetes in first degree relative

An area of controversy is whether screening for positive diabetes should include every pregnant woman or exclude women at low risk (Box 17-5). The US Preventive Services Task Force (Brody et al., 2003) and the American College of Obstetricians and Gynecologists (ACOG) (2001) recommend selective screening of high-risk women. However, most obstetrical practices find it impractical to select patients at high risk, and generalized screening is predominant.

BOX 17-6

Risk assessment and timing of screening for gestational diabetes

Low risk *All of the following:* ■ Member of an ethnic group with a low prevalence of GDM ■ No known diabetes in first-degree relatives ■ Age < 25 years ■ Weight normal before pregnancy ■ Weight normal at birth ■ No history of abnormal glucose metabolism	Blood glucose screening not routinely required
Average risk *One or more of the following:* ■ Member of an ethnic group with a high prevalence of GDM ■ Diabetes in a first-degree relative ■ Age ≥ 25 years ■ Overweight before pregnancy ■ Weight high at birth	Blood glucose testing at 24–28 weeks (one- or two-step procedure)
High risk ■ Marked obesity ■ Strong family history of type II DM ■ Previous history of GDM, impaired glucose metabolism or glucosuria	Perform glucose testing as soon as feasible

To determine the best time to perform the screening test, the Fourth International Workshop Conference on GDM (gestational diabetes mellitus) and the American Diabetes Association have recommended that an assessment of risk of GDM should be performed at the first prenatal visit. This assessment will classify pregnant women in three groups (Box 17-6). In high-risk patients testing should be performed as soon as feasible. The majority of patients will be at average risk and the best time to screen them is between 24 and 30 weeks of gestation. Low-risk patients will be less than 10% of the overall obstetrical population, and they will not require screening testing if the overall policy is that of selective screening. Patients at high risk with a negative initial screening should have the test repeated between 26 and 30 weeks of gestation.

Diagnosis of Diabetes in Pregnancy

Patients with an abnormal screening test should be followed by a 3-hour glucose tolerance test (GTT) with the exception of those whose 1-hour screening test demonstrates plasma glucose values larger than 200 mg/dl, because patients with this markedly abnormal response to the sugar load are diabetics and need treatment started without further testing. Other patients with an abnormal 1-hour screening test need a 3-hour GTT to confirm or to rule out the diagnosis of diabetes. It is not necessary to follow a special diet before the 3-hour GTT. Normal values for the test are shown in Box 17-7. If two or more of these values are abnormal, the patient has diabetes. If only one value is abnormal, the patient cannot be diagnosed as being a gestational diabetic, although she is at risk for complications, such as macrosomia (18.0%) and preeclampsia–eclampsia (7.9%). Patients with no abnormal values in their 3-hour GTT have respective risks of 6.6 and 3.3%. Even those patients with a normal 3-hour GTT following an abnormal screening test are at risk for macrosomia when compared with patients who have a normal screening value. This suggests that minimal alterations in maternal carbohydrate metabolism may have a significant impact on the fetus and that patients with minimal alterations also require strict glycemic control to decrease the frequency of abnormal outcomes.

BOX 17-7

Upper limits of normal for the 3-hour glucose tolerance test during pregnancy following a 100-g glucose load*

Fasting	95 mg/dl
One hour	180 mg/dl
Two hours	155 mg/dl
Three hours	140 mg/dl

* Venous plasma glucose.

From Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982; 144: 768–73.

Renal glycosuria

Some patients with normal GTT show significant glycosuria during the test. The presence of glucose in the urine when the blood sugar glucose level is within normal limits is called renal glycosuria and is thought to be secondary to a low threshold for the elimination of glucose by the kidneys. Renal glycosuria occurs frequently during pregnancy. In fact, the average renal threshold for glucose is 155 ± 17 mg/dl during pregnancy, compared to 197 ± 6.5 mg/dl in the nonpregnant patients. During pregnancy glycosuria can occur at blood sugar levels as low as 70–100 mg/dl. Renal glycosuria during pregnancy is not completely benign and these women are at high risk for preterm delivery and for the development of fetal macrosomia.

Most pregnant patients with renal glycosuria have normal kidneys and the abnormality disappears after delivery. In some cases renal glycosuria during pregnancy is a manifestation of renal tubular damage secondary to chronic pyelonephritis. Such patients frequently develop recurrent urinary tract infections and have asymptomatic bacteriuria.

Management of renal glycosuria consists of (a) performing frequent urine testing to detect asymptomatic bacteriuria, (b) instructing the patient to have several small meals per day, rather than three large meals, to avoid postprandial elevations in the blood sugar and glycosuria, (c) staying alert for early signs and symptoms of preterm labor.

Patients with renal glycosuria may lose as much as 100 g/day of glucose in the urine. Such large losses decrease the amount of glucose available for their caloric needs, and lipolysis is activated to a maximum. This causes production of ketones and a tendency toward ketoacidosis (starvation ketosis). These patients gain little weight during pregnancy and require dietary counseling to compensate for their abnormal metabolic situation.

Hypoglycemia during the GTT

Approximately 5% of women submitted to a 3-hour GTT experience hypoglycemia during the test. Usually they become symptomatic with nausea, cold perspiration, tachycardia, and fainting. The blood glucose during these episodes is usually below 60 mg/dl. Most probably this reactive hypoglycemia is the result of the release of a large amount of insulin by the pancreatic beta-cells in response to the glucose load. Hypoglycemia during the GTT is benign and women who experience this problem can be reassured because they have a lower incidence of gestational diabetes and fetal macrosomia than those who do not have hypoglycemia during the GTT (Weissman et al., 2005).

CLASSIFICATION

Diabetic patients are classified as proposed by the National Diabetes Data Group, or NDDG (Box 17-8). Type I corresponds to the old juvenile-onset diabetes and is the result of an autoimmune process that destroys the pancreatic beta-cells, resulting in absence of insulin. Type II, or non-insulin-dependent diabetes, corresponds to the old adult-onset diabetes and is the most common form of diabetes characterized by insulin resistance, obesity, and relative insulin deficiency. Type III or gestational diabetes is carbohydrate intolerance with variable degrees of severity with onset or first recognition during pregnancy. In addition to their different etiologies and pathophysiologic mechanisms, classification as type I or type II is useful to the clinician with respect to the prognosis and potential for complications during pregnancy.

To complement the NDDG classification of diabetes during pregnancy, many use the classification system of Priscilla White (Box 17-9). This system separates patients into groups according to the age of onset and the years of duration of the disease as well as the presence or absence of micro- and macrovascular changes. White's classification has been valuable because it has established a basis to compare the management of pregnant diabetics between different institutions. Unfortunately, White's classification is not ideal and should not be used alone because the number of groups is large and because patients in the same group may have completely different prognoses. For example, some patients in class C may be type II, metabolically stable, with predictable insulin needs during pregnancy, and with excellent outcomes while other patients in the same group may be type I, unstable, prone to ketosis, and may have a high probability for a poor outcome. The current tendency is to classify the patients by type and then by White's class.

BOX 17-8

National Diabetes Data Group: etiologic classification of diabetes

Type I diabetes mellitus (beta-cell destruction usually leading to absolute insulin deficiency)
- Immune-mediated
- Idiopathic

Type II diabetes mellitus (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

Other specific types of diabetes
- Genetic defects of beta-cell function
- Genetic defects in insulin action
- Disease of the exocrine pancreas
- Endocrinopathies
- Drug- or chemical-induced
- Infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes associated with diabetes

Gestational diabetes mellitus

From American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2000; 23(Suppl 1): S4.

BOX 17-9

White's classification of diabetes during pregnancy

Gestational diabetes	Discovered during pregnancy, glycemia may or may not be maintained by diet alone and insulin may be required
Class A	Discovered before pregnancy, controlled with diet alone, any duration or age of onset
Class B	Onset age 20 year or older, duration less than 10 years
Class C	Onset age 10–19 year, duration 10–19 years
Class D	Onset age under 10 year, duration over 20 years, background retinopathy
Class R	Proliferative retinopathy or vitreous hemorrhage
Class F	Nephropathy with proteinuria over 500 mg/day
Class RF	Criteria for both classes R and F coexist
Class H	Arteriosclerotic heart disease clinically evident
Class T	Prior renal transplantation

From Hare JW, White P. Gestational diabetes and the White classification. Diabetes Care 1980; 3: 394.

GESTATIONAL DIABETES

Gestational diabetics are a heterogeneous group of patients whose disease onset or first recognition occurs during the present pregnancy. The majority of these women have carbohydrate intolerance because of the diabetogenic effects of pregnancy and will have normal carbohydrate tolerance after delivery. However, some of them have type II diabetes which was asymptomatic before pregnancy, some others have preclinical type I or type II diabetes that became apparent under the metabolic demands of pregnancy, and a few are type I or type II diabetics who had the onset of disease coincidently with pregnancy. Gestational diabetes affects 1–2% of all pregnancies. In the large majority of patients, it is mild and

BOX 17-10

High-risk gestational diabetes
- History of stillbirth
- History of neonatal death
- History of fetal macrosomia
- Concomitant obesity and/or hypertension
- Development of oligohydramnios, polyhydramnios, preeclampsia, or fetal macrosomia
- Inadequate metabolic control with diet alone

can be adequately controlled with diet alone but a minority will require glyburide or insulin. Women with gestational diabetes who obtain adequate metabolic control with diet alone are recognized as class A-1 in the White's classification. Gestational diabetics who require glyburide or insulin for adequate control are recognized as class A-2 and are at higher risk than class A-1 for poor outcome during pregnancy (Box 17-10).

Maternal Risks

The most significant maternal risk with gestational diabetes is the 35–50% probability of developing type II diabetes later in life. Older studies indicated a significant increase in the incidence of preeclampsia but recent evidence questions this finding (Naylor et al., 1996). The incidence of cesarean section is higher than in a nondiabetic population, but possibly this is a consequence of the diagnosis and not of the condition. Polyhydramnios occurs frequently in GDM particularly when the fetus is macrosomic.

Fetal and Neonatal Risks

Fetal macrosomia, defined as a birth weight greater than or equal to 4000 g, occurs in 17–29% of pregnancies with gestational diabetes as compared with 10% in the nondiabetic population (Adams et al., 1998). However, fetal macrosomia is not an adequate index of morbidity and better indicators are the incidence of shoulder dystocia with brachial plexus damage and clavicular fractures that are increased in neonates of women with GDM (Adams et al., 1998). The incidence of neonatal hypoglycemia is greater in GDM than in normal pregnancies (Garner et al., 1997). In a recent study neonatal morbidity was assessed by a composite outcome that included stillbirth, neonatal macrosomia/LGA (large for gestational age), neonatal hypoglycemia, erythrocytosis, and hyperbilirubinemia. Composite morbidity was present in 59% of untreated GDM, 18% of treated GDM, and in 11% of nondiabetic subjects (Langer et al., 2005). The most common complication was macrosomia/LGA which affected 46% and 19% of the newborns from treated and untreated mothers with gestational diabetes, respectively. The incidence of fetal death was 5.4, 3.6, and 1.8 per 1000 in untreated, treated, and nondiabetic mothers, respectively. Some gestational diabetic patients are at higher risk for complications than others (Box 17-10). The most important of these conditions are maternal obesity and hyperglycemia. Women at high risk should be identified soon after the diagnosis is made, because they need antepartum fetal surveillance testing and may require delivery before their EDD (expected date of delivery).

Fetal macrosomia

Fetal macrosomia, defined as an estimated fetal weight (EFW) equal to or larger than 4000 g, is a common occurrence in pregnant diabetics and particular efforts should be directed toward its diagnosis and management. Hence, all pregnant diabetics, perhaps with the exception of those who are not obese and have normal fundal height measurements, should have ultrasound examinations of the fetus every 4 weeks, starting at 20 weeks of gestation, to estimate the EFW and follow the fetal growth. Usually the first indication of developing macrosomia is an abdominal circumference larger than other measurements, resulting in abnormally elevated head to abdomen and femur to abdomen ratios. The EFW may be in the 60th–80th percentile between 26 and 32 weeks but by the end of the pregnancy will be above the 90th percentile.

The positive predictive value for the detection of macrosomia exceeds 90% when the abdominal circumference or the EFW is above the 95th percentile. However, there is a significant margin of error, and the baby's birth weight may differ from the ultrasonic estimation of fetal weight by as much as 25% (Farrell et al., 2004). This translates into an error of as much as 1000 g if the EFW is 4000 g.

The management of macrosomia is controversial. Most authorities agree that primary cesarean section is justified if the EFW at the end of the pregnancy is 4500 g or more. The controversy arises when the EFW is between 4000 and 4500 g. Some investigators argue that in the macrosomic fetus of the diabetic mother the shoulder and trunk fat pads are relatively larger than the head, favoring shoulder dystocia at the time of birth. For this reason, these authorities advise cesarean delivery for infants of diabetic mothers (IDM) if the infant's estimated weight is greater than 4000 g. Others believe that the margin of error of sonographic weight estimates in patients at term and the relatively small number of fetal injuries, approximately 1 in each 500 deliveries, when the fetus is between 4000 and 4500 g do not justify cesarean delivery.

Despite the existence of balanced arguments in favor of vaginal delivery and cesarean section, the present medical—legal climate in USA definitely inclines the balance in favor of cesarean delivery when the EFW is 4000 g or larger. If the patient is allowed a trial of labor, cesarean section should be performed with the development of any abnormality of labor such as protracted active phase or protracted descent, failure to descend, or secondary arrest of cervical dilatation. No vacuum or forceps should be used in these patients. Persistent occiput posterior presentations that do not rotate spontaneously should be delivered by cesarean section. Finally, the obstetrician should be prepared for the possibility of shoulder dystocia and

should be versed in the maneuvers necessary to relieve it. (For management of shoulder dystocia see the chapter on Prolonged gestation.) Also, if the EFW is closer to 4500 than to 4000 g it is better to proceed to a primary cesarean delivery.

Another problem related to fetal macrosomia is the practice of induction of labor 2 or 3 weeks before the EDD. The rationale of this practice is to avoid cesarean section that may be necessary if the baby remains "in utero" and continues to grow for 2 or 3 more weeks. There is no evidence that this is true, and some studies suggest that the fetal weight increase plateaus in the last 3 or 4 weeks of gestation. There are two conditions that are indispensable for this approach to be successful. First, it is necessary to have evidence of adequate fetal lung maturity if induction of labor is performed before 37 weeks. Secondly, the patient must have a ripe cervix with a Bishop's score of 6 or more because otherwise the risk of cesarean will be greater than 50%. If the cervix is unfavorable it is better to wait for cervical ripening or spontaneous labor. The probabilities of vaginal delivery of a large baby are better following spontaneous labor than after induction with cervical ripening agents.

Blood Glucose Monitoring

The obstetrician, a nurse, or a diabetes educator should inform the patient about the advantages of home glucose monitoring. Patients should be instructed in the correct technique to measure their capillary glucose (CG) levels using their own machine. Emphasis should be placed on the small details so that consistent and reliable results are obtained. The patient should perform the procedure several times under observation so that she may develop a proper technique. The patient should learn the blood glucose values above or below which she should call the physician for further instructions. Women with gestational diabetes should measure the fasting and the 1- or 2-hour postprandial CG using their own glucometer. Occasionally it will be necessary to measure the blood glucose levels before meals and during the night. The objective of treatment is to maintain the fasting capillary glucose (FCG) under 95 mg/dl and the 1- or 2-hour postprandial under 140 mg/dl and 120 mg/dl, respectively. The limit for preprandial blood glucose is 110 mg/dl. Patients with newly diagnosed gestational diabetes should meet these criteria within 2 weeks of the institution of dietary regulation or they need reevaluation of their therapy. Persistent elevations of the FCG indicate increased hepatic neoglucogenesis and require treatment with glyburide and possibly with insulin. Abnormalities in postprandial glucose can usually be corrected by dietary manipulation.

Nutritional Treatment

Women with gestational diabetes should be counseled by a nutritionist who will obtain a nutritional history and instruct them about the caloric requirements of pregnancy, the caloric value of different foods, the importance of meal timing, the need for a balanced diet, and other aspects of a healthy meal plan. This knowledge will be reinforced in follow-up visits. Proper nutrition is the most important component of the care of GDM and the objective is to provide the calories and nutrients necessary for the mother and the fetus without causing postprandial hyperglycemia. Unfortunately, this is a goal difficult to achieve. Ethnic origin, socioeconomic conditions, individual preferences, and numerous misconceptions are some of the factors that make the dietary management of diabetic pregnancies difficult. In large medical centers the physician has the help of professional nutrition specialists, but this is not true for most obstetricians working in small communities where they are the only source of information and guidance.

The first important concept in the dietary management of the GDM and any other diabetic pregnant woman is that a healthy diet for them is not different from a healthy diet for any other nondiabetic pregnant woman. However, she should know that food, particularly the carbohydrate content of the food would increase her blood glucose levels above normal limits and that persistently abnormal elevations of the blood glucose levels are harmful to almost all the cells in the body. To be able to control the abnormal elevations of blood glucose the diabetic patient needs to understand the quantity or servings of carbohydrate present in her meals and snacks and the effects of different types of carbohydrate on her blood glucose levels. As long as these basic concepts are understood and result in a healthy meal plan, pregnant diabetics can eat the same foods as people without diabetes.

Total daily caloric intake

The first step in the meal planning for GDM or other pregnant diabetics is to calculate the optimal total daily caloric intake. The total daily caloric intake is responsible for the weight gained during pregnancy, and excessive weight gain causes insulin resistance and increases diabetogenic tendency. There is controversy about how much weight should be gained during pregnancy by women with diabetes. The classic teaching is that these women should gain approximately 25 lbs and should not persistently spill large amounts of acetone in the urine. However, women weighing more than 150% of their ideal weight should gain less than 15 lbs or have no weight gain during their pregnancies. Studies have demonstrated that newborn birth weight is optimal when morbidly obese women gain less than 3 kg or gain no

weight during pregnancy (King and Allen, 1990). One argument against obese GDM women losing weight or gaining too little weight during pregnancy is that when the caloric intake is limited, they metabolize fat for energy purposes with development of starvation ketosis. However, elimination of small or moderate amounts of acetone in the urine is not necessarily a poor prognostic sign, and dietary intervention is more effective in preventing fetal macrosomia if the mother is maintained just above the ketonuric threshold (Jovanovic-Peterson and Peterson, 1990).

Calculation of the total daily caloric intake is based on the number of calories necessary to maintain 1 kg of body weight, which is 30 kcal for the average normal-weight women (80–120% ideal body weight), 35–40 kcal for women who are underweight (less than 80% ideal body weight), 25 kcal for overweight women (121–150% ideal body weight), and 12 kcal/kg for morbidly obese women (more than 150% ideal body weight). This number is multiplied by the body weight in kilograms to obtain the total number of calories that the patient should consume during a 24-hour period (Box 17-11). When the patient strictly follows this recommendation the weight gain during pregnancy will be minimal or nonexistent.

For the majority of women with GDM the optimal total daily caloric intake will be between 2000 and 2500 cal/day. In the third trimester of pregnancy, when the caloric needs of the mother are increased, it is prudent to add 300 kcal to cover the additional caloric needs of the pregnancy. The total caloric intake is split into three meals and one to three snacks depending on the patient's habits. Many can have one snack at mid-morning, a second in mid-afternoon and a third at bed time while many others prefer only one snack at bed time or no snacks at all.

The total daily caloric allowance should be distributed among the different food groups in such a way that approximately 40–50% of the calories come from complex carbohydrates. The carbohydrate content of the diet should be distributed as 10–15% at breakfast, 20–30% at lunch, and 30–40% at dinner. Snacks should have 0–10% of the total carbohydrates. The rest of the caloric intake comes from fat (30–40%), predominantly unsaturated, and protein (Peterson and Jovanovich-Peterson, 1990). However, it is important to be flexible and accommodate the individual patient's habits. For example, some women like most of their carbohydrates at breakfast and as long as this is not reflected in a large increase in post breakfast glucose, they should have their choice.

BOX 17-11

Ideal body weight and recommended caloric intake during pregnancy

Height (without shoes)	Nonpregnant ideal body weight (kg)	Recommended caloric intake (35 kcal/kg)
4′10″	48.6	1701
4′11″	50.0	1750
5′0″	51.4	1799
5′1″	52.7	1845
5′2″	54.1	1894
5′3″	55.9	1957
5′4″	58.2	2037
5′5″	60.0	2100
5′6″	61.8	2163
5′7″	63.6	2226
5′8″	65.7	2300
5′9″	67.3	2356
5′10″	69.1	2419

According to Metropolitan Life Insurance tables.

Carbohydrate counting

Postprandial elevations of blood sugar are due almost exclusively to the carbohydrate content of the diet. Therefore the dietary care of the diabetic patient should consist of determining the amount of CHO ingested with meals and snacks, so-called "carbohydrate counting." Carbohydrate counting estimates the amount of CHO in a meal by determining CHO servings. Each 15 g of CHO is equivalent to one CHO serving. Examples of one serving of CHO are one small apple, four to six crackers, half a cup of ice cream, one cup of fat-free milk, and one-fourth of a large baked potato. When a healthy meal plan is elaborated for a person with diabetes and pregnancy, it is necessary to plan in advance the number of CHO servings that will be consumed with each meal or snack. For a 2200 cal diet, four CHO servings at breakfast, four at lunch, five at supper, and two servings with each mid-morning, mid-afternoon, and bed time snacks will provide approximately 285 g of CHO with a caloric value of 1140 kcal. The other 50% of the caloric intake will come from fat and protein. Most of the dietary CHO should be in the form of complex carbohydrates, but this does not mean that other sugars are prohibited as long as the prescribed daily amount of CHO is not exceeded. The ability to substitute different foods—keeping in mind the necessary limitations in CHO and caloric ingestion—has made the dietary management of the diabetic easier and has increased compliance with the meal plan. In the present era the diabetic can eat the same food that the nondiabetic as long as carbohydrate and caloric counting are performed and the limits established in the healthy meal plan are not exceeded.

The majority of the dietary carbohydrate of the diabetic should be in the form of unrefined, high-fiber foods. There are two types of dietary fiber. Insoluble fiber increases the fecal bulk and accelerates the gastrointestinal transit time

but has little effect on the blood glucose. In contrast, soluble fiber found in vegetables, fruits, and legumes reduces glucose absorption from the intestine, slowing the rise in postprandial blood glucose and decreasing the requirements for prandial insulin.

Women with GDM should be instructed to determine the CHO serving's content of food by looking at the serving size and total carbohydrate information contained in the Nutrition Facts food label of canned and packed products. To determine the CHO content of food without Nutrition Facts labels such as meats and fruits, patients should buy one of the many available books containing this information. There are also numerous Websites about nutrition that are useful to women with diabetes and pregnancy. It should be emphasized that the serving size is important because the information about the carbohydrate content of the food is based on one serving and not on the whole content of the food package. For example, the Nutrition Facts label on a box containing 10 ice cream bars will state that the serving size is 1 bar and the carbohydrate content per serving is 30 g. This means that 1 bar of ice cream is equivalent to 2 CHO servings.

Glycemic index

Different carbohydrate products have different impacts on blood glucose levels. To account for these differences the concept of the glycemic index has been developed. The glycemic index of a particular carbohydrate is the blood glucose response to that product in a given period of time compared to the blood glucose of a similar amount of carbohydrate in a standard food, usually white bread. For example, one serving of corn flakes or baked potatoes results in a higher blood glucose level than a serving of fruit or ice cream. Several studies in nonpregnant populations have demonstrated that ingestion of carbohydrates with low glycemic index results in better blood glucose control and better serum lipid profiles.

Other components of the meal plan

In addition to CHO, a healthy meal plan should contain specific instructions about servings of protein and fat. Meats and fat have little effect on blood sugar levels but they contain calories which could have a significant impact on weight gain. For a 2200 cal diet the total daily requirement of protein is fulfilled with about 6 oz of meat or meat substitute (cheese, eggs, nuts). Ideally, meats or meat substitutes should have 3 g or less of fat per 1 oz and it is important to limit the consumption of saturated fats such as bacon, butter, and cream. The type of fat is also important and patients should be told that unsaturated fats such as olive or canola oil have the same calories as saturated fat but they have significantly less effects on the heart and blood vessels.

Some patients find that the amount of food provided by their new diet exceeds what they were ingesting prior to pregnancy. Usually these are patients who had been on caloric restricted diets before pregnancy. In these cases, the caloric intake can be reduced to 20–25 cal/kg of ideal weight until the patient feels comfortable with the diet. It is customary to check the urine for ketones in women ingesting a low number of calories and if the urine starts to show consistently marked acetonuria (>3+ in qualitative examination) the amount of dietary CHO needs to be increased. Ketonuria in these cases is the result of starvation ketosis. If ketonuria disappears when the caloric intake is increased to a point that precipitates postprandial hyperglycemia, the patient needs treatment with glyburide. The other indication for glyburide treatment is persistent elevation of the FCG.

Glyburide

The treatment of gestational diabetics poorly controlled with diet has dramatically changed since the demonstration of the effectiveness and lack of fetal effects of glyburide (Langer et al., 2000). Before this finding these women were treated with insulin and frequently required large doses to overcome their insulin resistance. In this study 404 women with gestational diabetes and requiring pharmacologic treatment were randomized to receive either insulin or glyburide, and the maternal and neonatal outcomes were not significantly different. Only 4% of women in the glyburide group were not adequately controlled and required insulin treatment. No glyburide was present in the umbilical cord serum of any newborn. The usual starting dose of glyburide is 2.5 mg once or twice daily but some patients are well controlled with 1.25 mg once or twice daily. The total daily dose may be increased up to 20 mg daily if necessary. The peak plasma level occurs 2–4 hours after administration and the duration of action is 10–12 hours. Women with fasting hyperglycemia and normal prandial blood glucose levels may do well with a single dose of glyburide at bed time. Glyburide is a sulfonyl urea and its primary mechanism of action is stimulation of the release of insulin from the storage granules of the pancreatic beta-cells. This effect is secondary to closure of the potassium channels and influx of intracellular calcium. Secondarily glyburide decreases insulin resistance. Gestational diabetics requiring pharmacologic treatment with glyburide should follow similar programs with respect to blood glucose monitoring, antepartum testing, and intrapartum management as that followed by gestational diabetics receiving insulin. The main side effect of glyburide is hypoglycemia. Glyburide is nonteratogenic and is classified as a category B drug.

Insulin

Approximately 4–10% of gestational diabetic women on glyburide will require insulin for metabolic control. They should be instructed on the properties of the different types of insulin. The onset, the peak of action, and the duration of action of different insulins are concepts that the patient should firmly grasp. The concentration of insulin in units per milliliter and the measurement of a given number of units in insulin syringes are important points of the instruction. The patient should be taught to inject herself using an aseptic technique, and to alternate the sites of injection. Using sterile distilled water, the patient should practice by injecting an orange. The instructor should use this opportunity to correct mistakes and improve her technique. Ideally, the patient will be supervised the first few times, to assure that she does not make any serious errors.

Patients receiving insulin for the first time must be instructed on how to recognize and treat hypoglycemic reactions. They should be instructed to carry glucose tablets or candy with them for ingesting when hypoglycemia develops and other carbohydrates are not immediately available. Also, the patient and her husband should be instructed on the administration of glucagon in cases of severe hypoglycemic reactions.

The most common indication for insulin treatment in GDM women is persistent elevation of the FCG value. This reveals altered hepatic neoglucogenesis not modified by glyburide. The large majority of these patients do fine with a single injection of intermediate- or long-acting insulin. We prefer insulin glargine (Lantus), starting with a dose of 20 U in the morning. A second choice is 10 or 15 U of NPH insulin at bed time. Postprandial hyperglycemia can be modified by dietary intervention and only a few GDM women will require short-acting insulin (Humolog or Novolog) before meals. The interested reader will find more information about insulin therapy in the section on Type I diabetes.

Fetal Surveillance

Low-risk gestational diabetic patients who achieve adequate control with diet alone and do not develop macrosomia, polyhydramnios, or preeclampsia do not require antepartum fetal surveillance testing before 40 weeks. In fact, the risk of fetal distress in these patients is as low as in nondiabetics and fetal well-being can be assessed by teaching the patients about fetal movements and asking them to fill up a chart for kick counts. On the other hand, high-risk gestational diabetics and patients on glyburide and/or insulin should have antepartum fetal surveillance testing starting at 32–34 weeks of gestation. There is no consensus as to what is the best test for these patients. Weekly or twice-weekly nonstress tests (NST) are the most popular. However, the biophysical profile (BPP), the modified biophysical profile (MBPP), and the contraction stress test are also used. We prefer to use a weekly or twice per week MBPP.

Delivery

There is no reason to deliver low-risk gestational diabetics before term. They may be allowed to develop spontaneous labor and to deliver at term. Once the uncomplicated gestational diabetic reaches 40 weeks, labor should be induced irrespective of cervical ripening or the patient should be delivered by cesarean if the EFW is > 4000 g. In women with an unripe cervix, induction should be preceded by cervical ripening with misoprostol or a prostaglandin E derivative. However, induction failure is frequent and cesarean may be necessary in up to 50% of these patients.

High-risk gestational diabetic patients should have their labor induced when they reach 38 weeks with the exception of those with a macrosomic fetus (EFW > 4000 g) who should be delivered by cesarean section because of the increased risk of shoulder dystocia. When the decision is induction of labor and the cervix is unripe it is necessary to use cervical ripening agents before induction of labor. Unfortunately, in many cases induction of labor is unsuccessful and cesarean delivery will be required.

Most insulin-treated GDM do not need insulin during labor or after vaginal or cesarean delivery. Usually CBG is measured every 2–4 hours during labor and upward deviations from normal are corrected with small doses of Regular insulin or low-dose IV insulin to maintain the blood glucose between 100 and 120 mg/dl. Occasionally, low blood glucose levels will need correction with 50–100 ml boluses of D5NS.

Gestational diabetes may reoccur in a future pregnancy and approximately 55% of patients, usually those who are obese or with prior macrosomic infants, will show glucose intolerance in a subsequent pregnancy (Philipson and Super, 1989). It is important to perform a 75 g GTT after delivery in gestational diabetics who required treatment with glyburide or insulin, had elevated fasting serum glucose levels during pregnancy, or had the diagnosis of gestational diabetes before 24 weeks. In these patients the incidence of type II diabetes is between 9 and 44% (Kjos et al., 1990). Other gestational diabetics should occasionally measure their fasting and postprandial blood sugars during the first 6 weeks postpartum to be certain that the abnormality has disappeared. In the majority of cases the need for a restricted diet or insulin disappears following delivery.

Gestational diabetics should be informed that they are at high risk for becoming type II diabetics later in their lives. Roughly 40–60% will be overt diabetics when they

are in their fifth decade. Weight loss, dietary control, and exercise will obviously help to prevent overt diabetes later in life (Grant et al., 1986).

TYPE II DIABETES

Type II diabetes is the predominant form of diabetes in USA especially among African-Americans and Mexican-Americans. Type II diabetes rarely occurs before 25 years of age and has a strong hereditary component. Obesity and especially abdominal obesity (waist to hip ratio greater than 0.9) is a major risk factor. Hypertension, dyslipidemia, and low socioeconomic status are other important risk factors. In these patients the main pathogenic factor is insulin resistance that initially is compensated by increased production of insulin by the pancreas. With persistent insulin resistance, there is a loss of the compensatory beta-cell ability, beta-cell exhaustion, and minimal insulin production. Blood glucose values increase progressively with duration of the diabetes as a result of decreasing beta-cell function. Once insulin production is compromised, type II diabetics behave similarly to type I diabetics with unrestrained glucose production by the liver and poor glucose utilization in the muscle and adipose tissue. However, since the secretion of endogenous insulin is not completely suppressed, ketogenesis is inhibited and diabetic ketoacidosis (DKA) is rare. Polyuria and polydipsia are usually mild. These patients follow a predictable course of increasing insulin requirements with the progression of pregnancy. The prognosis is usually good and the main complication is fetal macrosomia. The exact locus of the insulin resistance in these patients is unknown.

The American Diabetes Association defines insulin resistance as an impaired metabolic response to either exogenous or endogenous insulin. Unfortunately, the glucose clamp technique that is the most accurate test to measure insulin sensitivity is expensive, labor intensive, and is mostly used as a research technique. The alternative is to use fasting levels of insulin and glucose, levels of C-peptide, or the 3-hour GTT, which are indirect and imprecise measures. A fasting glucose (mg/dl) to insulin (μIU/ml) ratio of less than 4.5 has been used as a surrogate index of insulin resistance. Another method is to measure insulin levels simultaneously with glucose levels at the time of the 3-hour GTT. Peak insulin levels during the test are under 100 μIU/ml. Values between 100 and 150 μIU/ml indicate mild insulin resistance, between 150 and 300 μIU/ml indicate moderate insulin resistance, and values greater than 300 μIU/ml indicate severe insulin resistance.

Metabolic Syndrome

The metabolic syndrome, syndrome X, insulin resistance syndrome, or deadly quartet, is closely associated and frequently precedes the development of type II diabetes. This syndrome has been defined by the World Health Organization and the National Cholesterol Education Program's Adult Treatment Panel III as shown in Box 17-12. Although the definitions vary, they agree in the four fundamental components of the syndrome: glucose intolerance, obesity, hypertension, and dyslipidemia.

BOX 17-12

Definition of the metabolic syndrome according to the World Health Organization and the National Cholesterol Education Program Adult Treatment Panel III (NCEPATPIII)

World Health Organization

- Diabetes, impaired glucose tolerance, impaired fasting glucose and/or insulin resistance

Plus at least two of the following:

- Abdominal obesity (waist to hip ratio > 0.85 in women or > 0.9 in men and/or body mass index > 30 kg/m^2)
- Triglycerides > 150 mg/dl and/or HDL < 40 mg/dl in women or < 35 mg/dl in men
- Blood pressure ≥ 140/90 mmHg
- Microalbuminuria: urinary albumin excretion ≥ 20 μg/minute or albumin to creatinine ratio ≥ 30 mg/g

NCEPATP III

At least three of the following:

- Fasting plasma glucose > 110 mg/dl
- Abdominal obesity (waist circumference > 35 in. in women or > 40 in. in men)
- Triglycerides > 150 mg/dl; HDL < 50 mg/dl in women or < 40 mg/dl in men
- Blood pressure ≥ 130/85 mmHg

The metabolic syndrome is age dependent and in the USA is present in 7% of individuals between 20 and 29 years of age and in 44% of those aged 60–69 years (Ford et al., 2002). The syndrome is closely associated with type II diabetes and with cardiovascular disease. It is present in 23% of women older than 20 years, reflecting the increased frequency of obesity that is the number one health problem in USA. Identification of type II diabetics with metabolic syndrome is important because they need lifestyle modifications to avoid morbidity and particularly to avoid death from cardiovascular disease.

Nutritional Treatment

Like any other diabetics, an adequate nutritional plan is a fundamental part of the management of pregnant type II diabetics. As mentioned before the basic pathophysiology of their diabetes is insulin resistance and one of the most effective ways to modify this fundamental problem is caloric restriction to limit the weight gain during pregnancy to the minimum, consistent with adequate fetal growth. The nutritional plan for type II diabetics has the following objectives:

1. To maintain a total caloric intake adequate for the caloric needs of the pregnant woman but allowing minimal weight gain.
2. To minimize wide variations in postprandial CG values by consuming a predetermined number of CHO servings with each food and snacks.

Minimal weight gain during pregnancy includes the weight of the products of conception (fetus, placenta, amniotic fluid), the additional weight caused by uterine and breast hypertrophy, and the weight derived from the increase in blood volume that occurs during pregnancy. This minimal pregnancy-related weight gain is between 15 and 20 lbs which is the maximum weight gain that ideally should be attained by pregnant type II diabetics. It is even better not to gain weight because this represents a loss of 15–20 lbs during the pregnancy which will have a significant impact in insulin resistance and in blood glucose levels. Unfortunately, few type II diabetics are capable of maintaining a minimal weight gain or no weight gain during pregnancy. Studies in nonpregnant populations indicate that less than 40% of the diabetics ate within 20% of their prescribed caloric intake and there is significant variation from day to day in the consumption of carbohydrates, protein, and fat (Close et al., 1993). However, the problem of maintaining a minimal weight gain or losing weight is not entirely due to dietary indiscretions. A large part of this problem may occur as a result of the decrease in metabolic rate that follows caloric restriction in the diet.

The effects of caloric restriction in blood glucose levels can be appreciated in a few days, probably because of the decrease in hepatic glycogen content and hepatic glucose output caused by the diet. The possibility of success is determined, to a large extent, by the fasting blood glucose levels. The general rule is that the higher the fasting blood glucose, the greatest the weight loss that will be required to normalize the blood glucose levels.

To determine the total caloric intake, the carbohydrate content of the meals, and the caloric index of different carbohydrates the reader is referred to the topic on "Nutritional management" in the section on Gestational diabetes.

Glyburide

The large majority of type II pregnant diabetics need pharmacologic therapy that was traditionally provided with insulin. This has changed since the demonstration of the benefits on blood glucose control and lack of fetal/neonatal effects of glyburide. Glyburide is a sulfonylurea which acts by closing potassium channels in the cell membranes of the pancreatic beta-cells, causing calcium influx and secretion of insulin from storage granules. Secondarily glyburide causes decreased insulin resistance. Because of its mechanism of action, glyburide is more effective in normal weight or moderately obese type II diabetics who have had diabetes for less than 5 years and still have good beta-cell function. Glyburide is more effective when taken in two daily doses. For most patients the initial dose is 1.25 or 2.5 mg twice daily. However, if the FCG is greater than 200, they may be started at 5 mg twice daily. The maximum dose is 10 mg twice daily.

The main side effects of glyburide are hypoglycemia and weight gain. Hypoglycemia may be severe and when it occurs, the patient needs to be admitted to the hospital for closer observation since the effects of glyburide may last for up to 7 days. Weight gain is related to the stimulation of insulin secretion by glyburide and is not apparent with other hypoglycemic agents that act by decreasing insulin resistance.

Insulin

Pregnant women with type II diabetes and persistent hyperglycemia despite adequate nutritional intake and therapy with glyburide require insulin therapy. The majority will respond to continuation of treatment with glyburide plus a single injection of glargine insulin (Lantus) in the morning or NPH at bed time. The rationale for using a combination of oral hypoglycemic agent plus insulin is that insulin can suppress hepatic neoglucogenesis, which is the primary cause of elevated fasting hypoglycemia. Also, there is evidence in nonpregnant subjects that combination therapy is more beneficial than insulin alone (Johnson et al., 1996). The usual starting dose is 20 U subcutaneously of either product. The use of insulin glargine results in less episodes of nocturnal hypoglycemia than that of NPH. The optimal time for insulin administration depends of the type of insulin being used. NPH seems to be more effective at bed time while insulin glargine provides better control when given in the morning. If the CG values remain elevated when using insulin glargine, the dose may be increased by 5 U every 5 days until adequate blood glucose control is obtained. Once the daily dose of insulin glargine reaches an amount equivalent to the total insulin requirements of an insulinopenic patient (0.6–1.0 U/kg depending of the trimester of pregnancy), it is not necessary to continue the administration of glyburide. An obese patient with a total daily requirement of 0.8 U/kg may require as many as 50–75 U/day of insulin glargine given in a single dose every morning in order to achieve normalization of blood glucose values.

Markedly obese pregnant women with type II diabetes may require large amounts of insulin for control of the blood glucose levels. Doses of 1 U/kg are common and occasionally some patients may require more than 400 U/day. In these cases the use of Regular insulin

U-500 is useful to avoid the injection of large volumes of medication.

Type II diabetics rarely develop ketoacidosis. On the other hand, they may develop hyperosmolar hyperglycemic nonketotic coma, or HHNC, which is characterized by marked hyperglycemia (>600 mg/dl) and serum hyperosmolarity (>320 mOsm/L) in the absence of ketonemia. Patients with HHNC are severely dehydrated and have a preponderance of neurologic symptoms. The fluid deficit may be as large as 12 L and these patients require aggressive hydration, insulin, and potassium. This complication occurs more frequently in elderly diabetics or in patients who have had disease for a long time and is rarely seen during pregnancy.

Assessment of Blood Glucose Control

The impact of treatment on blood glucose control is assessed by daily measurements of CBG and by determining the concentration of hemoglobin A1C (HbA1C). CG should be obtained during fasting, 1 or 2 hours after meals, and at bed time. The choice between 1- or 2-hour postprandial is that of a patient. More patients tend to forget the 2-hour measurement and prefer to do the assessment 1 hour after meals. Occasionally it is necessary to measure the blood glucose level before meals, but the need for this measurement is rare if the patient is managed with insulin glargine and fast-acting analogues.

HbA1C is the product of the nonenzymatic glycosylation of hemoglobin and reflects the average blood glucose levels for the preceding 2–3 months. The upper limit of normal HbA1C concentration is 6% and this is the target to be achieved with the medical management of type II diabetics. Although in type II diabetes there is a good correlation between CG values and concentration of HbA1C, it is recommended to measure the concentration of HbA1C each trimester of pregnancy to have evidence of the adequacy of metabolic control. An HbA1C of 8% reflects a mean blood glucose level of 180 mg/dl. This value changes by 30 mg/dl for each 1% above or below 8%.

Another glycosylated product with some value in the assessment of blood glucose control is fructosamine. This test measures a variety of serum proteins that have been glycosylated and reflects the overall blood glucose control in the 2 weeks before the measurement. Fetal hyperinsulinism is rare at fructosamine levels below 2.6 mmol/L (Hofmann et al., 1990).

TYPE I DIABETES

Preconceptional Counseling

Occasionally women with type I and type II diabetes are referred by their primary care provider for preconceptional counseling so that they can acquire a clear understanding of the characteristics and demands of their care during pregnancy. The counseling of the diabetic patient planning pregnancy should emphasize the following points.

1. The importance of blood glucose control

The patient should be informed that inadequate blood glucose control often results in a higher incidence of first trimester abortion, fetal congenital abnormalities, fetal macrosomia, polyhydramnios, and stillbirths. She should understand that the frequency of these abnormal outcomes approaches that of the nondiabetic population if the blood glucose is strictly controlled before conception and during the pregnancy. It is noteworthy that the highest risk of fetal malformations is during the periconceptional period and the period of organogenesis and that the risk can be greatly reduced by adequate glycemic control before and during early pregnancy (Kitzmiller et al., 1991). The fear of anatomic deformities in the offspring is powerful motivation to control blood glucose levels before conception.

2. The importance of self-monitoring of blood glucose

The next step is to emphasize that strict control is best achieved through self-monitoring of blood glucose levels. The patient should be informed that frequent measurements are critical because they allow early detection and immediate correction of abnormalities. The patient should be told that pregnancy will produce various gastrointestinal symptoms that will cause fluctuations in the ingestion of food and, therefore, in blood glucose levels. She should also understand that during pregnancy the fetus continuously obtains nutrients from the mother and this, combined with the other factors mentioned, produces significant changes in blood glucose levels that need to be recognized promptly to institute appropriate therapy. It should also be emphasized that frequent monitoring will decrease the probability of serious complications, such as ketoacidosis, because alterations in blood glucose levels will be detected and treated before metabolic derangement occurs.

3. The importance of fetal surveillance

The different problems affecting the fetus as well as the methods for their detection should be explained during preconceptional counseling. Emphasis should be placed on the problem of diabetic embryopathy and the need for determination of glycohemoglobin early in pregnancy, screening for aneuploidy in the first or the second trimester, a fetal anatomical survey at about 20 weeks, and a fetal echocardiogram at about 24 weeks to rule out the most common fetal abnormalities. Fetal growth

should be followed with serial ultrasound examinations to detect macrosomia or growth retardation. Fetal well-being should be assessed during the last several weeks by using tests such as the nonstress test or the MBPP. The reasons for these tests should be carefully explained to the mother to increase her motivation and compliance.

4. The cost of the diabetic pregnancy

The prospective pregnant diabetic frequently does not realize the amount of time that she will spend in providing adequate care for her pregnancy. In many cases, the patient has a demanding job that is incompatible with frequent office visits and intense perinatal testing. She may need to leave her job, adding financial strain to those already present. Also, medical disability plans and insurance programs frequently do not cover the time loss and the expenses associated with the care of a complicated pregnancy. Patients should be encouraged to discuss potential medical leaves with their employer and to obtain detailed information from their insurance providers regarding potential limitations of coverage.

Maternal Complications

Pregnancy has a negative effect on diabetes and may cause worsening of many diabetic associated abnormalities (Box 17-4). The primary negative effect is on blood glucose control which becomes significantly more difficult when the insulin resistance of pregnancy is added to the insulinopenia of type I diabetes. Pregnancy also increases the tendency toward starvation ketosis and DKA due to the enhanced lipolytic activity of pregnancy. In addition, pregnancy aggravates or worsens the microvascular damage caused by diabetes in target organs. One example is the aggravation of proteinuria and development of nephrotic syndrome in the pregnant women with diabetic nephropathy. Another example is the worsening of diabetic retinopathy that frequently occurs during pregnancy. Pregnancy-associated complications are more common in diabetics and the incidence of preeclampsia is two to three times that in the nondiabetic population.

Fetal/Neonatal Complications

IDM have significant problems that may be preventable by prepartum intervention. The obstetrician caring for pregnant diabetics should explain these problems to the mother as part of the preconceptional or the pregnancy counseling. The most common problems affecting the infant of the diabetic mother are the following:

1. Congenital anomalies
2. Neonatal hypoglycemia
3. Neonatal hyperbilirubinemia
4. Neonatal respiratory distress syndrome (RDS)
5. Hyperviscosity syndrome
6. Feeding difficulties

Congenital anomalies

Congenital abnormalities are the most frequent cause of neonatal mortality and morbidity in the pregnant diabetics. This problem is potentially preventable through strict control of maternal blood sugar levels in the periconceptional period.

Neonatal hypoglycemia

Neonatal hypoglycemia is the problem that most frequently affects IDM. In the majority of cases, neonatal hypoglycemia is secondary to excessive insulin production by the newborn's pancreatic beta-cells which are enlarged and hyperactive as a result of maternal hyperglycemia. Strict regulation of blood sugars in the days prior to delivery may prevent this problem.

Neonatal hyperbilirubinemia

Neonatal hyperbilirubinemia is a frequent problem in the IDM, usually caused by immaturity of the infant's liver function and specifically of the bilirubin catabolic system, glucuronyl transferase. Maternal administration of medications that induce the production of the necessary enzymes for bilirubin degradation may prevent hyperbilirubinemia. Phenobarbital offers promise in this respect, but more research is necessary before it can be adopted into routine clinical use.

Neonatal RDS

Neonatal RDS secondary to hyaline membrane disease has decreased significantly during the past decade. Among the most important factors responsible for this decrease are the availability of better tests to determine fetal pulmonary maturity and the decreased frequency of diabetic patients delivering preterm. However, cases of RDS secondary to pulmonary hypertension or to diabetic myocardiopathy still occur sporadically.

Hyperviscosity syndrome

Hyperviscosity is diagnosed when the neonatal hematocrit is 65% or more. Many of these infants are asymptomatic but others present with RDS, necrotizing enterocolitis, renal vein thrombosis, or cerebral infarcts. The cause of this abnormality is not completely clear, but the evidence suggests that it is due to excessive production of erythropoietin in response to chronic fetal hypoxia.

Feeding problems

Poor feeding is a common problem in IDM and is often associated with other neonatal complications. It is also a common reason for prolonged stays in the nursery. Prevention of this problem requires more knowledge about its etiology.

Incidence

The incidence of type I diabetes in the obstetrical population is 1 in 200 to 1 in 1000. Most of these patients have their diabetes diagnosed before pregnancy and know how to self-administer insulin and to use a glucometer. Many of them are compliant, measure their blood sugars frequently, and follow their diets. Some of them have difficulties with the life modifications introduced by the diabetes treatment, are not compliant, and are more difficult to manage. They require continuous efforts to improve their education and their motivation so that they will meet the multiple demands of their pregnancies.

Objectives of Prenatal Care

The care of type I diabetes during pregnancy has the following objectives:

1. Detection of diabetic embryopathy
2. Strict control of blood sugar levels
3. Detection of fetal macrosomia
4. Detection of fetal distress and prevention of antepartum death
5. Timing the delivery to improve maternal and fetal outcome
6. Choose between cesarean or vaginal delivery to improve maternal and fetal outcomes
7. Adequate intrapartum and postpartum management

In addition to these objectives the obstetrician or the maternal–fetal medicine specialist should be ready to take care of pregnant women with unstable diabetes and diabetics with end-organ damage.

Detection of Diabetic Embryopathy

The main cause of perinatal morbidity and mortality in type I diabetics is congenital malformations of the fetus (Box 17-13). The most frequent abnormalities involve the heart and the central nervous system. Most common are anencephaly, spina bifida, transposition of the great vessels, and ventricular septal defects. The lesion classically associated with diabetic embryopathy, the "caudal regression syndrome" is rare, with an incidence of 1.3 per 1000 diabetic pregnancies.

Efforts to detect diabetic embryopathy should start soon after conception by measuring the patient's glycosylated hemoglobin or HbA1C. As mentioned before, HbA1C results from the combination of hemoglobin and glucose by a nonenzymatic reaction that is directly dependent on the concentration of blood glucose. When this test is performed 4–6 weeks after conception it will reflect the levels of blood sugar that the patient had in the periconceptional period. There is good evidence indicating that levels of HbA1C greater than 8.5% are associated with a 20–25% probability of fetal developmental abnormalities. When the concentration of glycosylated hemoglobin is normal the probability of major malformations is less than 2%.

All type I and II diabetic women and particularly those at high risk for congenital malformations of the fetus as indicated by their HbA1C concentration should have vaginal probe ultrasound examination at 10–14 weeks. Some defects such as anencephaly and prosencephaly can be detected very early using this technique. Also, blighted ova will be easily detected at this time. This is also the optimal time for first trimester screening for aneuploidy, which includes measurement of the nuchal translucency of the embryo, which is frequently increased in chromosomally abnormal fetuses and in those with congenital heart disease, plus the measurements of free beta-HCG and PAPA-A (pregnancy-associated plasma protein A).

A negative first trimester screening is important but does not end the search for diabetic embryopathy. These women should have evaluation of the maternal serum alpha-fetoprotein (MSAFP) at 16 weeks to screen for open neural tube defects. MSAFP is one of the analytes included in the triple and quadruple screening tests. Normally, MSAFP is lower in diabetic women and the laboratory should make the necessary corrections. An abnormal MSAFP indicates the need for comprehensive ultrasound examination of the fetal spine and in a few cases the need for genetic amniocentesis.

BOX 17-13

Most common congenital abnormalities in infants of diabetic mothers

Central nervous system
- Anencephaly
- Holoprosencephaly
- Encephalocele

Heart and great vessels
- Transposition of the great vessels
- Ventricular septal defect
- Aortic coarctation
- Atrial septal defect

Skeletal and spinal
- Caudal regression syndrome

Genitourinary
- Renal agenesis
- Ureter duplex

Gastrointestinal
- Anal atresia

All type I diabetics, irrespective of the results of the first and second trimester screening, should have a detailed anatomical survey of the fetus or comprehensive ultrasound examination at 18–20 weeks of gestation. This will permit the detection of malformations not seen on earlier ultrasounds. The fetal survey must include a fetal echocardiogram, but in some cases this is not possible due to maternal obesity and fetal size and position. In those cases the fetal echocardiogram needs to be performed at 22–24 weeks. Unfortunately, some of the most common cardiac abnormalities associated with diabetes (transposition of the great vessels and aortic coarctation) are difficult to detect and require a considerable amount of expertise of the sonographer.

Blood Glucose Control

A fundamental objective of the care of every insulin-dependent pregnant diabetic is strict control of the blood glucose levels to achieve mean daily CBG ≤ 95 mg/dl. To obtain this objective the obstetrician uses nutritional and insulin therapy. To determine if this objective is being achieved patients should measure their fasting and 1- or 2-hour post prandial glucose levels daily. The concentration of CBG is determined by one of several commercially available instruments (Glucometer, Accu-check, Glucoscan, One-Touch, etc). The values obtained should be recorded with the time at which each measurement is made and the time of food ingestion. The patient should call the diabetic educator with the CBG results or bring this information to each prenatal office visit so that the obstetrician may adjust the patient's regimen as needed.

Nutritional therapy

All the nutritional considerations made in the case of gestational diabetes and type II diabetes apply to pregnant type I diabetics. In addition, women with type I diabetes receiving a combination of Regular and NPH insulin require consistent timing of their food intake to facilitate insulin dosage and avoid hypoglycemia. Strict timing is not as essential in type I diabetics using a combination of insulin glargine and insulin lispro or aspart.

Knowing the amount of CHO ingested with each meal or snack is essential to calculate prandial doses of insulin. Motivated patients can determine ahead of time how many servings of CHO they will have with each meal and, therefore, how many units of prandial insulin they will need. Other patients find it easier to ingest the same amount of CHO and use the same amount of insulin, at the same time every day. The important thing is to respect the patient's preferences because when the meal plan and the timing of eating is substantially different from what the patient is used to having, compliance with the dietary recommendations is rare.

Insulin therapy

Insulin therapy in type I diabetics should cover the basal needs (basal insulin) and the elevations in blood sugar that occur after meals (prandial insulin). In addition to basal and prandial coverage many patients require a correction-dose supplement to control sporadic elevations of the blood sugar. Regular and NPH insulin are the most commonly used preparations for the treatment of diabetes during pregnancy although the use of insulin lispro, insulin gargline, and insulin detemir is increasing rapidly. Both Regular and NPH contain insulin structurally identical to that produced by the human pancreas, which is obtained from bacteria genetically modified by the incorporation of the human insulin gene. As shown in Box 17-14, the time of onset and the peak of action of Regular and NPH insulin are different and when used in combination, each will have basal and prandial functions.

Regular insulin has a relatively slow absorption, making it necessary to administer at least 30 minutes before meals. Also the duration of action is relatively long and its peak of action frequently coincides with times of increased activity of NPH insulin, resulting in episodes of hypoglycemia in the interval between the three main meals. This tendency toward hypoglycemia necessitates the ingest of mid-morning and mid-afternoon snacks in the majority of patients treated with Regular/NPH combinations. The tendency for hypoglycemia between the main meals may be solved with the use of rapidly acting insulin analogues, the insulin lispro and the insulin aspart. Insulin lispro differs from Regular human insulin because the position of a proline and a lysine in positions 28 and 29 of the beta-chain is inverted—a change that results in a reduction in the formation of dimers and hexameres and accelerated absorption. In insulin aspart the proline in position 28 is substituted by aspartic acid achieving the same result. The peak of action of insulin lispro and insulin aspart is approximately twice as rapid as with Regular insulin, and the medication should be taken immediately before meals. These new insulins are used for prandial insulin and for insulin-pump therapy. They are

BOX 17-14

Time of onset and peak of action of insulins

Type of insulin	Onset (hour)	Peak (hour)	Duration (hour)
Regular	0.5–1.0	2–3	6–8
Lispro	0.25–0.5	1–2	4–6
Aspart	0.25–0.5	1–2	4–6
NPH	1.0	4–8	10–14
Glargine	1.5	None	30

better than Regular insulin for the control of postprandial elevations in blood glucose and for normalization of glycosylated hemoglobin in patients on insulin pumps (Raskin et al., 2001). With the use of rapidly acting insulin analogues, snacks between meals and at bed time become optional and the timing of the meals does not need to be rigorously consistent.

Inhaled insulin has been recently approved for human use by the FDA and experience with its use in pregnant women is not available at the time of this writing. The pharmacokinetic properties of inhaled insulin are similar to those of rapid-action insulins, and it is recommended in the treatment of type II diabetics who cannot achieve adequate blood glucose control with oral hypoglycemic agents. In type I and in some type II diabetics inhaled insulin must be given in conjunction with injected basal insulin. Decreased pulmonary function has been observed in the first several weeks of treatment with inhaled insulin, and the medication is not recommended in patients who smoke or have underlying lung disease. Pulmonary function testing should be performed frequently in patients receiving inhaled insulin even in the absence of pulmonary symptoms.

Another recently available insulins are the long-acting analogues insulin glargine (Lantus) and insulin detemir (Levemir). Insulin glargine differs from human insulin by the substitution of a glycine for asparagine at position 21 in the alpha-chain and the addition of two arginines molecules at position 30 in the beta-chain. These changes result in insulin that precipitates in the subcutaneous tissue and is released slowly with little or no peak activity and with duration of action of approximately 24 hours. Insulin glargine is the form of insulin that most closely resembles the basal physiologic secretion of insulin by the pancreas. The combined use of insulin glargine for basal needs and insulin lispro for prandial elevations is the therapeutic modality closest to normal physiology but has the disadvantage that injections of insulin lispro are necessary before every meal and also to cover the blood glucose elevations that occur after snacks.

Insulin detemir links to fatty acid chains, resulting in slower absorption and protracted clearance after absorption. The duration of action ranges from 6 to 24 hours depending on the medication dose. More than half of patients on insulin detemir require a second daily injection to maintain adequate control. The experience with insulin detemir during pregnancy is limited.

Total daily insulin requirement

The total daily insulin requirement for patients receiving multiple subcutaneous doses is usually 0.6 U/kg of current weight in the first trimester, 0.7 U/kg of current weight in the second trimester, and 0.9 U/kg of current weight in the third trimester. The total daily dose is less (0.3–0.5 U/kg current weight) for individuals using continuous subcutaneous infusion by pump. A woman weighting 60 kg in the second trimester of pregnancy will require approximately 42 U of insulin per day. The total daily requirement is divided between intermediate- or long-acting insulin (basal insulin) which is necessary to suppress hepatic neoglucogenesis between meals and during fasting, and short-acting or prandial insulin which is necessary to reduce the elevation in blood glucose that will occur after each meal. One way to divide the total daily dose is 1/6 at bed time as NPH, 1/6 before dinner as Regular, and 4/6 before breakfast, 2/3 as NPH, and 1/3 as Regular. A person requiring a total daily dose of 40 U should have approximately 7 U of NPH at bed time, 7 U of Regular before supper, and 18 U of NPH and 8 U of Regular before breakfast. Another approach is to give 21 U insulin glargine (Lantus) at bed time and 7 U insulin lispro (Humolog) before each meal.

Insulin to carbohydrate ratio

One method to calculate the amount of prandial insulin is by means of the insulin to carbohydrate ratio (insulin/carbohydrate ratio, or insulin/CHO ratio), which is an estimation of how many grams of carbohydrate will be covered by 1 U of Regular insulin. This method is mainly used by individuals using continuous subcutaneous infusion by pump but can be applied to patients using multiple subcutaneous doses. The insulin/carbohydrate ratio is directly related to the total daily requirement, and women with high total daily requirements will need more insulin to cover a certain amount of carbohydrates than those with lower total daily insulin requirements. The insulin/carbohydrate ratio can be estimated using the 500 rule that consists of dividing the number 500 by the total daily requirement. A person requiring a daily insulin dose of 60 units will have an insulin/CHO ratio of 8.3, meaning that 1 U of insulin will cover the elevation in blood sugar produced by 8.3 g of dietary carbohydrate. Since dietary carbohydrates are measured in 15-g servings, that person will need approximately 2 U of insulin per each carbohydrate serving. Typically the insulin/carbohydrate ratio is in the range of 10–15, meaning that one unit of insulin will be required to cover the effects of the ingestion of 10–15 g of carbohydrate. A patient requiring a total daily dose of 40 U who ingests four CHO servings at breakfast and lunch and five CHO servings at dinner will need 4–6 U before breakfast and lunch and 6–8 U before dinner to cover her prandial needs. Patients on insulin lispro or insulin aspart will inject before each meal. However in patients on a regimen of Regular/NPH, glucose control after lunch is maintained by the NPH (long acting) insulin taken before breakfast. In this case the

insulin will be distributed as 9 U of NPH at bed time, 8 U of Regular before dinner, and 6 U of Regular and 17 of NPH before breakfast. The individual variation in insulin/carbohydrate ratio is a function of the insulin sensitivity of each person that, in turn, is directly related to that person's weight. The more overweight a person is, the greater will be his/her insulin resistance. Also there are variations in insulin sensitivity at different times of the day, and insulin typically covers fewer grams of carbohydrate at breakfast than at lunch or dinner. An easy rule to remember is that in most cases 1 U of insulin lispro or aspart will lower blood glucose 30 mg/dl, one serving of CHO will raise the blood glucose 30 mg/dl, and, therefore, 1 U of insulin will cover the blood glucose elevation caused by one serving of carbohydrates.

Insulin sensitivity factor

To determine the amount of supplemental insulin that the diabetic woman should take in addition to the regular doses to control blood glucose outside target values, it is necessary to calculate the insulin sensitivity factor. The sensitivity factor is the estimated drop in a person's blood glucose per unit of Regular insulin and is inversely related to the total daily insulin required to maintain target blood glucose levels. The drop in blood glucose following insulin administration will be less marked in the individual requiring a high daily dose than in those with relatively small daily requirements. It is determined using the 1500 rule that consists of dividing 1500 by the total daily requirement. For a person with a total daily dose of 60 U the sensitivity factor will be 25 (1500/60 = 25), indicating that the blood glucose will drop approximately 25 mg/dl per each 1 U of insulin. To calculate how much supplemental insulin a person needs, the difference between the actual blood glucose and the desired blood glucose is divided by the sensitivity factor. For example, if the 2-hour postprandial blood glucose is 220 mg/dl, the desired postprandial is 120 mg/dl and the sensitivity factor is 20 the amount of supplemental insulin will be 220–120/20 = 5 U. This type of calculation is useful to make up a sliding-scale guide. There will be variations with each individual patient and the best way to determine the total daily requirement, the basal and prandial doses, the sensitivity factor, and the amount of supplemental insulin for sliding-scale is through observation of the patient's blood glucose values and her response to insulin treatment.

Abnormalities in blood glucose control

Elevations of fasting blood glucose above 95 mg/dl reflect excessive glucose production by the liver and require adjustment in the dose of basal insulin. Postprandial elevations (>140 mg/dl 1 hour or > 120 mg/dl 2 hours after meals) are the result of excessive carbohydrate ingestion or inadequate prandial insulin. A relatively common cause of wide blood glucose fluctuations is iatrogenic and results from the use of insulin preparations (Regular and NPH, Lente and Regular) with overlapping basal and prandial effects secondary to their rate of absorption and peak of action.

Prandial elevations in blood glucose values are usually the result of changes in the amount of carbohydrate intake. Diabetic patients need to be questioned frequently about CHO ingestion and need to be reminded about the importance of measuring the CHO content of food. Some patients with long-standing diabetes falsely believe that they can calculate the weight or the size of a given portion of food without the use of a scale or a measuring tape. Some other diabetic patients are careless in the evaluation of the CHO content of their meals because they believe that blood glucose variations can be corrected by supplemental insulin doses. These patients need frequent and extensive explanations about the need to follow a different, more restricted meal plan during pregnancy in order to avoid wide fluctuations in their blood sugars and its effects on the fetus.

A frequent problem affecting blood sugar control in patients using Regular/NPH combinations is variable timing of meals and insulin injections. Some patients follow an erratic schedule and constantly change the intervals between meals and insulin injections, thus making adequate control extremely difficult. They should be instructed that during pregnancy they should follow a more organized schedule, resulting in a more predictable response to treatment and facilitating tight glucose control.

No regimen for insulin administration is applicable to all diabetic pregnant patients. Many of them can achieve control with two doses of a combination of short- and intermediate-acting insulin. Some patients require three or more daily doses. For patients on Regular/NPH insulin the morning dose of Regular insulin is determined by the glucose level 2 hours after breakfast or immediately before lunch. The evening dose of Regular insulin is determined by the glucose level following the evening meal and the blood sugar at bed time. The morning dose of NPH is reflected in the blood sugar after lunch and before supper, and the evening NPH dose by the fasting blood sugar as well as presence or absence of nocturnal hypoglycemia.

Patients on insulin pumps

Patients on continuous subcutaneous insulin infusion by micro-pump constitute a special group. The majority of these patients are highly motivated and frequently monitor their CG values. Most are long-standing diabetics with a fair knowledge of their disease and the relationship of glucose levels to diet, insulin, and exercise.

The most common problem found in these patients is hypoglycemia of varied severity. Because they are long-standing diabetics, the efficacy of their counter-regulatory

mechanisms is limited and they can have prolonged, severe hypoglycemia. Such episodes mandate a reduction in the preprandial boluses or in the day time nocturnal basal rate, depending on the timing of the hypoglycemic crises. A second common problem with these patients is infection at the injection site. Emphasis on aseptic technique and frequent changing of injection site may minimize this problem. An exaggeration of one of the objectives of their treatment and that of the patient's independence and self-management of her disease may also be a problem. Frequently, these patients sense that the physician input in their treatment is unnecessary, and find it difficult to follow recommendations.

Assessment of Fetal Well-Being

There is universal agreement that insulin-dependent diabetics need some method of fetal surveillance during the last 6–10 weeks of pregnancy. However, the best test to use and when to start the testing are points of discussion. Some investigators prefer weekly OCTs (oxytocin challenge tests); others prefer biweekly NSTs or weekly BPPs.

Initiation of antepartum surveillance depends on the severity and stability of the maternal diabetes. Mothers with brittle diabetes, those who require more than 100 U insulin per day, or those with growth-restricted fetuses should have fetal surveillance starting as early as 28 weeks. Stable, type II insulin-dependant diabetic mothers may start fetal surveillance as late as 34 weeks.

Labor and Delivery

Preterm labor

The use of intravenous beta-adrenergic drugs to stop preterm labor in pregnant diabetics should be discouraged. These agents increase glycogenolysis and lipolysis and, consequently, the tendency toward metabolic acidosis. Most diabetic patients require continuous intravenous insulin to antagonize the diabetogenic effect of the labor-inhibiting medications. The potential morbidity from the intravenous administration of beta-adrenergic agents to diabetic pregnant patients contraindicates their use.

The drug of choice for tocolysis in diabetic women is nifedipine. Once the contractions have subsided, the patient should be maintained on calcium channel blockers. Oral terbutaline, in doses no more than 2.5 mg every 4–6 hours, may be used in patients who do not tolerate nifedipine. Before 32 weeks, indomethacin may also be used.

A significant number, approximately 40% of these patients are in preterm labor as a result of intrauterine infection. Amniocentesis with Gram stain and culture of the amniotic fluid may be necessary for correct diagnosis in the diabetic patient with preterm labor before 32 weeks of gestation.

Preterm premature rupture of membranes

Every time a pregnant diabetic has spontaneous rupture of the membranes, there is a strong possibility that infection is present. Obstetric infections occur more easily in diabetics and they may be more severe than in nondiabetics. Thus, expectant management of diabetics with premature rupture of membranes should be the exception rather than the rule.

Time of delivery

There is no need to interrupt the pregnancy before term in stable insulin-dependant diabetics. However, once these patients reach term they should be delivered. This will avoid adding the fetal complications resulting from prolongation of pregnancy to the fetal complications of diabetes. The unstable insulin-dependent diabetics should be managed differently. These patients are better served by delivering them as soon as fetal lung maturity is attained. Fetal and maternal complications in the unstable patient are numerous and there is no advantage of further pregnancy prolongation once the baby's lungs are mature.

Mode of delivery

It is not necessary to deliver all insulin-dependent diabetic patients by cesarean section. Although there are multiple indications for cesarean section in these patients, more than 50% of them can be safely delivered vaginally.

Intrapartum management

The insulin requirements of insulin-dependent diabetics during labor and delivery are low. Labor is a form of exercise and has a glucose lowering effect. At the same time, glucose is necessary during labor to avoid hypoglycemia and starvation ketosis. Insulin-dependent diabetics should eat their usual evening meal and bed time snack the evening prior to induction or cesarean delivery. They should also have their usual evening insulin dose. However, they should omit their morning dose of insulin the day of induction or cesarean delivery. Following admission to labor and delivery they should have a determination of CG and if it is within a normal range (70–110 mg/dl) an intravenous (IV) infusion with 0.9% saline solution will be started. If the CG is above 120 mg/dl a continuous infusion of insulin, 50 U in 500 cc of 0.9% saline solution is started at a rate of 0.5 U insulin per hour. If the CG is below 70 mg/dl the initial IV solution should be 5 or 10% dextrose in 0.45% saline solution. The CG and urinary ketones should be measured every 2 hours or at more frequent intervals if the patient has hypoglycemic symptoms and the rate of administration of insulin or dextrose or the type of IV fluids modified

accordingly. Approximately 70% of insulin-dependent diabetics, in particular class A-2 and type II diabetics, will remain euglycemic during labor and delivery (Davies et al., 1998) and will not require insulin or dextrose. Once patients enter the active phase of labor, the possibility of hypoglycemia and/or starvation ketosis increases and it will be prudent to switch the type of IV fluids from 0.9% saline solution to 5 or 10% dextrose in 0.45% saline solution (Jovanovic, 2004). The same recommendations apply to diabetic patients having planned cesarean sections. Ideally their surgery should be performed early in the morning to avoid dealing with the fluctuations in CG associated with the loss of effect of the insulin taken the night before surgery on hepatic neoglucogenesis and the consequences of prolonged starvation. Similarly to the diabetic that is being induced, the type of IV fluids in the diabetic having a planned cesarean will depend on the CG values at the time of admission.

Postpartum management

Immediately after delivery of the placenta there is a sudden loss of insulin resistance and the majority of patients will not require insulin for 24–48 hours. Once their fasting or postprandial CG starts to rise, insulin therapy should be restarted using one-half to two-thirds of the dosage that the patient was receiving before delivery. This initial dose is adjusted according to the patient's response.

Unstable Type I Diabetics

The care of unstable insulin-dependent diabetics presents a significant challenge to the obstetrician because control of blood glucose in these patients is difficult, they require frequent office visits and frequent telephone communication, and also require frequent hospital admissions for metabolic regulation. These patients should be under the care of a specialist in maternal–fetal medicine. "Split" management between a general obstetrician and an internist or endocrinologist is an open invitation to a poor outcome. Some of the most common problems that these patients may develop are as follows:

1. Diabetic ketoacidosis
2. Somogyi's phenomenon
3. Dawn phenomenon
4. Hypoglycemic episodes
5. Changes in peak of action and duration of insulin action
6. Problems peculiar to patients on continuous infusion pumps

Diabetic ketoacidosis

DKA is a serious emergency that requires adequate treatment to save maternal and fetal lives. DKA results from a deficit in insulin and the response to that deficit by counter-regulatory hormones. As a result of decreased cellular glucose consumption and increased neoglucogenesis, the blood sugar concentration reaches high levels. This severe hyperglycemia causes osmotic diuresis with depletion of the intravascular volume and electrolyte changes. Simultaneously, the cells start to use fatty acids as a source of energy (lipolysis) with production of ketoacids that consume the body buffers, resulting in a high anion gap and metabolic acidosis. If uncorrected, this may lead to maternal and fetal death. This emergency requires early diagnosis and aggressive treatment with identification and elimination of the precipitating event.

The diagnosis of DKA requires the following:

1. A blood glucose concentration greater than 250 mg/dl. However, during pregnancy DKA may develop with blood glucose concentrations below 250 and occasionally in the normal range (euglycemic ketoacidosis)
2. Ketone bodies in urine and plasma
3. Arterial pH less than 7.3
4. Serum bicarbonate less than 15 mEq/L

The initial laboratory evaluation of these patients requires measurements of blood glucose, serum and urine ketones, blood gases, electrolytes, CBC, electrocardiogram, and chest x-ray (Box 17-15). Some of these examinations should be repeated frequently to follow the evolution of the disease.

Patients in DKA are deeply dehydrated with intracellular and extracellular deficits that may reach 7 L for a 70-kg person and adequate fluid replacement is as important for them as insulin therapy. Upon admission to the hospital, an intravenous line should be placed and hydration started with 1000 ml of normal saline in the 1st hour (Box 17-16). The administration of IV fluids should continue at about 300–500 ml/hour until blood pressure and pulse rate are back to normal. This usually requires a total of 6–10 L in 24 hours. If the patient is in shock, plasma

BOX 17-15

Monitoring of DKA

1. Cumulative intake and output every 1–2 hours
2. Vital signs every 1–2 hours
3. Capillary blood glucose every 1–2 hours
4. Serum potassium every 2–4 hours
5. Serum ketones or serum beta-hydroxybutyrate every 4 hours
6. Arterial pH and blood gases at admission: if pH < 7.0 on admission, recheck as necessary until pH exceeds 7.1
7. Serum phosphate, magnesium, and calcium levels on admission: if low, repeat every 4 hours, otherwise every 8–12 hours
8. Spot-check urine for ketones and glucose every 4 hours
9. EKG on admission; repeat if follow-up serum potassium is abnormal or unavailable

BOX 17-16

Fluid therapy in DKA

Initial two hours: 0.9% NaCl at 1000 ml/hour

- Bicarbonate 1 amp (44 mEq) to be added per liter of infusion when blood pH is < 7.0 or total CO_2 < 5 mmol/L. Discontinue bicarbonate when CO_2 is > 8–10 mmol/L
- Potassium chloride (40 mEq/L) should be added to the IV fluids if potassium at admission is normal or low to replace body potassium stores over 2–3 days
- If phosphate is low, replace 10–20 mEq of potassium chloride for potassium phosphate

After two hours: decrease initial rate to half, and change to 0.45% NaCl if hypernatremia develops

- Change to 5% dextrose in 0.45% NaCl when blood glucose < 250 mg/dl
- 6–8 Liters should be given over the first 24 hours
- Urine output should be at least 30–60 ml/hour
- After 4 hours of no vomiting and adequate urinary output, start clear liquids orally (100–200 ml/hour as tolerated) and reduce IV fluids accordingly
- After 8–12 hours of clear liquids and bicarbonate > 15 mmol/L begin solid food

expansion with 5% albumin, 10 ml/kg/hour, is indicated because 100% of the albumin solution volume will be retained as intravascular volume. In contrast, every liter of normal saline will expand the IV volume about 250 ml and a liter of half normal saline will expand the IV volume about 100 ml.

Hypokalemia is the rule in DKA and the total deficit reaches between 300 and 600 mEq. The serum potassium is not an adequate index of this deficit because it only measures extracellular potassium, which is only about 2% of the total body stores. Furthermore, the potassium deficit is usually not apparent at the time of admission because the water and electrolyte losses are disproportionate and the electrolyte concentration may appear normal in the face of severe dehydration. If the serum potassium is below 4 mEq/L at the time of admission, replacement should be immediately initiated using 30–40 mEq of potassium chloride per hour. Once the potassium level is greater than 4 mEq/L, administration of 10–20 mEq/hour will suffice.

Insulin therapy should be started soon after the initial evaluation. Typically, an initial intravenous bolus of 0.2 U/kg is given and followed by a continuous infusion of insulin using 0.1 U/kg/hour. With this treatment, blood glucose should decrease approximately 10% per hour. If blood glucose levels do not decline by at least 30% in the first two to three hours, the continuous infusion of insulin should be increased to twice the initial dosage. Once the blood sugar is between 200 and 250 mg/dl, the IV fluids should be changed from normal saline to 5% dextrose in half normal saline and the insulin dosage should be adjusted to avoid hypoglycemia (Box 17-17).

BOX 17-17

Insulin therapy in DKA

1. Dissolve 50 U regular insulin in 500 ml of normal saline. Administer insulin piggyback
2. Initial IV bolus: 0.2 U/kg actual body weight
3. Follow with continuous infusion of 0.1 U/kg actual body weight
4. Double rate of infusion if blood glucose does not decrease 40–80 mg/dl in 2 hours
5. Decrease insulin infusion and start 5% dextrose in 0.45% saline when the blood glucose reaches 250 mg/dl
6. Start subcutaneous insulin the following day after several hours of stable blood glucose values

To facilitate the changes in insulin, electrolytes, and fluid administration it is ideal to have two IV lines. One will be used solely for the purpose of administering insulin. The other IV site should be connected to a "two bag system" (Grimberg et al., 1999). One of the bags contains fluid and electrolytes and the other fluid and electrolytes plus 10% dextrose. This system allows a rapid response to manipulations in total fluids, insulin, electrolytes, and dextrose administration.

In DKA glucose passage into the cells is impaired and it is necessary for the patients to utilize fatty acids to generate energy, resulting in an excessive production of acetone, acetoacetic acid, and beta-hydroxybutyric acid. Unfortunately, the nitroprusside reagent used to determine the concentration of ketones in plasma and urine measures mainly acetoacetic acid, reacts weakly with acetone, and does not react at all with beta-hydroxybutyric acid. The concentration of acetone in the plasma is usually 3–4 times the concentration of acetoacetic acid, but acetone does not consume base or contribute to the acidosis and is eliminated through the lungs. The concentration of beta-hydroxybutyric acid is 3–15 times greater than the concentration of acetoacetic acid. Beta-hydroxybutyric acid is transformed into acetoacetic acid and thus the nitroprusside test may remain positive in blood and urine after clinical improvement of the DKA. Acetoacetic and beta-hydroxybutyric acid consume the base reserves and are the cause of the drop in pH. If the arterial pH is below 6.9, 88 mg of sodium bicarbonate should be given every 2 hours until the pH rises above 7.0.

A fundamental component of the treatment of DKA is the identification of the precipitating events. Frequently it is a viral or bacterial infection. In the latter case, treatment with antibiotics is necessary to adequately control the ketoacidosis.

The prognosis of DKA during pregnancy is guarded. With modern, aggressive treatment, maternal mortality is approximately 2%. The prognosis is worse if the patient

has symptoms of central nervous system dysfunction or is in shock on arrival. Fetal mortality is high in all cases.

Somogyi's phenomenon

Somogyi's phenomenon (Somogy, 1959) should be suspected in patients who have high fasting blood glucose and complain of sleep disturbances such as nightmares or nocturnal sweating. The elevated fasting blood glucose is due to nocturnal hypoglycemia secondary to excess insulin followed by an exaggerated counter-regulatory response. Documenting hypoglycemia between 1:00 and 5:00 am confirms the diagnosis. The treatment is to decrease, rather than increase, the amount of long- or intermediate-acting insulin that the patient takes before supper or at bed time.

Dawn phenomenon

Some patients have high fasting blood sugars in the absence of nocturnal hypoglycemia. This is called the dawn phenomenon (Bolli and Gerich, 1984). The mechanism responsible for this has not yet been clarified. Treatment requires an increase in the long-acting insulin taken with dinner or at bed time. However, large changes in insulin dosage should be avoided because the severity of the dawn phenomenon is variable and its occurrence is irregular.

Hypoglycemic episodes

Severe hypoglycemia requiring assistance is a common emergency in unstable insulin-dependent diabetics. The majority of these patients are type I, requiring relatively large amounts of insulin. Most likely the root of their problem is some degree of impairment in their counter-regulatory mechanisms. Patients with long-standing diabetes have an obtunded response of their counter-regulatory hormones, epinephrine, growth hormone, and cortisol to hypoglycemia. Also, when large amounts of insulin are required for metabolic control, the blood glucose threshold for the release of counter-regulatory hormones is lowered. Therefore, these patients may have marked hypoglycemia without eliciting a compensatory response and only manifest clinical symptoms when the blood glucose is dangerously low.

An integral part in the prevention and treatment of hypoglycemic reactions is educating those living with the patient because often in such situations, the patient will be unable to respond to her own needs. The husband and/or relatives should be able to recognize the behavioral changes that accompany hypoglycemia and the emergency treatment of the situation. In mild to moderate reactions, treatment consists of giving the patient some liquid containing carbohydrate. A glass of milk, orange juice, sugar water, pancake syrup dissolved in water, or three tablets of glucose (5 g each) are an effective treatment for most episodes. For severe reactions administration of glucagon is necessary. One milligram of glucagon intramuscularly or subcutaneously is sufficient if the patient is unconscious. As soon as she awakens, oral carbohydrates should be given because the effect of glucagon is transient. If the patient remains unconscious after the glucagon injection, she should be taken immediately to an emergency room for intravenous glucose administration. Usually 20 ml of 50% glucose is adequate to awaken the patient, but in severe cases the injection may have to be repeated. Treatment with 5 or 10% dextrose may have to be continued for several hours until the blood glucose levels remain in the normoglycemic range.

Changes in insulin pharmacokinetics

Unstable insulin-dependent pregnant diabetics may have marked variations in the time of onset, time of peak of action, and total duration of action of the insulin preparation they are using. These alterations in the pharmacokinetics of insulin complicate the management of these patients and should be suspected in long-standing diabetics with large fluctuations in blood glucose levels that do not respond predictably to dosage changes. Two potential reasons for this problem are the development of insulin antibodies and irregular absorption from the injection site. In these cases, it is necessary to measure the blood glucose every hour for 24-hour periods and to graphically plot the values, the time of meals, and the time of administration of insulin administration. These 24-hour profiles may reveal that the time of peak action and the total duration of action of insulin are prolonged.

When an altered insulin pharmacokinetics is diagnosed or strongly suspected, the patient must switch to a different insulin preparation. Many long-standing diabetics are using beef or pork insulin and the problem is the presence of anti-insulin antibodies. If that is the case, these patients will show predictable responses to human insulin. When switching insulins, it is best to start patients at doses one-half to two-thirds of what they were previously receiving because these patients may develop hypoglycemia with equivalent doses of a different insulin.

Irregular absorption from the injection site is also closely related to changes in the pharmacokinetics of insulin. It is well known that absorption is more rapid when insulin is injected in extremities where activity increases regional blood flow. A more steady rate of absorption is obtained from subcutaneous injections in the abdomen. Absorption is also erratic when the same areas are used repeatedly, and patients should be encouraged to rotate the sites of infection frequently.

Diabetics with End-Organ Damage

Type I diabetics can be divided in two large groups depending of the absence or presence of end-organ damage. Women in White's Class B and C make up the first group. The second group is women in White's classes D, F, R, RF, H, and T. Women in the second group have end-organ disease secondary to micro- and macrovascular lesions. This particular group of patients is at high risk for both maternal and fetal complications. As with the unstable insulin-dependent diabetics, these patients should be under the care of a specialist in maternal–fetal medicine.

For a long time it was believed that pregnancy was contraindicated in women with diabetic end-organ damage and therapeutic abortion or surgical sterilization were frequently advised. Today, most of these patients can have a successful pregnancy. However, vascular complications will not only generate significant fetal risks but will also shorten the maternal life span.

Diabetic nephropathy

The characteristic features of patients with diabetic nephropathy are the presence of proteinuria and hypertension in the first or second trimester of pregnancy. These signs are usually mild in early pregnancy but by 20–24 weeks most of these patients have increases in proteinuria, blood pressure, and serum creatinine (Reece et al., 1988). Edema is almost always present, and by the third trimester it is difficult to determine whether the symptoms are due solely to the diabetic nephropathy or to superimposed preeclampsia.

Pregnancy has an adverse effect on advanced diabetic nephropathy and patients with serum creatinine > 1.5 mg/dl or proteinuria larger than 3 g/24 hours may progress to end-stage renal disease (Purdy et al., 1996). Also, these women are at particularly high risk of developing superimposed preeclampsia, which affects 50% of pregnant diabetics with renal disease. The main fetal disorders occurring in patients with diabetic renal disease are prematurity and fetal growth restriction. Prematurity results from preterm labor and from intentional medical intervention because of aggravation of the disease in the third trimester. The incidence of preterm delivery in these patients is approximately 45%. Fetal growth restriction affects approximately 20% of these pregnancies, and it should be diagnosed early to institute adequate fetal surveillance and to prevent fetal death.

Another concern with these patients is the potential for proliferative retinopathy. Ninety percent of patients with diabetic nephropathy have retinopathy but only 20% of them have the proliferative type. A complete ophthalmologic examination is necessary in all patients with diabetic kidney disease. Another concern is the reduced longevity for these patients, once diabetic nephropathy is diagnosed. Usually, end-stage renal disease will occur within 2–4 years and the best hope for survival is through renal transplantation.

Diabetic retinopathy

Diabetic retinopathy affects approximately 40% of all insulin-dependent diabetics. Unfortunately, pregnancy seems to accelerate the progression of diabetic retinopathy. In approximately 80% of the cases, the lesions are not severe and are called "background retinopathy." The other 20% of these patients have neovascularization along the retinal surface, and this is named "proliferative retinopathy." The important group to identify is the latter because the new vessels are fragile and may bleed profusely with the changes in intraocular pressure that occur during labor, leading to sudden vision loss. Therefore, labor is contraindicated in these patients because Valsalva efforts may increase intraocular pressure, causing vitreal hemorrhage and retinal detachment.

Diabetic neuropathy

The most common form of diabetic neuropathy seen during pregnancy is gastroparesis. Pregnant women with diabetic gastroparesis vomit continuously and frequently develop starvation ketosis. Their treatment is challenging, although sometimes they benefit from intermittent gastric intubation or from the administration of metoclopramide or erythromycin.

Diabetic cardiomyopathy

The maternal and fetal prognosis for patients with diabetic cardiomyopathy is poor. Maternal and fetal mortality occur frequently. These patients need to be identified early in pregnancy and will require intensive care to increase the probability of a good outcome.

INDIAN EXPERIENCE OF DIABETES COMPLICATING PREGNANCY

With improvement in antenatal care and routine screening of all pregnant women for carbohydrate intolerance, an increasing number of cases of diabetes are being detected. Of all cases of diabetes complicating pregnancy, the majority (about 90%) are cases of gestation diabetes. The incidences quoted by Indian authors are presented in Table 17-1. In summary, the incidence of gestation diabetes is about 3–5% in India.

In studies on the effects of diabetes in pregnancy, the following pertinent observations were reported.

- The incidence of GDM (9.84%) was high in women undergoing spontaneous abortions (Zargar et al., 1995), particularly in those with poor glycemic control.
- The incidence of GDM varies widely even within the

Table 17-1. Incidence of diabetes complicating pregnancy in India

Authors	Year	Incidence (%)
Goel and Bathla	1999	2–5
Ganguli et al.	1995	0.25
Maheshwari et al.	1989	4.9
Bhattacharya et al.	2001	3.0
Kumar et al.	1993	5.5
Sridhar and Nagamani	2003	12.7
National Diabetes Data Group	2003	4.5

Adapted from Daftary SN, Desai SV. Diabetes complicating pregnancy. In: Daftary SN, Desai SV, eds. Selected Topics in Obstetrics and Gynecology (1st edn). New Delhi: BI Publications, 2005.

same metropolitan area (Ramachandran and Snehalatha, 1998).

- Excessive weight gain was observed in 32% of women with GDM as compared to 1.7% in controls (Jindal et al., 2001).
- Fetal macrosomia was observed in 32% of GDM women as compared to 6.8% in controls (Jindal et al., 2001).
- Incidence of pregnancy-induced hypertension was 48% in GDM group as compared to 18.8% in controls.
- Incidence of hydramnios reported was 28% in the GDM group as compared to 4.3% in controls (Jindal et al., 2001).
- Candidal vulvovaginitis was reported in 4% in the GDM group as compared to 1.3% in controls (Jindal et al., 2001).
- Incidence of intrauterine fetal deaths was 12% in the GDM group as compared to 1.7% in controls (Jindal et al., 2001).
- Incidence of fetal malpresentations was 16% in GDM group as compared to 6% in controls (Jindal et al., 2001).
- Cesarean section was required in 44% of GDM group as against 13.3% in controls (Jindal et al., 2001).
- Postpartum complications are also much higher in the GDM group (Buckshee and Rohatgi, 2003).
- Maternal mortality is 10 times higher in GDM patients (Buckshee and Rohatgi, 2003).
- Perinatal morbidity increases in GDM patients (Agarwal et al., 1993; Ramachandran and Snehalatha, 1998).
- Strict glycemic control of GDM improves obstetric outcome significantly. The glycemic control should ideally precede onset of pregnancy.
- Prescribing pyridoxine 40 mg twice daily in GDM patients helps to reduce insulin requirements to control glycemic control (Vijaykumar et al., 1991; Arjun, 1998).

IMPORTANT POINTS

1. There is a progressive increase in insulin resistance during pregnancy. This is the result of the anti-insulinic effect of human placental lactogen, progesterone, and estriol and the accelerated destruction of insulin by kidney and placental insulinases.
2. Diabetes during pregnancy is associated with a greater than normal incidence of preeclampsia, infection, postpartum bleeding, cesarean delivery, and neonatal morbidity and mortality.
3. The risk of fetal anomalies in the pregnant diabetic can be greatly reduced by adequate glycemic control (mean CBG ≤ 95 mg/dl) during the periconceptional period.
4. There are no reliable signs or symptoms allowing clinical identification of patients with gestational diabetes. This condition can be diagnosed only through the systematic screening of pregnant women with a 1-hour 50 g GTT.
5. Gestational diabetics truly compliant with their diets gain little or no weight during pregnancy and may show small acetonuria. Dietary intervention in these patients is more effective in preventing fetal macrosomia if the mother is maintained just above the ketonuric threshold.
6. The patients with gestational diabetes should measure the fasting and the 2-hour postprandial blood glucose. The objective of their treatment is to maintain the fasting blood sugar under 95 mg/dl and the 2-hour postprandial under 120 mg/dl. Control of blood glucose is fundamental in the prevention of fetal macrosomia and neonatal hypoglycemia.
7. The high-risk gestational diabetic patient should have antepartum surveillance starting at 34 weeks and should be delivered between 38 and 40 weeks.
8. The detection of diabetic embryopathy involves determination of glycosylated hemoglobin 4–6 weeks after conception, first and second trimester screening, detailed fetal anatomical survey with ultrasound at 20 weeks, and fetal echocardiography at 24 weeks.
9. Most authorities agree that primary cesarean section is justified in pregnant diabetics if the EFW at term is 4000 g or more.
10. There is a sudden loss of insulin resistance after delivery of the placenta, and the majority of pregnant diabetics do not need insulin for the initial 24 hours' postpartum.
11. The diagnosis of DKA requires (a) a plasma glucose concentration greater than 250 mg/dl, (b) ketone bodies in urine and plasma, (c) arterial pH less than 7.3, and (d) serum bicarbonate less than 15 mg/dl.
12. The drug of choice for initial tocolysis in the pregnant diabetics is nifedipine.

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18

Hematologic Disorders in Pregnancy

CHAPTER OUTLINE

Hematologic problems may affect the formed cellular elements of the blood or plasma factors. In the adult individual, the blood cells have a common precursor in the totipotential stem cells of the bone marrow that differentiate among several hematopoietic cell lines. The myeloid stem cells give rise to the red cells, platelets, monocytes, neutrophils, eosinophils, and basophils and the lymphoid stem cell to the B-lymphocytes and T-lymphocytes. The maturation and release into the blood stream of all these different types of cells is under the control of hematopoietic growth factors or hematopoietic cytokines. The best known of these factors are erythropoietin, thrombopoietin, granulocyte colony-stimulating factor, and macrophage colony-stimulating factor. Each one of these factors binds only to its specific receptor, causing a series of changes that ultimately result in cell proliferation. The other element of the blood is the plasma that contains several factors regulating hemostasis.

The hematologic abnormalities that occur most frequently during pregnancy are those affecting the red cells and the hemostatic system. Other problems, such as those affecting the white cells, are rarely seen in pregnant women and will not be covered in this chapter.

PHYSIOLOGICAL CHANGES IN THE RED CELL COUNT DURING PREGNANCY

Hemoglobin concentrations less than 12 g/dl and hematocrit below 36%, which define anemia in the general population, are not indicative of anemia in pregnant patients because of a physiologic change called "hemodilution of pregnancy." This phenomenon was described by Scott and Pritchard (1967) who measured the hemoglobin/hematocrit (H/H) concentrations of a large group of healthy young women with proven normal iron and folate stores. They found an average drop in hematocrit of 5 U for a singleton and 7 U for a twin pregnancy during the second trimester of pregnancy. This is a consequence of the intravascular volume expansion which starts at 8–10 weeks of gestation and reaches its maximum during the second trimester. Initially the increase in plasma volume is larger than the rise

in red cell volume and the net result is a drop in the H/H. This is misleading because the total number of red cells in the circulation is, in fact, increasing.

ANEMIA IN PREGNANCY

There are limits to the physiologic drop in H/H that occurs during pregnancy. Most authors consider anemia to be present if the hemoglobin concentration drops below 10 g/dl or the hematocrit falls below 30%. Anemia is the most common hematologic abnormality diagnosed during pregnancy. It is most often caused by iron deficiency and occasionally by more complex conditions involving deficient production of or accelerated destruction of erythrocytes.

Effects of Anemia on Mother and Fetus

Most anemic pregnant women are asymptomatic and their condition is recognized during routine determination of the blood cell count at the beginning of pregnancy or at 28 weeks of gestation. Other patients present with nonspecific complaints, the most common being fatigue, weakness, and dizziness. Pica with ice or pagophagia is a rather specific symptom of iron-deficiency anemia. The most common sign of anemia is pallor of nonmelanocytic areas of the skin such as the palm of the hands and the nail beds, the oral mucosa, and the conjunctiva.

The signs and symptoms of anemia are usually aggravated following delivery of the fetus especially when it is by cesarean section. Many anemic women who were asymptomatic before delivery are at risk of developing severe symptoms including syncopal episodes in the first 24–48 hours following delivery.

The fetus tolerates quite well even advanced degrees of maternal anemia. This is the result of the high oxygen affinity of fetal hemoglobin (HbF) and the efficiency of the maternal oxygen transport system which is capable of delivering adequate amounts of oxygen to the tissues despite low levels of hemoglobin.

Effects of Pregnancy on Anemia

The expansion of plasma volume and the utilization by the fetus of substrates necessary for the building of hemoglobin molecules will aggravate any preexisting anemia. Patients who are mildly anemic before pregnancy will become markedly anemic and patients with severe anemia will become symptomatic by the end of the second trimester.

IRON-DEFICIENCY ANEMIA

Iron Metabolism

The iron concentration in women is approximately 40 mg/kg, which is the result of a balance between iron absorption and iron losses. In females the main source of iron losses are menstruation and parturition. Iron absorption depends on the amount of iron stored and the activity of the hematopoietic system. Low iron stores and increased hematopoiesis cause increased intestinal iron absorption while normal iron stores and decreased hematopoiesis result in decreased iron absorption. Most of the body iron is contained in the erythrocytes as hemoglobin and in the muscle as myoglobin. A small amount of the total body iron is attached to the transport protein transferrin, but most of the iron stores are in the liver and bone marrow, attached to ferritin.

Iron is absorbed through the brush border of enterocytes in the proximal small intestine by a mechanism that has not been completely clarified. Once internalized iron may be transported into the plasma or stored in the intestinal cells to be lost later when these cells are exfoliated. There is a continuous flow of iron from the intestine to transferrin to ferritin to the erythrocytes and from the erythrocytes through the monocyte-macrophage system back to transferrin and to ferritin.

Transferrin is the protein involved in iron transport through the plasma and extracellular fluid. Transferrin is a glycoprotein with two lobes, each capable of binding one atom of iron. The protein without iron is named apotransferrin. When the apoprotein binds one atom of iron it is named monoferric transferrin and when it binds two iron atoms it is named diferric transferrin. The saturation of transferrin by iron represents the percentage of iron-binding sites that are occupied by iron atoms and is an important index of iron deficiency.

Transferrin-bound iron enters the cell by attaching to specific transferrin receptors present in the surface of the cells. These receptors have more affinity for diferric transferrin than for the monomeric form. The transferrin–receptor complex moves inside of the cell within an endosome and the iron is released and taken by a divalent metal transporter that carries the ion through the endosomic membrane to be incorporated into iron-containing proteins or to be stored as ferritin.

Ferritin is the iron storage molecule and is a spherical protein shell that can store as many as 4500 iron atoms. Most of the ferritin is found in the hepatocytes and macrophages. Apoferritin is the empty protein shell without iron.

There are specialized macrophages in the bone marrow, liver, and spleen that recognize and phagocytize old erythrocytes, destroy their membranes, and liberate their hemoglobin which is rapidly catabolized into heme. Heme is further degraded into biliverdin and the iron is released and incorporated into ferritin or transported back to the plasma.

Iron Requirements During Pregnancy

Approximately 80% of all anemias in pregnancy result from iron deficiency. The reasons for the predominance of this etiologic factor are (a) the suboptimal iron content of the average American diet and (b) the insufficient iron stores in the majority of women during their reproductive years. The daily iron requirement for an adult is about 2 mg. Although the average diet in USA provides between 5 and 15 mg of elemental iron per day, only about one-tenth (0.5–1.5 mg) is absorbed. This amount of dietary iron is probably enough to compensate for the daily and the menstrual losses of a normal female, but it is not adequate for the formation of large iron stores. Consequently, more than 20% of all women in USA have no iron stores and probably twice that number have small stores which quickly become exhausted under the increased demands of pregnancy. The iron requirements of a normal pregnancy have been quantified by the Council on Foods and Nutrition as follows:

- To compensate for external iron losses 170 mg
- To allow expansion of maternal red cell mass 450 mg
- Fetal iron 270 mg
- Iron in placenta and cord 90 mg
- *Total* 980 mg

The gastrointestinal absorption of iron increases during the last two trimesters of pregnancy to about 1.0–3.0 mg/day. Even if this increased absorption is taken into consideration, the iron content of a regular diet cannot provide more than one- to two-thirds of the normal requirements of pregnancy. A pregnant woman must have at least 500 mg of stored iron at the beginning of pregnancy in order to fulfill the requirements of gestation without the need for iron supplementation. Even if this amount of stored iron is present, it will be completely exhausted at the end of gestation. It is also important to note that demands on maternal iron stores begin early in pregnancy, whereas increased gastrointestinal absorption of iron is apparent only after mid gestation.

Clinical and Laboratory Assessment

In patients with nutritional iron deficiency, the iron stores become depleted to maintain the production of erythrocytes and satisfy the needs of the pregnancy. Once the iron stores become depleted, the molecules of transferrin become less than 15% saturated with iron and erythropoiesis is impaired, resulting in microcytosis and hypochromia. Finally, the production of red cells by the bone marrow will decrease. Thus, iron-deficiency anemia can be divided into three stages: (a) depletion of iron stores, (b) iron deficient erythropoiesis, and (c) frank iron-deficiency anemia (Box 18-1). Ideally, iron-deficiency anemia should be detected and treated in its first stages.

BOX 18-1

Stages of iron deficiency anemia

Depletion of iron stores
- Ferritin < 20 ng/ml
- Normal hemoglobin/hematocrit
- Normal RBC indices

Iron-deficient hematopoiesis
- Ferritin < 20 ng/ml
- MCV < 80 mm^3; MCH < 26 pg/cell; RDW > 14.5%
- Transferrin saturation < 25%
- Serum iron < 60 mg/dl

Frank iron-deficiency anemia
- Ferritin < 20 ng/ml
- MCV < 80 mm^3; MCH < 26 pg/cell; RDW > 14.5%
- Transferrin saturation < 25%
- Serum iron < 60 mcg/dl
- Hemoglobin < 10 g/dl; hematocrit < 28%

Depletion of iron stores without overt signs of iron-deficiency anemia usually occurs during the first trimester of pregnancy. The status of iron stores can be assessed by measuring the concentration of plasma ferritin that is in equilibrium with the iron stored in the tissues. One nanogram per milliliter of serum ferritin is equivalent to 8 mg of iron stores. Serum ferritin is measured by radioimmunoassay, and the values reported by different laboratories vary because ferritin from different sources is used to prepare the antibodies used in the assays. The normal range of serum ferritin is 50–155 ng/ml, and any value less than 20 ng/ml is indicative of deficient iron stores. A serum ferritin below 12 µg/L indicates complete depletion of iron stores. A normal concentration of ferritin rules out iron deficiency.

The value of routine evaluation of the iron stores in pregnant women using serum ferritin determinations is controversial. Some investigators believe that iron supplementation for all pregnant women—on the assumption that they have decreased iron stores—costs less than screening all of them with serum ferritin. However, serum ferritin is invaluable to distinguish between anemia secondary to chronic disorders and iron-deficiency anemia.

Iron-deficient hematopoiesis can be suspected from the hematologic indices generated by the automated analyzers used to perform the blood count. The mean corpuscular volume (MCV), the mean corpuscular hemoglobin (MCH), and the mean corpuscular hemoglobin concentration are low because deficient hematopoiesis secondary to iron-deficiency anemia is characteristically microcytic and hypochromic. Another change that simultaneously occurs with microcytosis and hypochromia is an abnormal (>15%) red cell distribution width (RDW). The RDW is an index of the presence of a heterogeneous red cell population with different cell diameters. The changes in hematologic indices correlate well with the examination

of the blood smear that shows abundant, small, well-rounded erythrocytes with pale centers.

When iron-deficient erythropoiesis is present, there are diagnostic changes in serum transferrin, transferrin saturation, and serum iron. The serum transferrin value (normal 200–360 mg/dl), increases with the severity of the iron-deficiency state and is usually greater than 360 µg/dl in patients with iron-deficient hematopoiesis. The serum iron concentration (normal value 60–175 µg/dl) decreases and is usually below 60 µg/dl. The result of these changes is a decrease in transferrin saturation (normally 25–60%) to less than 25%.

A drop in the H/H concentration characterizes the final stage of iron-deficiency anemia. Furthermore, all the abnormal laboratory tests found in the earlier phases of the condition are present. Once frank iron-deficiency anemia is present (H/H below 10/28, abnormal cell indices, abnormal RDW), it is probably unnecessary to measure ferritin, transferrin, and serum iron to confirm the diagnosis.

Treatment

Every pregnant woman needs iron supplementation during pregnancy and it should be started as early as possible, usually when the patient is seen for her first prenatal visit. If the patient suffers from nausea and vomiting of early pregnancy, the administration of iron should be postponed until the gastrointestinal disturbances disappear in the second trimester. Multiple forms of iron are available, and although they vary in their content of elemental iron the hematologic response to them is similar (Box 18-2).

A pregnant woman needs only one tablet of iron per day for prophylaxis of iron-deficiency anemia. One tablet per day of any form of iron supplies enough iron to fulfill the needs of pregnancy, provided that it is taken for at least the last two trimesters and there is no preexisting anemia. More than one tablet of iron per day for prophylaxis is unnecessary, since the excess iron is not absorbed, resulting in gastrointestinal side effects.

Patients with defective hematopoiesis or frank iron-deficiency anemia need enough iron to correct their abnormality and to replenish their iron stores. Iron can be given orally or parenterally, but oral iron is the treatment of choice in the large majority of cases. One 300 mg tablet of iron sulfate orally three times daily after meals is adequate treatment for most patients with iron-deficiency anemia. This dosage provides 180 mg/day of elemental iron, of which 15–25 mg/day are absorbed. The patient's response to this dosage is fast, and a significant increase in reticulocyte count is observable 3–5 days after initiation of oral therapy. Hemoglobin rises from 0.3 to 1.0 g/week, and this is reflected in a significant elevation in H/H values 2–3 weeks after initiation of treatment. The H/H concentration is usually normal after 6 weeks of therapy.

BOX 18-2

Different types of iron supplements

	Molecular iron content (mg)	Elemental iron content (mg)
Ferrous sulfate	300	60
Ferrous gluconate	320	36
Ferrous fumarate	200	67

A prevalent problem associated with oral iron therapy is gastrointestinal intolerance, which is experienced by about 10% of patients undergoing treatment. The most common symptoms are nausea, vomiting, constipation, abdominal cramping, and diarrhea. Since the gastrointestinal side effects are dose-related, the treatment of choice is to reduce the doses to a tolerable level. Another useful maneuver is to give the iron pill with meals rather than after meals. Although this decreases the amount of iron that is absorbed and prolongs the time necessary to achieve normalization of the hematologic indices, it is frequently the only way to continue the treatment. Gastrointestinal toxicity depends on the amount of ionic iron which is the absorbable form of iron that contacts the gastrointestinal mucosa. Thus, preparations containing less absorbable iron produce fewer side effects.

Parenteral iron therapy is rarely indicated because of the risk of adverse side effects and should only be used in patients who cannot tolerate or absorb oral iron or who present with severe iron-deficiency anemia (hemoglobin less than 8 g/dl) a few weeks before their expected date of delivery, requiring rapid normalization of their hematologic indices that cannot be achieved with oral therapy. Parenteral iron therapy is hazardous and expensive when compared with oral administration. Up to 2% of patients receiving parenteral iron may develop acute, severe systemic reactions such as hemolysis, hypotension, circulatory collapse, vomiting, muscle pain, and anaphylactic shock. Other patients suffer delayed reactions characterized by pyrexia, myalgias, and arthralgias.

Before the administration of parenteral iron it is necessary to calculate the patient's iron deficit using one of the following formulas:

[(Normal Hb – patient's Hb) × weight (kg) × 2.21] + 1000 = milligrams of iron needed

For example, the iron required by a pregnant woman with a hemoglobin concentration of 7.1 g/dl and a weight of 140 lbs (63 kg) is:

[(14.0 – 7.1) × 63 × 2.21] + 1000 = approximately 1950 mg

Another formula, simpler and easier to remember is to give 250 mg of elemental iron for each gram of hemoglobin

below normal. In the hypothetical case just mentioned the calculation is:

250 mg × 6.9 g = 1725 mg

For intravenous administration, the iron dextran preparation (50 mg/ml) is dissolved in normal saline to achieve a dilution of 1.0–1.5 g/1000 ml. The medication is initially given at a rate of 1 ml/30 minutes. If no side effects are apparent, administration is continued at a rate of 150 ml/hour. A syringe with epinephrine must be at hand, as well as an ampoule of a suitable glucocorticoid for IV administration.

The iron dextran preparation for IV use contains 50 mg of elemental iron/ml and is also used for IM administration. The maximal recommended dosage of intramuscular iron is 2 ml/day and several injections may be necessary in order to correct the calculated deficiency. Because of the unpredictability of serious allergic reactions and the frequency of dark staining of the skin in the areas of administration IM, iron is used infrequently.

MEGALOBLASTIC ANEMIA

Megaloblastic anemia is characterized by defective DNA synthesis, caused by folic acid or vitamin B_{12} (cobalamin) deficiency. Cobalamin and folic acid are cofactors in the methionine synthase reaction that provides a methylene group to convert deoxyuridylate to thymidylate, which is a fundamental step in DNA synthesis. As a consequence, more cells are in a nonresting state, trying to slowly complete the doubling of their DNA. Since RNA and protein synthesis are not affected, these cells (megaloblasts) exhibit large, mature cytoplasms. These nuclear and cytoplasmic changes are the basic elements of megaloblastosis, and they affect not only the erythroid line but also the myeloid line, producing the hypersegmented neutrophils that are characteristic of megaloblastic degeneration.

Only 3–4% of women with anemia during pregnancy have megaloblastic anemia. In the vast majority of cases, megaloblastic anemia is the result of a folic acid deficiency and only 1 out of every 8500 pregnant women with anemia has vitamin B_{12} deficiency. The reason for the low incidence of megaloblastic anemia during pregnancy is the abundance of folic acid and vitamin B_{12} in the American diet. Folate is present in fruits, green vegetables, and meats; vitamin B_{12} is found in meat, fish, poultry, and dairy products.

Folic acid deficiency may result from inadequate intake, poor absorption, or increased utilization, and all three mechanisms may occur during pregnancy. Folic acid deficiency usually is not due to lack of availability but to prolonged cooking, which destroys the vitamin. Thus, poor cooking habits combined with a lack of raw food in the diet eventually lead to the production of megaloblastic anemia.

Poor absorption of folate despite adequate ingestion usually occurs because ingested folic acid polyglutamates cannot be degraded to absorbable monoglutamates. If an inhibitor of the enzyme responsible for this degradation is present in the diet or if the intestinal pH is acidic, folate malabsorption will occur. Decreased utilization of folate is seen in about 60% of patients with vitamin B_{12} deficiency.

Theoretically, inadequate ingestion, poor absorption, or increased use may also cause vitamin B_{12} deficiency. In practice, however, vitamin B_{12} deficiency results from poor absorption due to autoimmune gastritis and autoimmune antibodies against the gastric intrinsic factor (pernicious anemia), poor ileal absorption despite adequate amounts of intrinsic factor, or a pancreatic defect causing inadequate alkalinization of the intestinal content and poor removal of intrinsic factor binders. Until recently almost all cases of megaloblastic anemia of pregnancy were caused by pernicious anemia. In the last few years, however, defects in ileal absorption have risen in frequency mainly as a result of the popularization of surgical gastrointestinal procedures for the treatment of morbid obesity.

The similarities in morphologic effects on red and white blood cells caused by folate and vitamin B_{12} deficiencies as well as the fact that the anemia caused by the deficiency of one of them can be corrected by administering the other cannot obscure the fundamental difference between the two processes. Vitamin B_{12} deficiency causes progressive demyelinization, but folate deficiency does not and treatment of a vitamin B_{12} anemia with folate does not arrest the progression of neurologic damage. Therefore, differential diagnosis between these two major causes of megaloblastic anemia is important and necessary.

Both folate and vitamin B_{12} deficiencies may mask an iron deficiency. Red cell synthesis is inhibited during the vitamin deficiency, available iron is underused, and increased saturation of transferrin occurs. As soon as therapy with folate or B_{12} is initiated, red cell synthesis starts again, use of iron is maximal, and iron deficiency becomes apparent.

Diagnosis

The first indication of megaloblastic anemia in pregnancy is usually an elevated red cell MCV found on routine prenatal evaluation. In a few cases, the elevated MCV may be the result of hypothyroidism, but the presence of hypersegmented neutrophils strongly suggests that megaloblastic anemia is present. In the large majority of cases patients are asymptomatic but their history may reveal poor dietary intake or alcoholism in cases of folic acid deficiency or a family history of pernicious anemia or history of gastric bypass surgery in cases of cobalamin

deficiency. As mentioned, folate deficiency is the most common cause of megaloblastic changes. However, the clinician should obtain serum levels of both folate and vitamin B_{12} in order to avoid missing the rare case of vitamin B_{12} deficiency. Characteristically, megaloblastic anemias exhibit normal or low reticulocyte count.

The serum vitamin B_{12} level may be low in cases of folic acid deficiency, and the serum folate may be low in cases of vitamin B_{12} deficiency, reflecting the intimate biochemical relation that exists between these two nutrients. A serum level less than 100 pg/ml is diagnostic of vitamin B_{12} deficiency. A combination of a serum folate less than 2 ng/ml and a red cell folate less than 150 ng/ml is diagnostic of folate deficiency. Red cell folate is the best reflection of the amount of folate in tissue, it has fewer fluctuations in value, and it is the test of choice for the diagnosis of folic acid deficiency.

Treatment

Treatment of folic acid deficiency requires 1 mg/day of folic acid. The daily requirement of folic acid probably does not exceed 400 µg even in the presence of anemia. Treatment of megaloblastic anemia secondary to vitamin B_{12} deficiency requires 1000 µg of parenteral cyanocobalamin every week for 6 weeks followed by 1000 µg IM every month. In patients with pernicious anemia, oral preparations of vitamin B_{12} are adequate for long-term maintenance because a small amount of cobalamin is absorbed even in the absence of intrinsic factor. In severely anemic patients, especially if they are near delivery, exchange transfusions of packed red cells followed by parenteral therapy with folic acid (1 mg/day) or cyanocobalamin (1000 µg every day for 1 week) may be necessary.

The reticulocyte count should show an appropriate response to therapy in 4–6 days. The hypersegmentation of leukocytes usually disappears after 2 weeks. An underlying iron deficiency may be detected a few days after initiation of therapy for megaloblastic anemia if an appropriate follow-up is carried out.

HEMOLYTIC ANEMIAS

Hemolytic anemias may occur because of erythrocyte defects such as abnormalities of hemoglobin structure, metabolic disturbances, or membrane abnormalities. Almost all erythrocyte defects causing hemolysis are hereditary in nature. Hemolysis may also occur due to the presence of substances in the plasma that attack and destroy the erythrocyte such as is the case in autoimmune hemolytic anemia.

A normal red cell lives for about 120 days. This lifespan is shortened in the case of hemolytic anemias because of premature destruction of red cells, which may occur extravascularly (i.e., acquired immune hemolytic anemia) or intravascularly (i.e., microangiopathic hemolytic anemia of preeclampsia). Although classification of these anemias according to the site of hemolysis is important for an adequate interpretation of the laboratory tests and for differential diagnosis, in many hemolytic processes destruction occurs in both compartments and laboratory tests are ambiguous.

Extravascular hemolysis is the most common type of hemolytic anemia. The red cells are destroyed in the reticuloendothelial system, liberating hemoglobin which is converted to bilirubin. An increase in indirect bilirubin is apparent in the patient's serum. The products of bilirubin metabolism, fecal and urinary urobilinogen, also increase. Erythropoiesis increases markedly, and reticulocytosis occurs. Thus, elevated unconjugated bilirubin, increased urinary urobilinogen, and reticulocytosis are the laboratory hallmarks of extravascular hemolysis.

In certain circumstances, damage to the erythrocyte cell membrane is extensive and intravascular hemolysis occurs. Hemoglobin is liberated and the alpha-chains bind to haptoglobin, an alpha-2 globulin, and the hemoglobin–haptoglobin complex is rapidly cleared in the liver. Thus, a decrease in plasma haptoglobin is a reliable sign of intravascular hemolysis. After the haptoglobin becomes saturated, free hemoglobin appears in the plasma and when the amount of hemoglobin in the plasma exceeds the reabsorptive capacity of the tubular cells of the kidney, hemoglobinuria occurs. The free plasma hemoglobin becomes oxidized to methemoglobin. Methemalbumin forms when the heme groups of methemoglobin bind to albumin molecules. To compensate for hemolysis, bone marrow erythropoiesis increases markedly, resulting in an increase in the reticulocyte count. Thus, the diagnostic hallmarks of intravascular hemolytic anemia include a decreased or absent haptoglobin and the presence of free hemoglobin, methemoglobin, methemalbumin, and reticulocytosis. Also, abnormalities in red cell morphology are frequently seen in the blood smear.

Intravascular and extravascular hemolysis both cause a bone marrow response characterized by marked erythroid hyperplasia and reticulocytosis. In some cases the erythropoiesis is so active that there is passage of immature cell lines into the bloodstream. Also, in all cases of accelerated red cell destruction, plasma lactic dehydrogenase (LDH) increases as a consequence of the liberation of a LDH isoenzyme from the red cells.

The most common form of hemolytic anemia seen during pregnancy is the intravascular microangiopathic hemolysis, which is a part of the HELLP syndrome. More infrequently the obstetrician sees the hemolytic anemia associated with defects in hemoglobin structure, particularly sickle cell disease (SCD). Extremely rare during pregnancy are the metabolic abnormalities of the

erythrocyte such as glucose-6-phosphate dehydrogenase deficiency or the antibody-mediated hemolysis characteristic of autoimmune hemolytic anemia.

Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia occurs during pregnancy in patients with a severe form of preeclampsia known with the eponym of HELLP syndrome. The reader will find more information about this condition in the chapter of this book about Hypertensive disorders of pregnancy. It is suffice to say that intravascular hemolysis is the hallmark of this serious pregnancy complication. Extremely rare is the microangiopathic hemolytic anemia present in pregnant women with thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and herpetic hepatitis. In all these conditions the blood smear shows fragmented red cells, schistocytes, and helmet cells. Thrombocytopenia is always present. Immunofluorescent studies show marked and generalized fibrinogen deposition in the microvasculature, especially in the kidney, liver, and brain. Delivery of women with HELLP syndrome is followed by progressive improvement in the indicators of hemolysis but maternal mortality and severe morbidity are frequent. Delivery does not have a similar beneficial effect in women affected with TTP or HUS.

Hemolytic Anemias Associated with Hemoglobinopathies

Under normal conditions, there is a coordinated synthesis of alpha- and beta-hemoglobin chains, resulting in the formation of adult hemoglobin (HbAA), which is composed of two alpha- and two beta-chains ($\alpha 2\beta 2$). Most of the hemoglobinopathies of obstetrical interest are the result of abnormalities in the quality or the synthesis of hemoglobin. In USA the most commonly found are (a) sickle cell trait, (b) beta thalassemia minor, and (c) SCD.

Sickle cell disease

SCD is the most important hemoglobinopathy encountered during pregnancy because of the severity of the complications associated with this condition. SCD is an autosomal recessive condition caused by the substitution of a valine for glutamine in position 6 in the beta-globin chains of the hemoglobin molecule, resulting in the production of sickle cell hemoglobin, or HbSS. The condition affects 0.2% of the African-American population of USA. The disease is characterized by chronic hemolytic anemia and by the occurrence of acute, life-threatening vaso-occlusive crisis.

The fundamental pathophysiologic problem in SCD is the decreased solubility of the sickle cell hemoglobin. When HbSS is oxygenated, its solubility is similar to that of normal hemoglobin (HbAA) but in the deoxy form solubility decreases and in a reduced oxygen environment the HbSS will polymerize into long tube-like fibers, which causes morphological changes characterized by sickling of the erythrocytes. The abnormal erythrocytes are removed and destroyed in the reticuloendothelial system, resulting in chronic extravascular hemolysis. HbF inhibits the polymerization of HbSS and patients with elevated levels of HbF have milder forms of the disease.

In certain situations such as increased deoxygenation, prolonged capillary transit time, increased concentration of corpuscular hemoglobin, and acidosis, clusters of sickle cells occlude the microvasculature, producing ischemic infarction and severe inflammatory reactions that clinically translate into a painful sickle cell crisis. Avascular necrosis of the bone marrow is a common component of the sickle cell crisis and produces prolonged, excruciating bone pain. Acute chest syndrome (pulmonary infiltrates, fever, chest pain, tachypnea, wheezing, and coughing) is another relatively common complication of sickle cell crisis and is the leading cause of maternal mortality.

Maternal mortality in SCD has decreased dramatically in the last 35 years. Rates as high as 11.5% reported in 1972 (Hendrickse et al.) have dropped to between 2.1 and less than 1.0% in recent years (Smith et al., 1996; Serjeant et al., 2004). Perinatal mortality has also significantly decreased in frequency and severity with advances in medical care, transfusion medicine, and neonatal care. Early reproductive failure due to spontaneous abortion affects close to 20% of all pregnant patients with SCD. The study of Powars et al. (1986) revealed a decrease in maternal mortality from 4.1% before 1972 to 1.7% after 1972 and a decrease in perinatal mortality from 52.7 to 22.7% in the same period. The same study showed that approximately 14.2% of all pregnancies in patients with SCD end with the delivery of stillborn infants and neonatal mortality is approximately 84.5 per 1000 live births. Another study shows a perinatal mortality as low as 11.0% (Sun et al., 2001). The frequency of infants with birth weights less than 2500 g in patients with SCD is 37.5%. A large number of these infants are born at term and are growth restricted. Growth restriction is also present in a significant number of the stillborn babies delivered by patients with SCD.

Maternal mortality has a regional variation and is greater in under developed countries. The causes of maternal deaths are multiple but acute chest syndrome secondary to pulmonary infection, pulmonary infarcts, and pulmonary embolization are predominant. Maternal morbidity is frequent, severe, and prolonged in pregnant patients with SCD. Painful vaso-occlusive episodes or sickle cell crisis, acute chest syndrome, pyelonephritis,

cerebrovascular accidents, and preeclampsia are common in these patients.

Acute chest syndrome is the most common cause of mortality in patients with SCD. It is characterized by chest pain, respiratory distress with tachypnea, coughing and wheezing, fever, decreased oxygen saturation, abnormal pulmonary function studies, and radiologic evidence of a pulmonary infiltrate involving at least one complete lung segment. It frequently occurs in the course of a vaso-occlusive crisis. Multilobar involvement is common. The most common causes are infection, infarction, and fat embolization (Vichinsky et al., 2000). Fat embolization has a particularly poor prognosis and the diagnosis is made by microscopic analysis of sputum or bronchial samples.

Treatment

Blood transfusions are utilized to decrease the incidence and severity of pregnancy-related problems in patients with SCD. Transfusions can be given prophylactically or used only when specific indications such as sickle cell crisis, infection, or arrest of erythropoiesis are present.

The purpose of prophylactic administration of red cells is to prevent fetal and maternal problems. However, there is no agreement on the value of prophylactic transfusion for pregnant patients with SCD. Preventive transfusions reduce the frequency of sickle cell crisis and the number of admissions to the hospital. On the other hand, frequent transfusions have a risk of infection and are associated with iron overload and the possibility of red cell alloimmunization. The National Institutes of Health had a Consensus Development Conference on transfusion therapy in pregnant patients with SCD and concluded that the risks and benefits have not been established and this treatment is not ready for routine clinical use.

Two methods have been used for prophylactic transfusions. In the first, the patient has a partial isovolumetric exchange transfusion at 28 weeks of gestation to achieve a hematocrit value of 35% and a concentration of hemoglobin A1 of at least 40%. The procedure is repeated if a crisis occurs, if the hematocrit value drops below 25%, if the hemoglobin A1 drops below 20%, or when the patient reaches 36–38 weeks of gestation. In the second method, packed red cells are given by simple infusion, starting as soon as the diagnosis of pregnancy is established and then intermittently throughout the rest of the pregnancy. The objective of the serial transfusions is to keep the hematocrit value above 25% and the concentration of HbSS below 50%.

Proponents of the first method believe that the most serious complications in patients with SCD appear in the last trimester of pregnancy, that these complications are prevented by this method, and that fewer transfusions are given than with serial intermittent transfusions. Those who use the protocol with intermittent transfusions beginning early in pregnancy believe that it is better to correct the maternal oxygen-carrying capacity as early as possible to avoid problems both in mid pregnancy as well as in late pregnancy.

Koshy et al. (1988) compared the benefits and risks of prophylactic transfusions initiated at the start of the observation period with transfusions given only in emergency situations. They found that patients receiving prophylactic transfusions had significant pain relief and lower rates of SCD-associated complications. However, no difference between the groups was found in other respects such as obstetrical complications, alloimmunization, and perinatal outcome. It seems, therefore, that transfusion only when there is a specific indication is the best method for managing SCD in pregnancy. With this approach, the hazards associated with prophylactic transfusions are decreased. Partial exchange transfusions may be carried out manually using phlebotomy followed by infusion (Box 18-3), or using an automated erythrocytapheresis with a cell separator. This technique allows a fast and rigorously controlled exchange that is valuable for the patient in crisis or congestive heart failure.

Sickle cell crisis is the most common reason for hospitalization of pregnant women with SCD and the most frequent indication for partial exchange transfusion. The common denominator of the crisis is pain that may be generalized but frequently is confined to the long bones and joints, chest, or abdomen. Fever, leukocytosis, elevated bilirubin, and LDH are also components of the crisis. The main objectives of treatment are relief of the severe pain, reduction in HbSS concentration, and diagnosis and treatment of infection. Secondary objectives are hydration and to increase oxygen supply to the tissues to decrease the likelihood of further sickling (Box 18-4). Treatment usually involves pain management, oxygen therapy, antibiotics, incentive spirometry, bronchodilators, and in most cases transfusion therapy.

BOX 18-3

Protocol for isovolumetric partial exchange transfusion

- Obtain baseline hemoglobin, hematocrit, and Hb electrophoresis
- Type and crossmatch four units of leukocyte-poor packed red cells
- Infuse 500 ml of normal saline solution (1 hour)
- Remove 500 ml of blood from the opposite arm (30 minutes)
- Transfuse 2 units of packed red cells, warmed, under pressure (1–2 hours)
- Rest patient for 4 hours
- Repeat procedure
- Obtain postprocedure hemoglobin, hematocrit, and Hb electrophoresis

BOX 18-4

Management of sickle cell crisis

- *IV hydration*—1 L of Ringers lactate at 250 ml/hour, then at 125 ml/hour. Careful assessment of input and output
- *Pain relief*—IV morphine, Demerol, or fentanyl by pump using patient-controlled analgesia
- *Transfusion*—Partial exchange transfusion of four units of leukocyte-poor RBCs. Partial exchange transfusion may be repeated the following day if necessary to achieve hematocrit between 30 and 35% and hemoglobin A between 50 and 60%
- *Antibiotic*—Use broad spectrum IV antibiotic until infection is ruled out
- *Oxygenation*—Administer oxygen per nasal cannula at 3 L/minute

The treatment of painful crisis during pregnancy is complicated because of the fear of fetal side effects and because of probably unfounded concerns about the mother becoming addicted to pain-relief medications. These fears should not interfere with pain-relief efforts. The effect of narcotics on the baby is transient and will disappear once the crisis is over and the mother is not taking narcotics. The fear of drug addiction is almost always unfounded and most of these women do not become addicts or drug seekers. Most of these patients require treatment with morphine, Demerol, or fentanyl. The preferred route of administration is by means of IV pump and patient controlled analgesia.

Infection is a frequent cause of sickle cell crisis but diagnosis is difficult because many of the signs and symptoms of a vaso-occlusive crisis are similar to those of infection. However, the potential benefits of antibiotic administration are larger than their potential side effects and antibiotic treatment should be initiated once the patient is admitted in crisis and continued until the possibility of infection has been ruled out.

Patients with SCD do not require iron supplementation during pregnancy unless laboratory evidence of iron deficiency is obtained. In contrast, they need adequate folic acid supplementation to compensate for the increased consumption of folate secondary to the active process of cell replication that takes place in their bone marrow.

Patients with sickle cell hemoglobin C disease and sickle cell beta thalassemia disease may have problems during pregnancy similar to patients with SCD, but the frequency and severity of these problems are substantially less. A similar relatively benign situation occurs in patients with SCD who have elevated (greater than 10%) concentrations of HbF. In these two groups of patients, the need for prophylactic transfusions is less than in those with SCD.

Sickle cell trait

Patients with sickle cell trait are heterozygous or carriers for the SCD mutation and have only one beta-chain affected (HbAS). The condition is present in about 10% of the African-American population of USA. Women with sickle cell trait are not at great risk for abnormal reproductive performance. One important problem for these patients is the possibility of transmission of the abnormal gene to their descendants. A second problem is that they are at increased risk for the development of preeclampsia (Larrabee and Monga, 1997).

Women with sickle cell trait should have preconceptional counseling, and the male partner should be examined to determine whether or not he also carries the trait. If the father is a carrier, there is a 25% chance that the infant will be homozygous and have SCD. In this situation early prenatal genetic diagnosis is important because it will allow the possibility of pregnancy termination. Early prenatal diagnosis is possible with the use of polymerase chain reaction (PCR). Another alternative for these couples is the possibility of preimplantation genetic diagnosis using one or two cells obtained by blastomere biopsy (Xu et al., 1999).

Beta thalassemia minor

Beta thalassemia minor, or beta thalassemia trait, is second in frequency to sickle cell trait among pregnant women with hemoglobinopathies. These women are heterozygous for one mutation in the beta-globin gene. This defect causes diminished synthesis of hemoglobin beta-chains and mild anemia. There are many point mutations in the globin gene that may cause beta thalassemia minor, and this explains the clinical variability of the condition. The anemia is microcytic and hypochromic, and there is basophilic stippling of the erythrocytes. The hemoglobin levels range from 8 to 10 g/dl. The diagnosis is frequently missed, and the patients are repeatedly treated with large doses of oral, and in some instances parenteral, iron without therapeutic response. This is dangerous because they may develop hepatic and cardiac hemosiderosis secondary to iron overload. An easy way to differentiate the microcytic hypochromic anemia of beta thalassemia minor from iron deficiency is to look at the red blood cells (RBC) count. Patients with low hemoglobin due to iron deficiency have a low RBC count while patients with similar low hemoglobin due to beta thalassemia minor have just a minimal decrease in the RBC count.

The diagnosis of beta thalassemia minor should be suspected when the MCV is 75 fl or less and the RBC is greater than 4.5–5.0 million cells/μL. If doubts remain, measurement of serum ferritin and serum iron will clarify the diagnosis. However, a patient with beta thalassemia minor may have coinciding iron deficiency, and to avoid

missing the diagnosis it is necessary to obtain a hemoglobin electrophoresis. This test is also necessary in every pregnant patient with microcytic, hypochromic anemia who does not respond to oral iron by an elevation of her hemoglobin concentration after 4 weeks of treatment. Patients with beta thalassemia minor characteristically show hemoglobin A2 (HbA2) concentrations greater than 3.5% and normal or increased serum iron concentrations. In 90% of the cases the HbA2 level is above 5%. Also, approximately 50% of women with beta thalassemia minor will exhibit a hemoglobin F concentration greater than 2%.

Patients with beta thalassemia minor have a reproductive performance similar to patients with normal hemoglobin. They do not require iron supplementation during pregnancy unless there is laboratory evidence of iron deficiency. If it is necessary to raise their red cell number, the only way to do it is through transfusions.

Immune Hemolytic Anemia

In Immune hemolytic anemia, the patient makes autoantibodies of the immunoglobulin (IgG) type or "warm antibodies" against red cell antigens, causing premature destruction of these cells. In other cases the RBCs are sensitized with both an IgG antibody and complement, usually C3. More rarely, the RBCs only exhibit complement and no IgG. This abnormality may occur in association with several diseases (leukemia, lymphomas, viral infections) or as a consequence of an immune reaction to certain drugs (penicillin, sulfas, quinidine). The most frequent cause of this abnormality in pregnant women is an autoimmune disorder. On a few occasions, no cause can be discovered and the disorder is named "idiopathic immune hemolytic anemia."

In immune hemolytic anemia, IgG antibodies and complement coat the red cell surface, making them stick to reticuloendothelial cells which contain receptors for both IgG and complement. When the red cells detach, some membrane fragments remain on the reticuloendothelial cells. As a consequence of this loss of membrane fragments, the erythrocytes are transformed into spherocytes and are easily destroyed in the spleen or the liver. The hemolytic process is extravascular and clinical or laboratory evidence of intravascular hemolysis is only seen when the hemolytic process is brisk and overwhelms the extravascular removal mechanisms.

The diagnosis of immune hemolytic anemia is made with the direct Coombs test. In this test, red cells of the patient are mixed with Coombs anti-human globulin antiserum, and since they are coated with IgG and complement, agglutination occurs immediately. This is different from the indirect Coombs where maternal serum is added to a panel of erythrocytes of known antigen specificity. In this case agglutination occurs if the maternal serum contains an antibody against an antigen contained in the red cells. The direct Coombs is used to detect IgG molecules already attached to the erythrocyte while the indirect Coombs is used to detect specific antibodies present in a serum sample.

It is important to rule out the possibility of a connective tissue disorder, mainly systemic lupus erythematous, in all patients with immune hemolytic anemia. This is done with laboratory tests to determine antinuclear antibody titers and anti-DNA antibodies. These tests are negative in idiopathic immune hemolytic anemia.

Treatment of immune hemolytic anemia consists of the administration of immunosuppressive drugs. Glucocorticoids, used in doses equivalent to between 60 and 100 mg of prednisone per day, are first choice. These steroids act preferentially by interfering with the reticuloendothelial cell recognition of the IgG and complement, covering the erythrocyte surface and, to a smaller extent, by interfering with the process of antibody synthesis.

In cases not responsive to glucocorticoids, the drug of choice is azathioprine. Splenectomy may be necessary to arrest the hemolytic process. However, not all patients respond to surgery. The degree of splenic entrapment of radioactively tagged red cells may identify those patients who would benefit from splenectomy.

Some patients with lupus-induced hemolytic anemia during pregnancy may exhibit hemoglobin concentrations less than 5 g/dl. Transfusions seem to be clearly indicated in these cases, but most patients quickly hemolyze the transfused red cells. The only hope of finding some compatible blood in these desperate situations is by in vivo crossmatching. For this purpose, a small amount of red cells from the potential donor is tagged with 51Cr and given to the patient. If the red cells are hemolyzed, radioactive chromium will be released from the cells and found in the plasma. If no hemolysis occurs, the radioactivity will remain contained in the red cells. In the majority of cases, the best management is to wait for the patient's response to glucocorticoids rather than to transfuse. In some critical patients, however, cells that are quickly destroyed must be given to keep the patient alive until the effect of the immunosuppressant drugs is apparent.

APLASTIC ANEMIAS

Aplastic anemias rarely occur during pregnancy, and fewer than 50 cases have been reported in the literature. The causes of aplastic anemia are diverse and include ionizing radiation, ingestion of myelosuppressant agents, toxins, immune disorders, infections, and malignant diseases. However, in most of these cases, no apparent cause is found. The diagnosis requires bone marrow biopsy. The

disease has a serious prognosis, and the maternal mortality is about 30%. However, recent advances in the treatment of aplastic anemias using bone marrow transplantation, antithymocyte globulin, high-dose corticosteroids, and cyclosporine may improve the maternal outcome.

ABNORMALITIES OF THE HEMOSTATIC SYSTEM

The hemostatic system seals vascular leaks and prevents bleeding. Alterations in this system resulting in deficient clot formation or in thrombosis are of interest to the obstetrician because they are serious and relatively common during pregnancy.

Adequate hemostasis is maintained through a precise interaction between the vessel wall, the platelets, the coagulation system, and the fibrinolytic system. The vessel wall actively participates in the hemostatic process by vasoconstriction and by production of substances necessary to inhibit platelet aggregation. Platelets are necessary for the formation of the primary hemostatic plug and for the production, storage, and release of substances required for the enlargement of the temporary clot. The coagulation system participates in the hemostatic process through a series of reactions that culminate in the transformation of fibrinogen into fibrin. The fibrinolytic system prevents the continuous enlargement of the hemostatic plug by breaking down fibrin into fibrin degradation products. The harmonious interaction of these four components is necessary in order to maintain the integrity of the vascular system.

Pregnancy brings about physiologic changes in the hemostatic system that result in a hypercoagulable state. This is due to an increase in several of the factors involved in the coagulation cascade and also to a depressed activity of the fibrinolytic system. These changes represent the maternal adaptation to tolerate the hemostatic challenge that occurs at the time of parturition.

A significant number of the abnormalities of the hemostatic system seen by the obstetrician are secondary to severe bleeding and are rapidly corrected with replacement of coagulation factors and control of the hemorrhage. The causes of obstetrical bleeding severe enough to cause alterations of the hemostatic system (placenta previa, placenta accreta, placental abruption, and postpartum hemorrhage) are described in Chapter 13. Less commonly the obstetrician is faced with the pregnancy care of women with platelet disorders or alterations of the clotting system, which are the subject of this chapter.

Platelet Disorders

The platelet disorders most commonly seen in obstetrical patients are thrombocytopenia and abnormalities of platelet function. Abnormalities in the number of platelets are classified as mild when the platelet count is between 150,000 and 100,000/mm^3, moderate when the count is between 100,000 and 50,000/mm^3, and severe when the count is less than 50,000/mm^3. Low platelet counts are tolerated well and the threshold for clinically significant spontaneous bleeding is a count of 10,000/mm^3. In the case of surgical interventions or delivery the threshold is higher, 50,000/mm^3.

Gestational thrombocytopenia, a benign common disorder, is the numeric platelet deficiency seen most frequently in obstetrics. Second in frequency is the thrombocytopenia characteristic of HELLP syndrome, a severe form of preeclampsia, which is described in a Chapter 16 of this book. The third type of thrombocytopenia, which is only seen rarely during pregnancy, is autoimmune thrombocytopenia, also called ITP (immune thrombocytopenic purpura). Also relatively uncommon are platelet dysfunction disorders secondary to dense granules deficiency.

Gestational thrombocytopenia

Gestational thrombocytopenia is the correct diagnosis in approximately 80–90% of all the cases of thrombocytopenia during pregnancy. The remainder of the cases correspond to the low platelet count which is associated with preeclampsia and HELLP syndrome and only rare cases will be the consequence of ITP.

The cause of gestational thrombocytopenia is unknown. It appears in about 8% of all pregnancies. The platelet count rarely drops below 70,000/mm^3. Women are asymptomatic and have a completely negative history of abnormal bleeding. The condition is benign and offers no risk for mother or infant.

The main problem associated with gestational thrombocytopenia is the reluctance of anesthesiologists to give epidural or spinal anesthesia if the platelet count is < 100,000/mm^3. This is regrettable and these women frequently are delivered by cesarean section under general anesthesia and have poor pain relief during labor. Treatment with steroids and IgG or platelet transfusion before delivery is sometimes necessary to raise the platelet count to a level acceptable to the anesthesiologist.

Immune thrombocytopenia

ITP is a disorder seen between 1 in 1000 and 1 in 10,000 during pregnancies, which is characterized by an autoantibody-mediated destruction of maternal platelets. These autoantibodies react with the platelet glycoprotein complex Iib/IIIa or more rarely with the Ib/IX complex in the platelet surface and the antibody-coated platelets are phagocyted by macrophages. The bone marrow increases platelet production and releases young large platelets into

the circulation. The patients are usually asymptomatic, but may complain of easy bruising or bleeding, and frequently have petechiae. Laboratory evaluation reveals thrombocytopenia, enlarged platelets, and normal erythrocyte and leukocyte counts. The diagnosis of ITP is reliable only when it is made before pregnancy or when the platelet count is under 50,000/mm^3 in pregnant women with a past history suggestive of a bleeding disorder.

When ITP appears during pregnancy, both the mother and the fetus may be affected. The greatest concern in these cases has been with the fetal effects, since 5–10% of the newborns will have a platelet count below 50,000/mm^3. This concern is unfounded since the possibility of intracranial bleeding during labor in these patients is minimal as demonstrated by a study of more than 15,000 women, 46 of them with ITP (Burrows and Kelton, 1993). Two of 31 infants born to mothers with ITP and thrombocytopenia had platelet counts of 21,000 and 28,000/mm^3 and 2 infants from 15 mothers with ITP and no thrombocytopenia had platelet counts of 36,000 and 49,000/mm^3. None of these 4 infants had adverse outcomes and none had evidence of intracranial bleeding. The same study indicates that the risk of intracranial bleeding is limited to infants with alloimmune thrombocytopenia, which is caused by platelet-specific PLA1 alloantibody. Fetal and neonatal thrombocytopenia in ITP are the result of transplacental passage of maternal antiplatelet antibodies that bind to antigenic sites on the surface of the infant's platelets and facilitate their destruction in the spleen. Since the antigenic composition of the infant's platelets is unknown, it is impossible to predict without measuring the baby's platelet count whether or not fetal thrombocytopenia is present.

The presence of elevated direct or indirect platelet-associated IgG antibodies (PA-IgG) in the plasma is not useful for the diagnosis of ITP. This test does not distinguish between the IgG of antiplatelet antibodies and the IgG normally released from the platelet alpha-granules. In addition to the poor specificity, the PA-IgG test is poorly standardized, has a large degree of interlaboratory variation, and does not distinguish between autoantibodies and HLA alloantibodies. Finally, measurements of maternal circulating or platelet-bound antibodies are unreliable for predicting fetal or neonatal platelet counts. The antigenic composition of the surface of the fetal platelets is different from that of the mother, and the concentration of maternal antibodies is irrelevant if those antibodies do not react with the infant's platelets. Similarly to PA-IgG the maternal platelet count cannot predict the fetal platelet count and mothers with platelet counts under 20,000/mm^3 may have newborns with normal platelets and a mother with a platelet count of >100,000/mm^3 may deliver a thrombocytopenic infant.

In pregnant women with ITP it is necessary to monitor the platelet count frequently especially in the last trimester because this is the time when thrombocytopenia gets worse. No treatment is necessary until the platelet count reaches 30,000/mm^3. When this happens, the treatment of choice is intravenous IgG. In most cases a single dose of IV IgG (1 g/kg IV over 6 hours) will raise the platelet count to over 50,000/mm^3. This treatment is expensive and its effects only last for 1–3 weeks, requiring repeated doses. The mechanism of action of IgG is not clear but it may be that the IgG blocks the receptors in the macrophages and prevents the accelerated removal and destruction of platelets.

The risk of intracranial bleeding in thrombocytopenic fetuses is less than 1%, and this is a problem that occurs in the neonatal period and it cannot be prevented by cesarean section (Payne et al., 1997). Therefore, it is not necessary to measure the fetal platelet count to determine the type of delivery. Women with ITP and platelet counts greater than 50,000/mm^3 must be managed conservatively during labor and delivery, and cesarean should be performed only for obstetrical indications.

The newborn of the mother with ITP requires frequent measurements of the platelet count because they will drop after delivery, reaching a nadir at day 2. Exceptionally the platelet count will be low enough to require treatment with IgG.

Disorders of platelet function

Conditions characterized by abnormal platelet function are rare and are not frequently diagnosed during pregnancy. However, they should be suspected in cases of late postpartum bleeding. These abnormalities may affect platelet adherence, platelet activation, platelet aggregation, or the interaction of platelets with coagulation factors. In addition to postpartum bleeding, patients with platelet dysfunction disorders frequently have a history of heavy menses, easy bruising, recurrent epistaxis, and bleeding from their gums. Bleeding after tooth extractions is another common complaint.

The abnormality of platelet function most frequently seen in women with recurrent postpartum bleeding is platelet granule deficiency. Patients with this abnormality have normal PT (prothrombin time) and activated partial thromboplastin time (aPTT) and platelet count. Platelet aggregation is frequently abnormal. The diagnosis is made by electron microscopy that reveals a low number of platelet granules. Treatment consists in the administration of platelets, preferably one single donor unit, before delivery. Treatment needs to be repeated if there is late postpartum bleeding.

Coagulation Disorders

Congenital disorders of the coagulation system are rare during pregnancy. The most common inherited coagulopathy seen in women of reproductive age is von Willebrand's disease (VWD).

Von Willebrand's disease

The von Willebrand's factor (VWF) is a high-molecular-weight glycoprotein produced by endothelial cells which is a major component of the factor VIII complex. A quantitative or qualitative deficiency in VWF results in VWD. VWF is necessary for the binding of platelet receptor glycoproteins to the subendothelial matrix at sites of vascular injury, the first step in the formation of a clot. The VWF is also a carrier protein for factor VIII and prolongs its half-life in the circulation. The VWF is composed of multimers with a molecular weight ranging from 0.5 to 20.0 million Da. VWF multimers 12 million Da or larger are the most effective in supporting platelet adhesion.

There are three types of VWD. Type 1 is the most common and affects approximately 75% of all patients with this condition. The disorder is usually inherited in an autosomal dominant manner and most cases are heterozygous. In type 1 disease the mutation causes the synthesis of an abnormal protein that forms dimers which are trapped in the endoplasmic reticulum and cannot be secreted into the plasma. Characteristically, these patients have a history of mild to moderate bleeding with minor cuts, heavy menstrual periods, easy bruising, and bleeding when they brush their teeth or blow their nose. Usually the bleeding disorder is discovered when they undergo surgery or trauma and have severe bleeding. Type 2 VWD is characterized by functional abnormalities of the VWF and a variable decrease in VWF antigen, ristocetin cofactor activity (functional VWF), and factor VIII concentration. The diagnosis of type 2 VWD is made by determining the multimeric composition of VWF which will reveal a loss of high-molecular-weight multimers. Type 3 VWD is very rare and corresponds to a homozygous or double heterozygous form of the disease. Bleeding in these cases is severe and factor VIII levels are markedly decreased.

Bleeding time was used in the past as a screening test for VWD. This test has wide variability and has been replaced by the automated platelet function-100 assay (PFA-100). In this test citrated blood is aspirated onto a membrane covered with collagen and epinephrine or collagen and ADP. The membrane has a small opening and the time that it takes for the blood to flow through the opening in the membrane (closure time) is a measure of platelet function. A deficiency in VWF concentration or function will affect the platelet adhesion to collagen and the closure time will be prolonged. Also, since VWF is a carrier protein for factor VIII the aPTT will be prolonged when VWF concentration is low.

Definite diagnosis of VWD requires determination of VWF and factor VIII levels. The VWF can be tested by immunological or functional methods. The functional test (ristocetin cofactor activity) measures the platelet aggregation induced by the addition of ristocetin to the patient's platelet rich plasma. The immunological test measures the percentage of normal VWF antigen present in plasma. These tests have large variability and are affected by the patient's blood type. Patients with blood type O have lower levels of VWF than patients with blood types A, B, or AB.

VWD must be suspected in any pregnant patient with an abnormal bleeding tendency, particularly with recurrent postpartum bleeding. Such a patient should be screened with PFA-100, aPTT, PT, and platelet count. If the platelet count is normal and the PFA-100 and aPTT are abnormal, the probability of VWD is high and a definite diagnosis should be obtained by measurement of factor VIII, VWF antigen, and ristocetin cofactor assay.

The course of pregnancy in the majority of patients with VWD is benign. The most frequent complication is bleeding during labor, delivery, or in the postpartum period. Pregnancy causes an increase in VWF, and the probability of bleeding is inversely related to the magnitude of this increase. In general, if VWF rises to about 50% of the normal concentration, the probability of intrapartum or immediate postpartum bleeding is small. However late postpartum bleeding occurs often and the patient is at risk for 2–3 weeks and especially during the first 5 postpartum days. If the concentration of VWF by the end of pregnancy is less than 25% of normal the possibilities of intrapartum bleeding are significant.

Desmopressin (DDAVP) is the drug of choice for postpartum bleeding in women with type 1 VWD. DDAVP is a vasopressin analogue which has been successfully used in patients with VWD to promote the release of the VWF from endothelial cells. The dose is 0.3 mg/kg given over 15–30 minutes. This dose causes the release of large amounts of VWF from endothelial cells stores which persist for 4–6 hours. The antepartum administration of DDAVP is not recommended because of the possibility of harmful stimulation of uterine contractions. Patients with type 2 and 3 VWD require therapy with Humate-P—a factor VIII concentrate that contains a large amount of VWF multimers or with cryoprecipitate. DDAVP may aggravate bleeding in patients with type 2 VWD. Each bag of cryoprecipitate contains approximately 100 units of VWF. In general, 15–25 bags of cryoprecipitate should be given as the initial dose, and 7–12 bags should be given every 12 hours to keep the level of VWF at around 30% of normal. Cryoprecipitate should only be used when Humate-P is not available. Humate-P may be given before

delivery in anticipation of epidural anesthesia or for the prevention of intrapartum bleeding. Humate-P administration should be continued for 7–10 days postpartum.

Thrombophilia

Thrombophilia is an affinity or predisposition to the formation of clots that may be acquired or hereditary in nature. Thrombophilia is important in obstetrics because deep vein thrombosis (DVT) as well as a significant number of poor obstetric outcomes are associated with the presence of thrombophilic disorders in the mother (Arias et al., 1998). The most important acquired thrombophilic condition is the antiphospholipid antibody syndrome—a condition described in Chapter 13 because of its relevance as a cause of second trimester abortion. There are many hereditary thrombophilias, but this discussion will be limited to those that occur relatively frequently. They are the factor V Leiden (FVL) mutation, prothrombin promoter mutation, protein S deficiency, protein C deficiency, and hyperhomocysteinemia. Rare problems that will be mentioned briefly include antithrombin III deficiency, 4G/4G mutation in plasminogen activator activity, and increased activity of factors VIII and XI.

Under normal circumstances injury of a vessel wall results in the formation of a clot that would continuously enlarge if the reactions leading to clot formation were not adequately counterbalanced by mechanisms that inhibit coagulation. Most hereditary thrombophilias directly or indirectly affect the normal mechanisms of anticoagulation, resulting in DVT except during pregnancy when the favorite target for the formation of clots is the placenta.

Pregnancy by itself is a prothrombotic state. Pregnant women undergo a series of physiological changes in their coagulation system in preparation for the hemostatic challenge of delivery. To avoid severe bleeding at the time of placental separation, pregnant women have a physiologic increase in fibrinogen, thrombin, and most of the coagulation cascade factors and a decrease in fibrinolytic activity, changes that are more apparent during the last trimester of pregnancy.

The placental circulation is characterized by low pressure and slow flow, conditions that favor the formation of clots. Therefore, it is not surprising that the combination of a low-pressure system and the prothrombotic changes of pregnancy make the placenta a preferred target organ for mothers with hereditary thrombophilias. Placental infarcts, spiral artery thrombosis, and excessive fibrin deposition in the intervillous space are lesions of the maternal side of the placental circulation that are seen with significantly increased frequency in mothers with thrombophilia than in normal subjects. In the fetal side of the placenta, thrombophilia is expressed as fetal thrombotic vasculopathy that corresponds to thrombosis of the umbilical stem vessels and areas of avascular, nonfunctional villi in the territory of the thrombosed vessel.

The placental damage caused by thrombophilia is associated with fetal loss in the first and second trimester, fetal growth restriction, fetal death, placental abruption, preeclampsia, and preterm birth secondary to preterm labor or rupture of the membranes. There is not a clear explanation for the varied clinical expressions of placental thrombophilia but the most logical explanation is that the host response to the placental lesion is determined by the host genotype.

Factor V Leiden

FVL mutation is responsible for approximately 40% of the cases of DVT during pregnancy. Its presence is associated with early pregnancy losses, preeclampsia, and fetal growth restriction. The mutation corresponds to the substitution of a guanine for adenosine in nucleotide 1691 of the factor V gene. This results in the substitution of arginine by glutamine in position 506 of the protein chain. As a result, factor V becomes resistant to inactivation by activated protein C (APC). FVL is an autosomal dominant mutation with variable penetrance. It is more prevalent in northern Europeans (5–15%) and uncommon in African-Americans (1.2%), and Asian Americans (0.45%).

Under normal conditions, factor V is activated by thrombin and the resulting factor Va serves as a cofactor for the conversion of prothrombin to thrombin. Factor Va is inactivated by APC. It has three cleavage sites, the first corresponding to the arginine in position 506. Individuals with FVL mutation will be resistant to the effect of APC because the arginine in position 506 has been changed to glutamine and inactivation of factor Va will proceed slowly leading to a prolonged aPTT. The prolonged aPTT can be corrected by the addition of normal pooled plasma or a standardized amount of APC. These facts were the basis for the development of an APC resistance assay that measured the ratio of aPTT performed in the absence and presence of added plasma or APC. The first-generation APC resistance assay had poor sensitivity and specificity and has been replaced by second-generation tests that have close to 100% sensitivity and specificity for the FVL mutation. The mutation can be identified directly by polymerase chain reaction probes specific for the nucleotide mutation.

FVL mutation poses a significant risk for DVT, cerebral vein thrombosis, pulmonary embolization with or without DVT, and placental thrombosis. The risk of thromboembolism increases with the presence of other risk factors such as ingestion of oral contraceptives, postmenopausal hormone replacement, advanced age, smoking, and increased body mass index. The risk of thrombosis also significantly increases when FVL mutation is combined with other

inherited coagulation defects such as protein S deficiency, prothrombin 20210 mutation, elevated factor VII levels, and hyperhomocysteinemia. Homozygosity to FVL also increases the risk of thromboembolism.

Heterozygosity for FVL during pregnancy has been associated with an increased risk of DVT and pulmonary embolization (Grandone et al., 1998) and to obstetrical complications such as placental abruption, fetal growth restriction, preeclampsia, and fetal death (Kupferminc et al., 1999). Patients with FVL mutation can develop pulmonary embolization in the absence of DVT (Bounameaux, 2000).

Not all carriers of the FVL mutation are at similar risk for systemic or placental thromboembolization. Advanced maternal age, obesity, multiparity, smoking, prolonged bed rest for the treatment of obstetrical complications, and cesarean section or other surgical procedures during pregnancy place these women at higher risk. However, the most important risk factor is a history of placental thrombosis or DVT in the patient herself or in a first degree relative (Zotz et al., 2003). A history of DVT increases the probability of DVT from 10 to 50% (Simioni et al., 2001). Similarly, although there are not adequate studies in this area, placental thrombosis and poor obstetrical outcome seem to have a high risk of recurrence. A similar lack of data confuses the meaning of paternal heterozygosity for FVL. Fetal carriage of the mutation has been associated with growth restriction, preterm birth (Gopel et al., 1999; von Kries et al., 2001), and placental infarcts in abortion specimens (Dizon-Townson et al., 1997). When both parents are carriers of the mutation, there is a 25% chance for the fetus being homozygous and the risk of placental thrombosis is significant.

Heterozygous carriers of FVL mutation require anticoagulation during pregnancy to avoid DVT and placental thrombosis. What is not clear is the degree of anticoagulation, prophylactic or therapeutic, necessary to prevent adverse outcomes. The only randomized clinical trial in this subject compared low-dose aspirin with prophylactic heparin (40 mg daily enoxaparin) and found that heparin was better than aspirin with respect to overall pregnancy outcome, birth weight, and incidence of fetal growth restriction (Gris et al., 2004). This investigation strongly suggests that the basic treatment for women with thrombophilia should be heparin in prophylactic (low dose) doses. However, there are situations where therapeutic anticoagulation is justified (Box 18-5).

Prophylactic heparinization can be achieved with unfractionated (regular) or with low-molecular-weight heparin (LMWH). Regular heparin is given subcutaneously every 12 hours at a dose of 5000 units in the first trimester, 7500 units in the second trimester, and 10,000 units in the third trimester. The medication should be discontinued at least 12 hours before induction or cesarean delivery and restarted the first postpartum day for 6 more weeks. There is no need to monitor the treatment with laboratory tests.

BOX 18-5

Indications for therapeutic anticoagulation in carriers of the factor V Leiden mutation

- History of DVT, PE, or placental thrombophilia
- Double heterozygous with other thrombophilia
- History of stillbirth(s)
- History of placental floor infarct
- Father heterozygous for factor V Leiden or other thrombophilia
- Mother homozygous for factor V Leiden mutation

Prophylactic anticoagulation with LMWH requires one subcutaneous injection daily. The dose of enoxaparin is 40 mg daily. This treatment does not require laboratory monitoring. Since LMWH has a prolonged action, it is better to substitute the medication for regular heparin after 36 weeks of gestation in anticipation of delivery. Unfractionated heparin should be discontinued at least 12 hours before delivery. LMWH may be restarted on the first postpartum day. Therapeutic heparinization is described later in this chapter under Treatment of pulmonary embolization.

Prothrombin 20210 mutation

This mutation consists of the substitution of a guanine for adenine at nucleotide 20210 in the prothrombin gene. The mutation is in the promoter region of the gene and results in increased synthesis of prothrombin and tendency toward coagulation. The mutation occurs more frequently in Southern Europe where it affects 3% of the population. In USA it affects 2.3% of Caucasians but it is rare in African-Americans and Asians.

Heterozygous carriers of the prothrombin 20210 mutation are at increased risk for deep vein and cerebral vein thrombosis. In a study performed in Italy, the mutation was present in 8.0% of patients with DVT as compared with 2.3% in the control population (Poort et al., 1996). Heterozygous carriers are at high risk for a second thrombotic defect, usually FVL, and double heterozygosity increase the odds ratio for DVT from 3.8 to 20.0. When DVT occurs during pregnancy, 31% of the cases had the prothrombin 20210 mutation (Grandone et al., 1998).

The diagnosis of prothrombin 20210 mutation is made by PCR. The elevated concentration of plasma prothrombin exhibited by these patients cannot be used for diagnosis because they frequently overlap with normal values.

Prophylactic treatment during pregnancy is similar to that suggested for carriers of the FVL mutation. Treatment

of DVT during pregnancy will be described later in this chapter.

Protein S deficiency

Protein S is a vitamin K-dependent protein that acts as a cofactor for the inactivation of factor Va and factor Xa by APC. Approximately 40–50% of protein S is in free form and has cofactor activity. A deficiency of protein S will slow the inactivation of factors Va and Xa, increasing the plasma procoagulant activity. Protein S has a relatively large gene localized in chromosome 3. Because of the large gene size and the presence of a pseudogene, identification of the protein S mutations has been difficult and the disease is defined on the basis of alterations in the concentration and activity of the plasma protein. Type I protein S deficiency is characterized by low levels of free protein S antigen and protein S functional activity. Type II deficiency is characterized by normal concentration of free protein S but decreased functional activity. In type III deficiency the total protein S (bound and free) is normal but free protein S and functional activity are decreased.

Protein S deficiency is a high risk factor for thromboembolism and placental clotting. This defect is more thrombogenic than FVL or protein C deficiency (Martinelli et al., 1998). The diagnosis is made by measuring free protein S antigen concentration using a monoclonal antibody and free protein S functional activity as a cofactor for APC.

Protein S functional and immunological levels are decreased during pregnancy (Comp et al., 1984), making the interpretation of these tests difficult during gestation. A normal result rules out the condition but an abnormal result needs to be confirmed outside of pregnancy.

Due to the thrombogenic potential of protein S deficiency pregnant women with this defect should be treated with therapeutic anticoagulation during pregnancy.

Protein C deficiency

Protein C is a vitamin K-dependent protein that after being activated by thrombin (APC) inactivates factor Va and factor VIIIa in a reaction that is enhanced by protein S. The gene for protein C is located in chromosome 2, and more than 160 different gene abnormalities have been associated with a deficient protein that is inherited in an autosomal dominant fashion.

There are two types of protein C deficiency. In type I both the concentration and the functional activity of the protein are under 50% of the normal value. In type II the concentration of protein C antigen is normal but the functional activity is decreased. Type I is the most common of the two subtypes.

Protein C deficiency is relatively uncommon and it is found only in 1–2% of cases of thromboembolic disease. During pregnancy protein C deficiency is associated with fetal death (Sarig et al., 2002). The normal concentration of protein C is from 70 to 140% of normal. A protein C concentration less than 55% is diagnostic of a deficiency and values between 55% and 70% require repeated testing. For screening, determination of protein C functional activity is a better test than determination of antigen concentration because the functional tests detect both subtypes of the condition.

Similarly to protein S, protein C deficiency conveys a higher risk of thrombosis than FVL. Homozygous or double heterozygous protein C deficiency is a cause of neonatal purpura fulminans—a life-threatening coagulopathy that presents in the first day of life and is characterized by extensive venous and arterial thrombosis and levels of protein C less than 1% of normal (Seligsohn et al., 1984). Treatment of purpura fulminans with heparin is ineffective, and these newborns require administration of concentrated protein C.

Because of the high thrombogenic potential of protein C deficiency, pregnant women affected by this condition should be therapeutically anticoagulated during pregnancy. Also, because of the potential severity of homozygosity in the newborn, the father should be screened for this condition.

Hyperhomocysteinemia

Homocysteine is an amino acid produced during the metabolism of methionine. Once it is formed, homocysteine is rapidly metabolized by a trans-sulfuration reaction catalyzed by the enzyme cystathionine-beta-synthase with formation of cysteine or transformed back into methionine by a methylation reaction catalyzed by the enzyme methionine synthase. Alterations in either of these metabolic pathways will result in hyperhomocysteinemia.

Enzymatic deficiencies in the trans-sulfuration pathway are rare and have severe clinical consequences. Alterations in the methylation pathway are relatively common but their clinical manifestations are subtle.

The most common form of genetic hyperhomocysteinemia results from a mutation causing alanine to valine substitution in amino acid position 677 (C677T) in the enzyme methylene tetrahydrofolate reductase (MTHFR). MTHFR is the enzyme providing the methyl group for the transformation of homocysteine into methionine. The amino acid substitution results in a thermolabile variant of the enzyme that has reduced enzymatic activity, causing accumulation of homocysteine. The MTHFR mutation is common, affecting 5–15% of the Caucasian population of USA.

Homocysteine causes vascular damage including endothelial dysfunction, thickening of the intima, inhibition of the production of nitrous oxide, hypertrophy of

the smooth muscle, platelet accumulation, and formation of thrombi. It also has prothrombotic effects including activation of factors V and VII, increased blood viscosity, and changes in thrombomodulin function. These changes are associated with premature coronary heart disease, myocardial infarction, and stroke. Elevated homocysteine is also a risk factor for DVT and pulmonary embolization. Elevated plasma levels of homocysteine significantly increase the risk of thrombosis in patients with other thrombophilias, such as FVL mutation or prothrombin promoter mutation. Women with preeclampsia, fetal growth restriction, abruption, and fetal death are more likely to exhibit the MTHFR abnormality (de Vries et al., 1997). However, there is no evidence supporting a causal role or a strong association between heterozygous and homozygous carriers of the MTHFR mutation and poor obstetrical outcomes. The importance of the MTHFR mutation in obstetrics is limited to its role in increasing the thrombogenic potential of inherited thrombophilias.

The normal concentration of fasting plasma homocysteine is between 5 and 15 μmol/L. Hyperhomocysteinemia is moderate if the plasma concentration is between 15 and 30 μmol/L, intermediate if it is between 30 and 100 μmol/L, and severe if it exceeds 100 μmol/L. The mean plasma concentration in normal pregnant women is 5.4 ± 1.4 μmol/L, which is significantly lower than that in the nonpregnant status (8.7 ± 1.7 μmol/L) (Bonnette et al., 1998).

Administration of folic acid lowers plasma homocysteine levels. Homozygous patients with homocysteine levels above 15 μmol/L should expect normalization of the plasma concentration after 2 weeks of treatment with 1–4 mg/day of folic acid, 10–25 mg/day of vitamin B_6, and 400–1000 μg/day of vitamin B_{12}. Heterozygous patients will need no more than the 400 μg of folic acid contained in most prenatal vitamins.

Thromboembolism During Pregnancy

Venous thromboembolism is one of the two leading causes of maternal mortality during pregnancy. Thrombosis occurs when the natural anticoagulant mechanisms are unable to control an abnormal tendency toward the formation of clots. There are multiple factors that cause activation of the clotting system, and pregnancy itself represents a high-risk situation for abnormal clotting. The tendency to hypercoagulability during pregnancy is in part the result of the physiologic increase in several coagulation factors and the decrease in the natural anticoagulant protein S that occurs in preparation for the hemostatic challenge of placental separation. A second important factor that predisposes pregnant women to venous thromboembolism is the increased venous stasis of the lower extremities due to the increased blood volume of pregnancy and the interference of the return circulation from the lower extremities by the pregnant uterus.

The majority of patients who develop thromboembolism during pregnancy belong to a population characterized by the presence of one or more of the following risk factors: (a) cesarean-section delivery, (b) obesity, (c) use of estrogen to suppress lactation, (d) obstetric complications involving prolonged bed rest (prolonged labor, multiple labor inductions, difficult deliveries, etc.), (e) age greater than 30 years and high parity, and (f) presence of a thrombophilic factor. The incidence of thromboembolism during pregnancy is between 1 in 500 and 1 in 2000 pregnancies. DVT and pulmonary embolization occur five times more frequently in the puerperium than during pregnancy.

Deep vein thrombosis

About 85% of venous thrombosis affects the proximal veins and the rest are confined to the calf veins. When the thrombosis is limited to the calf veins, the possibilities of pulmonary embolization are relatively small but they increase dramatically when the clot extends into the proximal veins.

An underlying thrombophilia can be found in approximately 60% of the cases of DVT. The most common are the FVL mutation, prothrombin 20210 mutation, protein S deficiency, and increased factor VIII activity. Antithrombin deficiency, protein C deficiency, hyperhomocysteinemia, and abnormalities in fibrinogen or fibrinolysis are uncommon.

The clinical diagnosis of lower extremity DVT is in error 50% of the time. When this diagnosis is being considered, the clinical impression must be confirmed or ruled out with laboratory tests. The most commonly used are venous ultrasonography, impedance plethysmography, and contrast venography. The gold standard for the diagnosis of DVT is contrast venography. Unfortunately, venography has side effects (pain, local chemical phlebitis, accidents due to the contrast dye, etc.) in one out of every four patients and, therefore, is not the procedure of choice.

Venous sonography is the preferred noninvasive method for the diagnosis of DVT. This technique allows visualization of the common and the superficial femoral veins, the popliteal vein, and the proximal calf veins, a process that is markedly facilitated with the combined use of pulsed and color Doppler (duplex Doppler). The veins are compressed with the transducer probe and the inability to fully obliterate the vein is diagnostic of the presence of a clot. Duplex Doppler has 95% sensitivity and 97–100% specificity when compared with venography in nonpregnant patients for the diagnosis of DVT (White et al., 1989).

Another test is impedance plethysmography using the occlusive cuff technique. This method measures the changes in electrical impedance that occur with changes in the blood volume of the leg. When the venous return is impaired with a cuff applied to the thigh, there is a local increase in blood volume followed by a rapid decrease when the cuff pressure is released. These changes in volume are reflected by changes in electrical impedance, which is altered when DVT is present. The test is highly specific (less than 5% false positives) and very sensitive (less than 5% false negatives) for the diagnosis of popliteal and suprapopliteal DVT.

The D-dimer is used in nonpregnant individuals to diagnose DVT and pulmonary embolization. The test measures the plasma concentration of D-dimer, which is a peptide formed by the degradation of cross-linked fibrin by plasmin. The test has an excellent negative predictive value, and a normal result may be used to rule out DVT or pulmonary embolus. Unfortunately, the test is not useful in obstetrical patients because the concentration of D-dimer increases during normal pregnancy, giving false positive results.

Once the diagnosis of DVT has been established, anticoagulation is mandatory. Twenty to thirty-five percent of patients who have episodes of DVT during pregnancy and receive no treatment, experience a recurrence, 19% will develop pulmonary embolism (PE), and 29% of those with PE die. Therapeutic heparinization will be discussed later in this chapter under Treatment of DVT and pulmonary embolization.

Pulmonary embolization

PE is an important cause of maternal mortality during pregnancy. The incidence is approximately 2.7 per 1000. In about 95% of the cases, PE is secondary to DVT of the ileofemoral veins and, in the majority of cases, it occurs in the immediate postpartum period.

All the clinical signs and symptoms of PE are inconsistent and unreliable. Dyspnea is the most common symptom followed by chest pain. Typically, these patients have arterial PO_2 below 80 mmHg and pCO_2 below 40 mmHg but, not uncommonly, the arterial blood gases are within normal range. The chest radiography and the electrocardiogram are usually normal or unspecific. The more useful diagnostic tests for PE are the ventilation/perfusion scan (V/Q scan), the spiral (helical) CT scan, and the pulmonary angiogram.

The test most frequently used for the diagnosis of PE is the V/Q scan. In this test lung perfusion is assessed by the intravenous injection of radiolabeled microaggregates of human albumin that get trapped in the capillaries of the lung. Ventilation is assessed by inhalation of a radioactive aerosol. The fundamental part of the test is the perfusion test, and if it is normal there is no pulmonary embolization. However, if one or more perfusion defects are present they are not specific and it is necessary to determine if ventilation is normal or not in the areas of abnormal perfusion. If there is normal ventilation in an area of abnormal perfusion, the test is highly suspicious for pulmonary embolization. Unfortunately only 40% of the V/Q scans in patients with PE indicate a high probability of the condition. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED, 1990) found that PE was present in 88, 33, and 12 of patients with V/Q scans indicating high, intermediate, and low probability of embolization, respectively. Patients with intermediate probabilities of PE by V/Q scan require further testing with spiral CT or pulmonary angiogram.

The spiral (helical) CT scan is a technological advance that permits complete image acquisition of the lung during a single holding of the breath. Therefore it can be used to capture images of the pulmonary arteries after the injection of a radiographic contrast substance. The method is highly sensitive and specific for pulmonary embolus in large or segmental branches of the pulmonary artery but is less specific for emboli located in the subsegmental arteries. Thus the helical CT scan cannot completely exclude a pulmonary embolus, and if the clinical suspicion is high the next test will be a pulmonary angiogram which is the definite test for the diagnosis of PE. Unfortunately the pulmonary angiogram is an invasive test, available only in large medical centers and with significant number of complications that include cardiac arrest, arrhythmias, and allergic reactions to the contrast medium.

Figure 18-1 shows the sequence of steps to be followed in the evaluation of patients suspected of PE. If the clinical presentation is strongly suggestive of PE, the diagnostic studies must be initiated after giving the patient an intravenous injection of 10,000 U heparin and the treatment with heparin discontinued later depending on the results of the diagnostic work-up. It is also important to look for proximal DVT of the lower extremities in all cases in which PE is suspected, since DVT is present in about 95% of all cases of PE. The following are the most important points to remember:

1. Most patients with PE have clear chest x-ray films.
2. A positive perfusion scan is required for the diagnosis of PE. If the perfusion scan is *negative* the patient does not have PE, and no further testing is necessary.
3. A V/Q mismatch is not diagnostic of PE, since there are other causes of pulmonary vascular obstruction (i.e., inflammation). However, the probability of PE is high.
4. A helical CT angiogram has 100% sensitivity for pulmonary emboli in the main pulmonary arteries, 85% in the lobar arteries, and 60% in the segmental

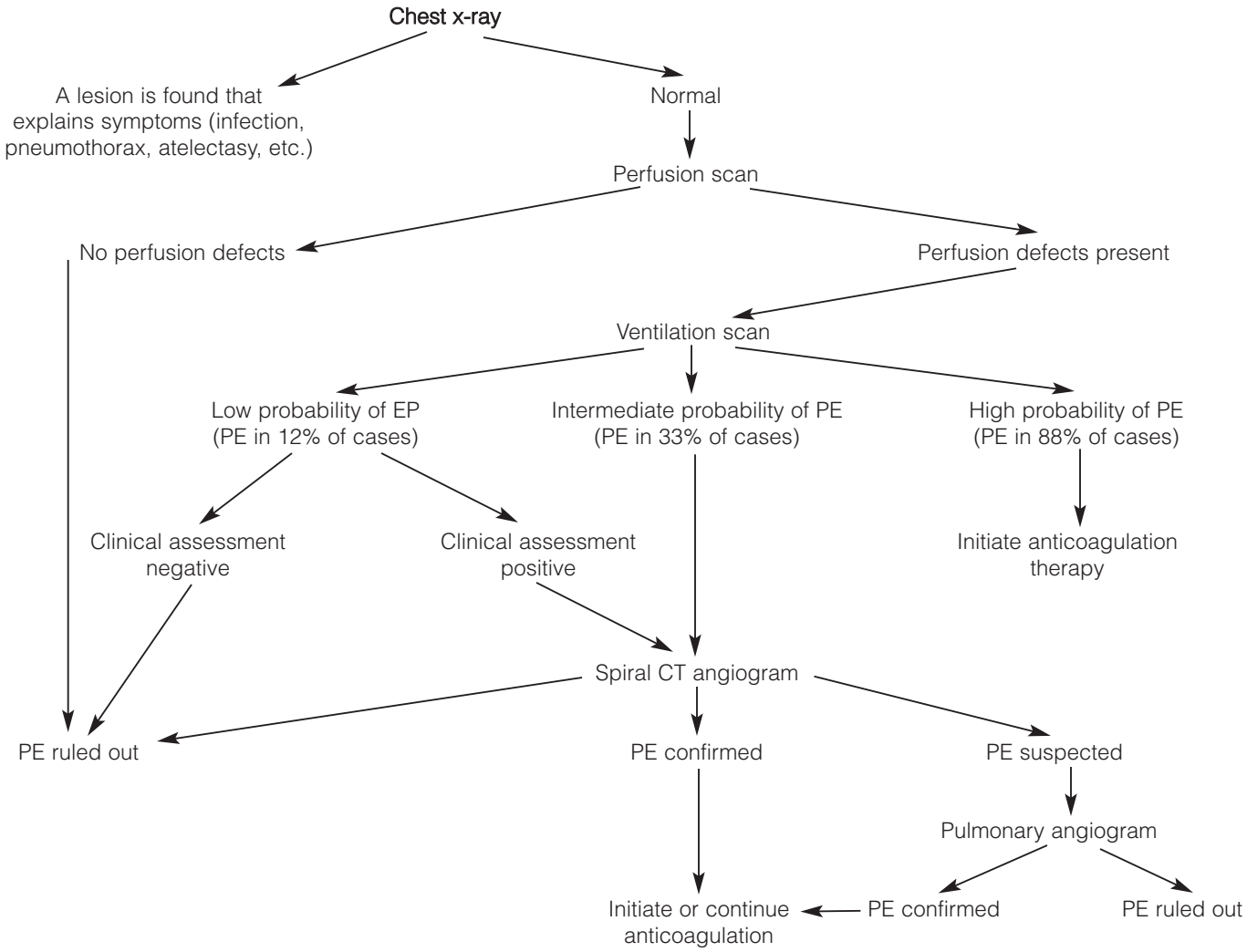

Figure 18-1. Diagnostic steps in patients suspected of pulmonary embolization.

arteries. Defects located in the subsegmental arteries require further investigation with pulmonary angiogram.

5. Pulmonary angiography is the only procedure to establish definitely the diagnosis of PE.

Treatment of DVT and pulmonary embolization

Therapeutic anticoagulation is necessary in cases of DVT or PE. Heparin is the drug of choice because of the teratogenic effects of coumadin and the lack of knowledge about the safety of thrombolytic agents and direct thrombin inhibitors. Heparin therapy has a low rate of maternal and fetal complications and is an effective drug for the prophylaxis and treatment of DVT and PE (Ginsberg et al., 1989).

Heparin is a glucosaminoglycan that acts as anticoagulant by binding to antithrombin and increasing the ability of this natural anticoagulant to inactivate thrombin, factor IXa, and factor Xa. There are two different types of heparin that may be used for anticoagulation during pregnancy: unfractionated heparin and LMWH. Unfractionated heparin has a half-life of 30 minutes, requiring two or three daily doses to maintain adequate anticoagulation. It binds to several plasma proteins that have variable concentration, resulting in considerable variability in the anticoagulation response. This makes it necessary to obtain frequent laboratory monitoring of the medication with aPTT. LMWH is obtained by depolymerization of unfractioned heparin and has a longer half-life (3 hours), allowing administration in one or two doses a day. LMWH binds significantly less to plasma proteins than unfractionated heparin, resulting in a more predictable anticoagulant effect obviating the need for laboratory monitoring. Despite these advantages unfractionated heparin continues to be used frequently due to the high cost of LMWH.

The initial anticoagulation with unfractionated heparin requires continuous intravenous administration of the medication. It is a common practice to administer a bolus

of 10,000 U followed by a continuous IV infusion. The initial amount of heparin to be given every hour by continuous IV infusion may be calculated using the following formula:

Heparin infusion rate = Css × K × V

where Css is the steady state concentration of heparin in serum, usually 0.2–0.3 μ/ml, which is the therapeutic level; K is the elimination constant (0.832 μ/hour); and V is the volume of distribution that varies from 60 ml/kg in the first trimester to 90 ml/kg in the third trimester. According to this formula, a patient in the second trimester of pregnancy weighing 140 lbs (63 kg) will require a heparin infusion rate of 917 units/hour (0.25 × 0.832 × 70 × 63).

A continuous IV infusion of heparin is monitored with daily measurements of the aPTT. The goal is to maintain the aPTT between 2.0 and 2.5 times the normal laboratory control or the patient baseline value. Once the desired PTT has been obtained and maintained without large fluctuations, the frequency of laboratory testing may be decreased.

Treatment with intravenous heparin is continued for a minimum of 7 days or in the case of women with DVT until the pain in the extremity has completely subsided. At this time subcutaneous administration of heparin is started and continued until delivery. The total daily IV dose is divided in two or three doses to be given SC every 12 or every 8 hours. The aPTT needs to be checked 6 hours after an SC dose and the amount of medication adjusted accordingly. One strategy is to start with one dose every 12 hours until the volume of injection necessary to achieve the aPTT goal exceeds 2 ml when it is necessary to change the timing of administration to every 8 hours to avoid giving an excessive volume with each injection.

The delivery of patients that are fully anticoagulated should be planned to minimize the possibility that they arrive to the hospital in active labor and require reversal of treatment. Induction of labor or cesarean delivery is usually scheduled at 38 weeks of gestation and the patient is instructed to withhold heparin treatment for 24 hours before delivery. If the patient develops labor unexpectedly and delivery is anticipated to occur less than 12 hours after a heparin dose, it may be necessary to reverse the effect of heparin. This is done by IV injection of protamine sulfate. The dose of protamine sulfate depends on the amount of heparin given and the time of heparin administration. If heparin was given less than 30 minutes before surgery or delivery it is necessary to give 1.0–1.5 mg of protamine sulfate per each 100 units of heparin; if heparin was given between 30 and 60 minutes, the dose is 0.5–0.75 mg of protamine sulfate per 100 U heparin; if heparin was given more than 2 hours before surgery or delivery the protamine sulfate dose is 0.25–0.375 per each 100 U heparin.

Heparin administration is restarted 12–24 hours after delivery. At this time the patient may be switched to oral anticoagulation with warfarin (coumadin). Coumadin is started at a dose of 5 mg daily the first postpartum day. Heparin is given simultaneously with coumadin at the same dose it was given before delivery and discontinued 3 or 4 days later when coumadin has taken effect as shown by elevated PT and international normalized ratio (INR) values. The dose of coumadin is adjusted up or down until the amount necessary to maintain the INR 2.0–2.5 times the control value is reached. Once the INR is at this level, the frequency of testing may be reduced to every week. Anticoagulation should be maintained for 3–6 months after delivery.

Therapeutic anticoagulation with LMWH can be achieved with one or two subcutaneous injections daily. The single daily dose is 1.5 mg enoxaparin per kilogram. When the medication is given in two doses, the amount of LMWH is 1.0 mg/kg every 12 hours. The goal of treatment is to achieve antifactor Xa levels of 0.6–1.0 U/ml 4 hours after the injection. It is unnecessary to test the antifactor Xa levels more frequently rather than testing every trimester of pregnancy. Women on LMWH should be switched to regular heparin at approximately 36 weeks and the regular heparin discontinued at least 12 hours before delivery. Therapeutic doses of LMWH may be restarted the first day postpartum and the medication given together with coumadin for 3 or 4 days until the INR is between 2.0 and 2.5 times the control value. The INR is checked every week once the therapeutic dose of coumadin has been found.

The side effects of heparin treatment are few and uncommon. The most serious is heparin-induced thrombocytopenia. This problem usually occurs at the beginning of treatment and may be detected by a platelet count after 1 or 2 weeks of treatment. Heparin-induced thrombocytopenia is less frequent with LMWH. Other problems relate to bruises and painful nodes at the injection site that usually respond to applied ice and pressure.

INDIAN EXPERIENCE OF ANEMIA COMPLICATING PREGNANCY

Anemia is widespread in India. Although it affects 13% of the population in the developed world, it is known to affect 44% of those living in the underdeveloped world. In India, the magnitude of this problem can be assessed from the fact that anemia affects about 13 million pregnant women out of the population of 22 million pregnant women.

About 0.5 million women in India die annually, as a result of complications related to pregnancy and childbirth. Anemia is a major contributor toward this

appallingly high maternal mortality. It is directly responsible for about 20% of maternal deaths and it is a contributory factor in another 20% of maternal deaths following obstetric hemorrhage, obstructed labour, sepsis, and other causes (Daftary and Desai, 2005). WHO reported an association of anemia in 64.4% of maternal deaths in India during 1992–1994 (Bhatt, 1997). Pregnancy anemia is often a continuation of the prepregnancy state. In India, poverty, malnutrition, illiteracy and ignorance, religious taboos, superstitions and unfounded beliefs, gender discrimination, early marriage, early childbearing, poor contraceptive acceptance, poor spacing of childbirths, social dependence, poor prenatal care, and the common practice of home deliveries or deliveries under poor supervision are important contributory causes of adverse obstetric outcome—inadequate obstetric and health services, which are not easily accessible due to poor transportation, combine to pose formidable problems in our national efforts to reduce maternal mortality.

An interesting survey of the ill-effects of anemia in pregnancy (Awasthi et al., 2001) is summarized in Table 18-1 to emphasize the importance of detecting and treating anemia during pregnancy.

It is evident from Table 18-1 that both the maternal and perinatal hazards increase with maternal anemia. Anemia is easily detectable and can be treated efficiently in most cases. Timely correction of the disorder holds an important key in the promotion of safe motherhood in India.

Table 18-1. Maternal and perinatal hazards of anemia in pregnancy

Maternal outcome	Severe anemia (Hb < 6.5 g/dl)	Moderate anemia (Hb 6.5–8.0 g/dl)	Non-anemic (Hb > 10.5 g/dl)
Preterm labour	13.2%	4.19%	3.1%
Normal delivery	42.2%	69.50%	89.0%
Cesarean section	24.5%	20.50%	5.0%
PIH (toxemias)	28.0%	13.00%	2.0%
Antepartum hemorrhage	10.5%	2.60%	2.0%
Postpartum hemorrhage	7.5%	1.39%	0.7%
Maternal mortality	7.1%	3.30%	2.0%
Perinatal outcome	**Anemic mothers (Hb < 8.0g/dl)**	**Nonanemic mothers (Hb > 10.5 g/dl)**	
Preterm births	9.5%	4.0%	
IUGR	37.5%	20.0%	
Neonatal asphyxia	7.0%	3.0%	
Congenital anomalies	1.5%	1.0%	
Stillbirths	6.5%	2.0%	
Early neonatal deaths	4.5%	1.0%	
Average birth weight	2.0 kg	2.5 kg	
Perinatal mortality rate	117.6/1000	30.6/1000	

Adapted from Awasthi A, Thakur R, Dave A, et al. Maternal and perinatal outcome in case of moderate and severe anemia complicating pregnancy. J Obstet Gynaecol India 2001; 51: 45.

Nutritional deficiencies (iron, folate, proteins, vitamin C) play a dominant role in the causation of anemia in India; apart from these, helminthiasis and chronic parasitic infestations (malaria), chronic blood losses, hemoglobinopathies (β-thalassemia is seen more often then sickle cell anemia), and rarely aplastic anemia may be encountered in practice. Iron deficiency accounts for more than 80% of cases of anemia in India. Screening of the entire obstetric population with a simple screening test of hemoglobin estimation at the first antenatal visit is of paramount importance in the early detection of anemia.

Blood indices and microscopic examination of the peripheral blood smear generally suffice to arrive at an etiological diagnosis. However, in selected cases special investigations like estimation of serum iron, serum total iron-binding capacity, serum ferritin, serum folic acid, and vitamin B_{12} estimations are recommended. Bone marrow smear testing and hemoglobin electrophoresis are recommended in selected cases. In India, an effort to detect malarial parasites in endemic areas is important. Lastly, a stool examination to exclude intestinal parasites is also important.

In an epidemiological study from Nagpur (Khandat et al., 2001) to identify high risk factors contributing to anemia, the following were recognized: age < 20 years or > 30 years; parity > two; low socioeconomic status, illiteracy, caloric intake < 80%; BMI, 18.5; vegetarian diet, unemployment, and worm infestation.

It is not uncommon in India to encounter severely anemic pregnant women (Hb < 5.0 g %) presenting with extreme weakness manifesting cardiac decompensation. These women fare well when treated with partial exchange transfusions and packed cell transfusions (Singh et al., 2001). β-thalassemia (Desai and Desai, 1997) is known to occur in certain communities in India (Sindhi and Lohana). Incidence of sickle cell anemia has been reported as 10.1% (trait) and 0.7% (sickle cell disease; Pada Patti and Rout, 2000) from western Orissa.

INDIAN EXPERIENCE OF THROMBOCYTOPENIA IN PREGNANCY

- An interesting case report of ITP in a pregnant primigravida was reported by Das et al. (2003) from Lucknow. This 23-year-old primigravida had been investigated 4 years earlier for recurrent gingival bleeding attributed to thrombocytopenia, and she did not respond satisfactorily to medical therapy (oral steroids) therapy; hence she was subjected to splenectomy. During her present pregnancy, the patient revealed a low platelet count of 50,000/ml. However during

Table 18-2. Correlation between severity of PIH and mean platelet counts

Patient type	Joshi-Kale and Sapre (2004)	Kulkarni and Suturia (1983)	Agarwal and Buradkar (1978)	Dube et al. (1975)
	Mean platelet count			
Normal: control	2.2 lakhs	2.50 lakhs	2.4 lakhs	2.3 lakhs
Mild PIH	2.0 lakhs	1.89 lakhs	2.1 lakhs	1.9 lakhs
Moderate PIH	1.4 lakhs	1.19 lakhs	2.1 lakhs	1.9 lakhs
Severe PIH	1.3 lakhs	1.18 lakhs	1.6 lakhs	1.8 lakhs

labour, the platelet count dropped to 20,000/ml. She was administered 4 units of platelets infusion, one unit of fresh blood transfusion, and 1.0 g prednisolone intravenously. There was no evidence of in the patient of thrombocytopenia after delivery, nor was there any evidence of neonatal thrombocytopenia.

- Biswas et al. (1994) reported on the occurrence of platelet disorders in pregnancy.
- Joshi-Kale and Sapre (2004) from Gwalior reported on the incidence of thrombocytopenia in patients with pregnancy-induced hypertension (PIH). Thrombocytopenia was related to the severity of the disease and predisposed to HELLP syndrome and DIC (disseminated intravascular coagulation). Joshi-Kale and Sapre reported a close correlation between severity of PIH and mean platelet counts observed and compared their findings with those reported from other centers in India as shown in Table 18-2.

  All the authors are in agreement that the platelet counts decrease in cases of hypertensive disorders complicating pregnancy. However, the mean drop in values does not often drop to the threshold required for manifest clinical bleeding disorders.
- Kaur et al. (2003) from Amritsar reported an incidence of 6.9% for hypertensive disorders complicating pregnancy. Of these cases 4.0% develop HELLP syndrome, and 49.33% developed partial HELLP syndrome (increased liver enzymes alone was reported in 67.5%, lowered platelet count alone was reported in 24.3% cases, and in 8.2% there was no hemolysis).
- Alauddin et al. (2001) reported on an interesting case of secondary postpartum hemorrhage after a normal delivery at the hospital 11 days earlier. She had been discharged from hospital well on the 3rd postpartum day. Five days after going home she suffered from secondary postpartum hemorrhage, epistaxis, and hematuria. At the time of her readmission, her hemoglobin had dropped to 5.0 g %. Bleeding and clotting times were within normal limits, but her platelet count was 46,000/ml. She required 8 units of fresh blood transfusions to bring her bleeding under control.
- Sud et al. (2001) reported on the efficacy of immunoglobulin therapy in HELLP syndrome with intractable postpartum following twin delivery. The patient delivered vaginally, and thereafter she developed severe atonic postpartum hemorrhage which did not respond to uterotonic agents. Hence she was subjected to an abdominal subtotal hysterectomy. Postoperatively she continued to deteriorate—intraperitoneal bleeding was suspected—hence the patient was subjected to another exploratory laparotomy, when on both sides the anterior division of the internal iliac arteries and ovarian arteries were ligated and a drain left behind, but as the bleeding continued, on the 5th postpartum day, investigations revealed raised liver enzymes and a platelet count of 28,000/ml. The patient was administered 3 units of fresh frozen plasma and 5.0 g immunoglobulins intravenously twice daily for five doses. After three doses of immunoglobulins, her platelet count rose to 68,000/ml and on the 9th postoperative day, the platelet count increased to 1.0 lac/ml. The patient made a smooth recovery thereafter.

IMPORTANT POINTS

1. Anemia is present during pregnancy if the hemoglobin concentration is less than 10 g/dl or the hematocrit is less than 30%. These values are lower than those in the nonpregnant state due to the physiological hemodilution that occurs during pregnancy.
2. Iron deficiency is responsible for approximately 80% of all anemias during pregnancy. The main reasons for this are inadequate dietary iron and insufficient iron stores to meet the demands of pregnancy.
3. Ideally, iron deficiency should be diagnosed when iron stores are depleted but abnormal erythropoiesis has not started. The best test to assess the status of the iron stores is serum ferritin.
4. In patients with iron-deficiency anemia, an abnormal RDW occurs before generalized microcytosis and hypochromia.
5. A pregnant woman needs 300 mg ferrous sulfate orally daily to prevent iron-deficiency anemia. Treatment of overt disease requires higher doses.
6. Most cases of megaloblastic anemia are due to folic acid deficiency. However, the laboratory assessment of these patients should include a serum vitamin B_{12} level. This avoids missing the rare patient who has vitamin B_{12} deficiency and may suffer progressive demyelinization.
7. The most common hemolytic anemia observed during pregnancy occurs in patients with severe preeclampsia and HELLP syndrome. The blood smear in these patients shows schistocytes, burr cells, helmet cells, and fragmented cells.

8. A microcytic, hypochromic anemia, and a hemoglobin A2 level greater than 3.5% are characteristic features of patients with beta thalassemia minor.
9. In the management of pregnant patients with SCD a controversy exists between proponents of prophylactic transfusion and those of transfusion for specific indications. Prophylactic transfusions decrease the frequency of painful crises and disease-associated complications but have no effect on obstetric complications, alloimmunization, or perinatal outcome.
10. Platelet counts less than 150,000/mm^3 are relatively common in pregnancy, but the majority correspond to gestational thrombocytopenia. Only 20% of those patients have preeclampsia or ITP.
11. The diagnosis of idiopathic ITP during pregnancy is difficult. It requires a platelet count less than 50,000/mm^3 and a history of abnormal bleeding before pregnancy. The presence or absence of antiplatelets antibodies is irrelevant to the diagnosis.
12. The maternal platelet count and the presence of antiplatelet antibodies cannot be used to predict the fetal platelet count in women with ITP.
13. Every woman of reproductive age with DVT or pulmonary embolization should be tested for thrombophilic factors. The most frequent are FVL mutation, prothrombin 20210 mutation, protein S, and protein C.
14. The gold standard for the diagnosis of DVT is contrast venography, but it has side effects in 25% of the patients. Duplex Doppler is the test of choice for the diagnosis of popliteal, femoral, or iliac thrombosis but is less accurate for calf thrombosis.
15. A V/Q mismatch is not diagnostic but indicates a high probability of pulmonary embolization. Angiography is the gold standard for the diagnosis of pulmonary embolization, but in many cases the diagnosis can be made using spiral CT angiogram.

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19

Abnormalities of the Urinary System During Pregnancy

CHAPTER OUTLINE

CHANGES IN THE URINARY SYSTEM DURING PREGNANCY

To better understand the effect of renal disease on pregnancy and the effect of pregnancy on preexistent kidney disease, it is necessary to briefly review the anatomic and functional changes that occur in the urinary system during gestation. The most important anatomic change in the urinary tract during pregnancy is the dilatation of the collecting system. The renal calices, the renal pelvis, and the ureters begin to dilate in the second trimester and remain enlarged for several weeks after delivery. The cause of this dilatation is unknown, although it is generally accepted that it is mediated by placental progesterone. After 18 weeks of gestation, compression of the ureters by the uterus at the level of the pelvic brim is another factor contributing to dilatation and stasis of urine in the upper part of the collecting system. Because of these changes the frequency and severity of urinary tract infections increases.

The most important physiologic changes that occur in the kidney during pregnancy are as follows:

1. Increase in renal plasma flow (RPF)
2. Increase in glomerular filtration rate (GFR)
3. Changes in tubular reabsorption of glucose, sodium, amino acids, and uric acid

The increase in RPF begins in the second trimester and is probably due to the combined effect of the increased cardiac output and decrease in renal vascular resistance that occur during pregnancy. It has been calculated that approximately 25% of the cardiac output during pregnancy is destined to flow through the kidneys. The effect of pregnancy on renal vascular impedance is the result of increased production of renal prostaglandins.

The most important consequence of the increased RPF is a 50% increase in the GFR, to an average of 137 ml/minute. For that reason, a 24-hour creatinine clearance of 110 ml/minute, normal outside of pregnancy, is

inadequate during gestation. Also, the serum creatinine and urea nitrogen concentrations will be lower than in the nonpregnant situation. The average serum creatinine concentration during pregnancy is 0.6 mg/dl and a value above 0.8 mg/dl is suspicious. Similarly, the average blood urea nitrogen (BUN) during pregnancy is 9 mg/dl and any value greater than 13 mg/dl is abnormal.

The renal handling of glucose is markedly altered during pregnancy and glucosuria frequently occurs in the presence of normal blood glucose values. This happens because of the increased GFR combined with an impaired tubular reabsorption of glucose. Glucosuria is a factor that favors urinary tract infections during pregnancy.

The average plasma sodium concentration during pregnancy is 136 mEq/L. This slight decrease in plasma sodium concentration during pregnancy is the result of an increased amount of filtered sodium secondary to the increased GFR. During pregnancy the amount of sodium presented to the tubules for reabsorption is approximately 30,240 mEq/day, while the nonpregnant woman filters only about 20,160 mEq. Although the efficiency of tubular sodium reabsorption during pregnancy is remarkable, the serum sodium equilibrates at a slightly lower level than in the nonpregnant status.

As a result of the increased GFR, serum uric acid concentration decreases slightly during the second trimester, but it returns to normal nonpregnant levels (4–6 mg/dl) during the third trimester. Some investigators believe that preeclampsia selectively affects the tubular reabsorption and causes a characteristic elevation of uric acid.

Maternal position has a profound influence on renal function. RPF, GFR, sodium excretion, and urinary production decrease when the patient is recumbent. All these indices return to normal when the patient assumes the lateral decubitus position. Also, the dorsal decubitus position worsens the compression of the ureters by the pregnant uterus.

RENAL DISEASE AND PREGNANCY

Following are the two most common situations that the obstetricians face when renal conditions complicate pregnancy:

1. The acute onset of signs and symptoms of renal disease in patients with no history of kidney problems before pregnancy, the most common being acute pyelonephritis and urinary stone disease.
2. The occurrence of pregnancy in a patient with preexistent renal disease.

The problems posed by each of these situations are different and require separate analysis.

URINARY CONDITIONS OF NEW ONSET DURING PREGNANCY

Urinary Tract Infections

Infections of the urinary tract occur frequently during gestation. The bacteria causing these infections originally reside in the rectal/anal area and from there colonize the perineum, vaginal introitus, urethra, bladder, and eventually the pelvocaliceal area and the kidney itself. In most cases the ascending bacterial infection affects only the lower urinary tract (asymptomatic bacteriuria, acute cystitis) but during pregnancy as many as 25–40% of these lower infections ascend to the upper tract and cause acute pyelonephritis. Acute cystitis is usually severely symptomatic and most patients with this type of lower urinary tract infection are recognized and adequately treated. The problem lies in the patient who has asymptomatic bacteriuria, which needs to be recognized and treated to prevent upper tract disease.

Asymptomatic Bacteriuria

Approximately 4–10% of all pregnant women, particularly multiparous patients, have asymptomatic bacteriuria and, if untreated, 25–40% of them will develop symptomatic urinary tract infection including acute pyelonephritis. Asymptomatic bacteriuria is also an important risk factor for preterm labor and perinatal mortality. The incidence of all the complications associated with asymptomatic bacteriuria is significantly decreased with adequate treatment (Smaill, 2001).

The criterion commonly used to make the diagnosis of asymptomatic bacteriuria is the growth in solid culture of 100,000 or more colonies ($>10^5$ colony-forming units or CFU) by a single midstream catch technique. Some women have lower colony counts that probably reflect the efficacy of the bladder washout and bacteriuria should be suspected if the colony count is between 20^5 and 100^5/ml. In these cases the urine analysis may be useful and if there are more than 10 leukocytes/ml or the dipstick reveals leukocyte esterase or nitrates, most likely the patient has asymptomatic bacteriuria with a low colony count. A CFU of 20^5/ml is also diagnostic of bacteriuria if the urine sample is obtained by catheterization.

Screening for asymptomatic bacteriuria should occur at the first prenatal visit (Nicolle et al., 2005). The screening is done by culture of a urine specimen obtained by midstream catch. A urine dipstick is not an adequate substitute for urine culture and has unacceptably high false positive and false negative results. A positive nitrate test is only given by enterobacteria that convert nitrate to nitrite and leukocyte esterase is positive only when significant pyuria is present. Unfortunately, screening only once early

in gestation will not detect more than one-third of the women who will develop pyelonephritis. The detection rate increases with a second and even more with a third screening during the pregnancy, but this is only justified in women at high risk for urinary infection or at high risk for some of the complications associated with bacteriuria, such as preterm labor.

Several antibiotic regimens can be successfully used for the treatment of asymptomatic bacteriuria. A 3-day course of antibiotic is usually effective. One of the most commonly used is nitrofurantoin, 100 mg orally twice daily for 3–7 days. Trimethoprim–sulfamethoxazole (one tablet orally twice a day, single or double strength for 3 days), amoxicillin (500 mg orally three times a day for 3–7 days), amoxicillin–clavulanate (500 mg orally twice daily for 3–7 days), and cephalexin (500 mg orally twice daily for 3–7 days) can be used with similar success. However, resistance to amoxicillin and sulfonamides is common and it is better to select a drug after determining the antibiotic sensitivity of the bacteria. The success of treatment should be confirmed by a repeat urine culture 1 week after finishing treatment and the sterility of the urine confirmed by monthly cultures during the pregnancy. If bacteriuria persists or reoccurs, the treatment should be repeated. If bacteriuria persists after two courses of treatment, it is necessary to give one dose of antibiotic (500 mg cephalexin, or 100 mg nitrofurantoin) every night for the duration of the pregnancy. Continuous daily treatment is also necessary for patients who have relapses following successful treatments or who are reinfected by a different bacterial species.

Acute Pyelonephritis

Acute pyelonephritis affects 1–2% of pregnant women during pregnancy (Cunningham et al., 1973). It usually occurs in the second trimester (>50% of the cases) but it may occur also in the first and third trimesters of pregnancy. It is manifested by the onset of malaise, fatigue, chills, fever, and back pain which is usually located in the upper lumbar area. Some patients also complain of changes in the characteristics of the urine and symptoms of a low urinary tract infection. Nausea, vomiting, and uterine contractions frequently occur. On physical examination the patients have fever, are dehydrated, and have costovertebral angle tenderness. Frequently it is possible to see changes in the urine, which may look turbid or bloody. Urinalysis will demonstrate red cells, leukocytes, white cell casts, and, in the majority of patients, microscopic examination of unspun urine will show bacteria. Most patients show some signs of renal dysfunction such as slightly elevated serum BUN and creatinine and a creatinine clearance that is abnormally low for pregnancy.

Histologically, acute pyelonephritis is characterized by infiltration of the renal interstitium and the tubules by polymorphonuclear leukocytes, with formation of white cell casts. Healing of the acute lesion leads to cortical scarring and caliceal dilatation.

Acute pyelonephritis during pregnancy may have serious consequences. Some of them are effects of bacterial endotoxin, which can cause septic shock or pulmonary injury. Some other consequences of acute pyelonephritis, such as chronic renal infection, are the result of incomplete or delayed treatment or of coexistent obstruction. The reason why acute pyelonephritis may have unusual severity and complications during pregnancy is unknown. Some predisposing factors are the changes in maternal immunity to avoid rejection of the fetus that may decrease the ability to respond to the infection. Another factor are the physiological changes induced, by pregnancy, in the urinary tract that result in a mild to moderate obstructive effect which favors bacterial proliferation. In the case of adult respiratory distress syndrome (ARDS) complicating acute pyelonephritis, there is evidence suggesting that activation of the complement system with increased production of the split product C5a, a potent proinflammatory peptide, may be a mechanism of disease (Soto et al., 2005).

Acute pyelonephritis is an ascending infection caused by bacteria originally present on the perineum or in the vagina. Usually, a single bacterial species is the cause of acute pyelonephritis. The most common offender is uropathogenic *Escherichia coli* that is identified in 70–95% of the cases (Scholes et al., 2005). Uropathogenic *E. coli* are bacteria clones that have acquired in their genetic code the ability to colonize and invade the urogenital tract. One of them, clonal group A is responsible for a large proportion of the antibiotic resistant urinary infections (Manjes et al., 2001). Uropathogenic E. coli have fimbriae (P-fimbriae or P pilli) covered by adhesins, which are substances that bind to specific glycoprotein receptors on the surface of the epithelial cells (Le Bouguenec et al., 2001), a property that increases their virulence and their selectivity for the urinary tract (Latham and Stamm, 1984). Other bacteria causing acute pyelonephritis are Gram-negative bacilli (*Klebsiella pneumoniae, Proteus mirabilis*), enterococci, or *Staphylococcus saprophyticus*.

Bacterial virulence is not the only important factor implicated in the severity of urinary tract infections. Another factor is individual susceptibility. It has been demonstrated that women with nonsecretor Lewis blood group phenotypes are highly susceptible to urinary tract infections. Another important factor is the presence of anatomical or functional abnormalities, such as vesicoureteral reflux, that allows a direct route for ascending infection.

Treatment of pregnant patients with acute pyelonephritis should be aggressive to avoid progression of the disease and the occurrence of serious complications. These

women should be admitted to the hospital, hydrated, treated with antibiotics, and carefully monitored. Laboratory evaluation should include assessment of their renal function and electrolytes, and also a hemogram. A specimen of urine obtained by catheterization should be sent to the laboratory for culture and sensitivity testing. Blood cultures are usually unnecessary but should be obtained when the patient has chills or temperature elevation.

Patients with acute pyelonephritis during pregnancy need assessment of their vital signs at least every 4 hours. Tachycardia and hypotension may indicate early endotoxic shock. Because of the high risk for ARDS, they also require continuous monitoring with pulse oximetry (Pearl and Dattel, 1990). Desaturation should be followed by a chest x-ray to rule out the possibility of ARDS. They also require continuous fetal monitoring. Preterm labor is a frequent problem and they require continuous observation for uterine contractions.

Two important aspects of the treatment of patients with acute pyelonephritis during pregnancy are the administration of IV fluids and intravenous antibiotic therapy. These patients are frequently dehydrated and oliguric and require rapid expansion of intravascular volume with crystalloid solutions. The antibiotic of choice for acute pyelonephritis used to be ampicillin, 2 g IV every 4–6 hours. Unfortunately, the microbial resistance of Gram-negative bacteria to ampicillin is increasing. Thus, pending the results of laboratory identification of the infectious species, and its sensitivity to antibiotics, the best therapeutic option is to give Cefazolin, 2 g IVPB every 8 hours. A small number of women with penicillin allergy are also allergic to cephalosporins. However, penicillin allergy is not a contraindication to treatment with IV Cefazolin unless the history of allergy is one of anaphylactic shock or laryngeal edema.

Other equally effective intravenous antibiotics are gentamycin (1 mg/kg IV every 8 hours) alone or with ampicillin (2 g IV every 6 hours), ceftriaxone (1 g IV daily), or piperacillin–tazobactam (3.375 mg IV every 8 hours). Most patients respond quickly to hydration and antibiotic therapy and can be switched to oral antibiotic, once they have been afebrile for 24–48 hours. Most patients do well with 7–10 days of oral treatment but 14 days seems to be the optimal duration of therapy (Stamm et al., 1987). The best oral agents are the quinolones (ciprofloxacin and levofloxacin), but they are not the first choice during pregnancy because of concerns about fetal safety derived from joint and periarticular side effects observed in pediatric patients. However, a recent systematic review of antibiotics during pregnancy concludes that quinolones are most probably safe (Nahum et al., 2006). Follow-up with urine cultures is necessary. Recurrence of bacteriuria demands antibiotic treatment for the duration of pregnancy.

Patients who do not respond to antibiotic treatment within 72 hours, are infected by an uncommon organism, or relapse after discontinuation of treatment require imaging testing to rule out the possibility of obstruction. A renal sonogram is indicated initially and, if necessary, a "modified IVP" or "limited IVP," which consist of only one or two x-ray exposures following the administration of contrast medium, should be obtained. Ureteral stents and percutaneous nephrostomy may be necessary in patients with demonstrated urinary obstruction.

Acute Nephrolithiasis

Acute nephrolithiasis occurs once in every 1500 deliveries, usually during the second and third trimester of pregnancy. Urinary stones may develop in any part of the urinary tract but are usually renal. There are four types of urinary stones. Approximately 80% are made of calcium oxalate and, less commonly, calcium phosphate. Another 15% are made of struvite (magnesium ammonium sulfate) and are associated with urinary infections by urea-splitting bacteria. Six percent of stones are made of uric acid and are the result of abnormalities in the metabolism of uric acid. Finally, less than 2% of stones are made of cystine (Pak, 1998). The majority of stones are formed because the material forming the stone is supersaturating the urine. This situation leads to the formation of crystals that stick to epithelial surfaces and increase in size over time. The crystals can be identified by microscopic examination of the urinary sediment. Uric acid crystals characteristically are rhomboid or form rosettes. Calcium oxalate crystals resemble a mail envelope or a dumbbell but may be needle shaped. Magnesium phosphate crystals resemble a coffin lid and cystine crystals are hexagonal in shape.

The main symptoms of urinary stone disease are severe flank pain and microscopic or macroscopic hematuria. The pain is usually severe, starts abruptly, and is constant with paroxysmal episodes most probably secondary to movement of the stone or to ureteral spasms. In many cases the pain is excruciating and requires a visit to the emergency room and parenteral analgesics. When the pain is in the flank the stone usually is in the renal pelvis and when the stone is in the lower part of the ureter the pain is usually in the lower quadrant with radiation to the groin and the external genitalia.

The presence of macroscopic or microscopic hematuria significantly increases the likelihood of the diagnosis. However, 20–25% of patients with urinary stones have no hematuria particularly if there is an interval of several days between the onset of symptoms and the urine test (Kobayashi et al., 2003). Other frequent symptoms are nausea, vomiting, and dysuria.

The diagnosis of urinary stones during pregnancy is confirmed by ultrasound, by an abdominal flat plate, or

by a limited intravenous pyelogram (IVP). Renal ultrasound is the diagnostic test of choice because it avoids fetal radiation exposure. Renal ultrasound is particularly inefficient in the diagnosis of stones in the distal part of the ureter. When the clinical presentation suggests this possibility the renal ultrasound should be followed by a transvaginal examination (Laing et al., 1994) that will help to detect distal stones. The sensitivity of renal ultrasound for the detection of urinary stones is only 60% (Butler et al., 2000) and many symptomatic patients will require radiologic assessment for the diagnosis.

A flat plate of the abdomen is useful for the diagnosis of radiopaque stones, which are the most frequent type of stones. However, the plain film of the abdomen will miss uric acid stones which are radiolucent and small stones overlying bone structures and may falsely suggest the presence of stones in patients with fecaliths or phleboliths. However, the combination of renal sonography and a plain film of the abdomen have a diagnostic value similar to the noncontrast helical CT scan that is the test of choice outside of pregnancy (Catalano et al., 2002).

A limited IVP is a single flat plate of the abdomen, taken approximately 5 minutes after the intravenous administration of a contrast material. The test has a high sensitivity (Butler et al., 2000) and the fetal radiation exposure is minimal. The IVP and the renal sonogram have the distinct advantage over the plain film of the abdomen in that they can detect obstruction.

Approximately 80% of pregnant women with acute urinary lithiasis will pass the stone spontaneously and can be managed expectantly with pain medications and hydration. Pain control is usually the most pressing and difficult issue with these patients. Nonsteroidal anti-inflammatory agents (NSAIDs) such as indomethacin, ketorolac, and ibuprofen have the potential for significant fetal side effects and are not used or are used only in special circumstances during pregnancy. Opioids also have the potential for maternal and fetal side effects and are used sparingly during pregnancy. As a consequence of these limitations, pregnant women with renal stones do not have adequate pain relief during their expectant management—a situation that generates pressure in favor of interventions such as ureteral stents or percutaneous nephrostomy. To avoid invasive procedures and facilitate patient management during the expectant period, morphine, demerol, Nubain, or fentanyl can be given by means of a patient-controlled infusion pump. Maternal and fetal exposure to those medications ideally should be limited to a few days.

If a pregnant patient develops symptoms suggestive of ureteral calculi, the following should be done:

1. All urines should be strained for the passage of gravel or stones.
2. The urine should be cultured. The finding of a P. mirabilis infection in a patient with a history of chronic recurrent urinary tract infections is strongly suggestive of the presence of magnesium ammonium phosphate (struvite) stones.
3. Most patients with underlying metabolic disorders such as the etiology of the stones can be diagnosed by chemical analysis of their serum and urine. In acute situations, there is not adequate time for this investigation, which should be performed when the patient is not pregnant. However, the metabolic panel that is usually performed in most patients admitted to the hospital and a 24-hour urine collection for calcium determination will be useful to identify women with common uncomplicated calcium stone disease, which characteristically will be normocalcemic, hypercalciuric (>250 mg/24 hour), and normouricemic in the absence of urinary tract infection. If hypercalcemia is present, it is necessary to investigate the possibility of hyperparathyroidism, a situation frequently associated with calcium oxalate stones. Hyperchloremia suggests renal tubular acidosis and calcium phosphate calculi. Hyperuricemia suggests uric acid stones (Table 19-1).
4. All women with urinary stones require a renal ultrasound. This examination is useful in the detection of stones in the upper urinary tract and for the diagnosis of upper urinary tract obstruction. Ultrasound is not useful in the diagnosis of ureteral stones, particularly those located in the lower third of the ureter. If the renal ultrasound is negative and the clinical suspicion is high, it is prudent to obtain a modified IVP to rule out ureteral stones.

Treatment of patients with acute nephrolithiasis during pregnancy depends on the severity and duration of symptoms and the presence of obstruction. The cornerstone of conservative management in pregnant women with urinary lithiasis is a high fluid intake to obtain a minimum urinary volume of 2 L/day. More than 50% of patients admitted to the hospital with symptoms of renal lithiasis pass the stones spontaneously. Analgesics and intravenous

Table 19-1. Laboratory studies in patients with renal stones

Test	Finding	Diagnostic possibility
Urine culture	Proteus mirabilis	Struvite stones
24-hour calciuria	>250 mg/day	Calcium oxalate stones
24-hour uric acid	>800 mg/day	Uric acid stones
Daily urine pH	Acid	Uric acid stones
	Alkaline	Struvite stones
Serum calcium	Hypercalcemia	Hyperparathyroidism
Serum uric acid	Hyperuricemia	Uric acid stones
Plasma chloride	hyperchloremia	Renal tubular acidosis

fluids to maintain an increased urinary output is all that is necessary for the treatment of these cases. With no evidence of obstruction, spontaneous passage of the stones should be expected and urologic intervention deferred. If the situation fails to improve after a reasonable period, attempting cystoscopic extraction is justified.

The diagnosis of obstructive hydronephrosis in pregnant women with urinary stones is difficult due to the presence of physiologic hydronephrosis, particularly on the right side, due to the ureteral compression by the pregnant uterus. Sonographic and radiologic criteria are unreliable to distinguish between physiological hydronephrosis and hydronephrosis due to obstruction by calculi. If one or both of these methods indicate the presence of bilateral unilateral hydronephrosis, more marked on the right side, and the patient is not severely symptomatic, most probably the hydronephrosis is physiologic. However, if the hydronephrosis is unilateral in the side of the patient's symptoms and the pain is relentless and severe, most probably the hydronephrosis is due to the stone. When acute hydronephrosis develops as a consequence of obstruction, cystoscopic passage of a ureteral stent and stone manipulation using retrograde ureteral catheterization may be attempted.

The course of pregnancy in women with a ureteral stent in place is difficult. They frequently require readmissions to the hospital because of recurrent pain and have urinary frequency and dysuria due to bladder irritation by the lower tip of the catheter. If the ureteral stent fails, it is necessary to perform a percutaneous nephrostomy. Operative removal of the stones in the second and third trimesters is difficult because of the increased vascularization and problems generated by the pregnant uterus. Such surgery is a last resource and ideally should be postponed until after delivery. There are minimally invasive surgical procedures that can be used in the postpartum period, including shock wave lithotripsy, percutaneous nephrolithotomy, and flexible ureteroscopy.

Once the acute crisis is over, further treatment depends on the etiology of the nephrolithiasis. For example, a low calcium diet and thiazide diuretics are beneficial for patients with idiopathic hypercalciuria. Patients with uricosuria and uric acid stones benefit from a low purine diet. Those affected by hyperparathyroidism stop producing stones, once the underlying problem is corrected. Magnesium ammonium phosphate stones require intensive treatment for chronic urinary tract infections.

Acute Renal Failure

The incidence of acute obstetric renal failure is 1 in 15,000 to 1 in 20,000 pregnancies in industrialized countries, but in developing countries the incidence varies from 1 out of every 2000 to 1 out of every 5000 pregnancies. This is due, in part, to the high incidence of septic abortions and the limited availability of abortion services and prenatal care in developing countries.

The most frequent causes of acute renal failure (ARF) in pregnancy are HELLP syndrome (36%), postpartum hemorrhage (26%), preeclampsia/eclampsia (15%), and placental abruption (10%) (Selcuk et al., 2000). Rare causes include sepsis with multiple organ failure, antiphospholipid antibodies syndrome, and ureteral obstruction by an overdistended uterus.

Definition

The term "acute renal failure" describes an abrupt decline in renal function, characterized by a urine output of less than 400 ml/24 hours or less than 20 ml/hour. ARF may be prerenal, renal, or postrenal. Prerenal failure is usually secondary to a severe deficit in blood flow to the kidneys due to a marked decrease in intravascular volume secondary to obstetrical bleeding. ARF secondary to renal conditions is usually the consequence of thrombotic microangiopathy in women with HELLP syndrome, hemolytic-uremic syndrome (HUS), or lupus nephritis. Finally, in a small number of cases obstetric renal failure is postrenal, usually the consequence or ureteral obstruction by an overdistended uterus.

Pathophysiology

Most cases of obstetrical ARF are secondary to HELLP syndrome, placental abruption with DIC (disseminated intravascular coagulation), severe preeclampsia and eclampsia, and obstetrical bleeding. ARF does not occur in women with mild preeclampsia. The pathophysiology of ARF in severe preeclampsia and eclampsia contains prerenal and renal elements. Prerenal factors that affect renal perfusion are decreased intravascular volume and vasospasm of afferent arterioles. The main renal factor is deposition of fibrinogen-like material in the glomerular endothelial cells, causing enlargement of these cells and partial or complete occlusion of the glomerular capillaries lumen (glomerular endotheliosis). Fortunately, these lesions disappear rather quickly following delivery of the placenta and in the large majority of women with severe preeclampsia and eclampsia, fast recovery should be anticipated. A different situation occurs in women with ARF secondary to HELLP syndrome. In these cases the fundamental problem is occlusion of small vessels by thrombi (thrombotic microangiopathy), causing a severe alteration in renal perfusion that usually results in tissue ischemia and acute tubular necrosis (ATN). In patients with abruptio placentae, acute disseminated intravascular coagulation with formation of microvascular thrombi in the renal vasculature is an important causal factor of decreased renal blood flow.

The most common causes of severe obstetrical bleeding are postpartum bleeding, placenta previa, and placental abruption, and in all these situations acute intravascular volume depletion and severe reactive vasospasm are responsible for the decreased renal perfusion. Studies using radioactive tracers have shown that following severe hypovolemia, blood flow to the renal cortex decreases, whereas the perfusion to the medullar area is preserved. Cortical ischemia results in a marked decrease in GFR, concentrating ability, and urinary volume. This stage of severe impairment in renal function is recognized as prerenal ARF. If cortical hypoperfusion persists, the functional changes will be followed by ATN or cortical necrosis. Renal hypoperfusion may also occur in patients with adequate intravascular volume if there is low perfusion pressure secondary to heart failure or decreased plasma colloid osmotic pressure secondary to nephrotic syndrome. Since inadequately treated prerenal ARF will rapidly progress to intrinsic renal damage and ATN, a correct diagnosis and adequate correction of the perfusion defect are extremely important because they avoid progression of the condition and deterioration of renal function.

Diagnosis

Obstetric patients with ARF may present in a variety of clinical settings. Some present after the onset of an obstetric emergency such as eclampsia, abruptio placentae, or placenta previa. Others develop oliguria or anuria in the course of a hospital admission. The overall clinical picture is of importance and may help to guide the diagnosis. Women with HELLP syndrome usually have ATN rather than prerenal failure. Women with abruption placenta have a prerenal component due to hypovolemia but many of them are in ATN because of microthrombosis caused by fibrin degradation products. Women with eclampsia and severe preeclampsia also have renal and prerenal components of their ARF but the prerenal factors are usually dominant. ARF following postpartum bleeding and bleeding because of placenta previa is prerenal. In patients with multifetal pregnancies or severe polyhydramnios, it is necessary suspect of the possibility of postrenal ARF due to ureteral compression.

The differential diagnosis between prerenal and renal ARF is of the utmost importance (Table 19-2). In most cases of ARF, it is possible to obtain a sample of urine, which should be sent for sodium, creatinine, and osmolality. A blood sample should be obtained simultaneously and sent for electrolytes, osmolality, BUN, and creatinine concentration. The initial renal response to hypoperfusion is to preserve intravascular volume and maintain body sodium. This results in the production of concentrated urine with a low sodium concentration, usually less than 20 mEq/L. If the situation remains uncorrected, the kidney will lose its ability to concentrate the urine and save sodium, and this will be reflected in a urine to plasma (U/P) osmolality ratio close to 1.0 and a urinary sodium concentration greater than 40 mEq/L. A urine osmolality above 500 mOsmol/kg indicates good tubular function and prerenal disease. Urine osmolality below 350 mOsmol/kg suggests ATN. A U/P osmolality ratio greater than 1.2 indicates that the oliguria or anuria is prerenal. In cases of ATN, the U/P osmolality ratio is 1.0 or close to 1.0, indicating the kidney's lack of ability to concentrate the urine. The urinary sodium is high (50–70 mEq/L) in ATN, reflecting the inability of the kidneys to reabsorb sodium.

Table 19-2. Differential diagnosis of acute renal failure

Urinalysis	Prerenal	Renal
Urinary Na	<20 mEq/L	>40 mEq/L
Urine osmolality	>500	<350
FE_{Na}	<1%	>2%

Examination of the urine sediment is valuable in the differential diagnosis between ATN and prerenal azotemia. The urine sediment of patients in ATN characteristically contains numerous renal tubular cells, renal tubular cell casts, and muddy-brown pigment casts. Many nephrologists accept pigment casts as pathognomonic sign of ATN.

The urine to plasma creatinine concentration is also useful in the differential diagnosis between prerenal ARF and ATN. Normally the creatinine concentration in the plasma should be equal to that in the glomerular filtrate and rise progressively in the urine when water is reabsorbed in the tubules. Patients with prerenal disease will have a high urine to plasma creatinine ratio (>40) because they are reabsorbing a high proportion of the filtered water to maintain the intravascular volume. Patients with ATN have lost some of their capacity to reabsorb water due to the tubular damage and exhibit a urine to plasma creatinine ratio below 20. Also useful is the plasma BUN to creatinine ratio. Also, in prerenal disease there is significant urea reabsorption, increasing the BUN to creatinine ratio to 20:1 or more (normal 10–15:1).

Perhaps the more useful test for differentiating prerenal disease from ATN is the fractional excretion of sodium or FE_{Na} test. This test depends on the different handling of sodium in prerenal failure, when the tubes avidly reabsorb sodium, than in ATN, when sodium reabsorption is impaired because of tubular damage. The FE_{Na} is calculated using the following equation:

$$FE_{Na} = \text{U/P sodium} / \text{U/P creatinine} \times 100$$

An FE_{Na} less than 1% indicates prerenal azotemia and a value greater than 3% indicates ATN.

Complete anuria is rare and indicates obstructive uropathy or profound kidney damage.

Treatment

Patients with prerenal ARF usually respond well to adequate management. Depending on the nature of the primary problem and the presence of complications, packed red cells, fresh frozen plasma, salt-poor albumin, low-molecular-weight dextran, cryoprecipitate, and crystalloid solutions may be used to treat intravascular volume deficits. For example, in cases of abruptio placentae it is necessary to expand volume and improve oxygen-carrying capacity and the agent of choice is packed red cells. Cryoprecipitate and fresh frozen plasma are used if there is a deficit in coagulation factors.

Insertion of a central venous pressure (CVP) line or Swan–Ganz catheter is occasionally necessary for diagnosis and monitoring of therapy. An elevated CVP or pulmonary wedge pressure (PWP) suggests ATN or cortical necrosis and IV fluids should be restricted. In contrast, if the CVP or PWP are low, intravascular volume depletion is present, and IV fluids should be administered. The therapeutic expansion of intravascular volume in anuric or severely oliguric patients should be monitored with frequent CVP measurements. The CVP reflects right atrial filling pressure and indicates the capacity of the right heart to accept a fluid load. The CVP should remain between 10 and 15 cm H_2O during treatment, and any elevation above 15 cm H_2O should be followed by a decrease in the rate of fluid administration.

In most cases intravascular volume expansion may be achieved by administering 500–1000 ml of normal saline solution over 30–60 minutes. This should cause a modest elevation of the CVP and result in increased urine production in patients with prerenal azotemia. Some people prefer to use a "synthetic extracellular fluid" solution (750 ml of 0.9% NaCl, 225 ml of 5% dextrose in water, and 25 ml of a solution of sodium bicarbonate containing 3.75 g/50 ml) for the fluid challenge. After the fluid challenge, administration of isotonic NaCl should be continued at 125–200 ml/hour. The treatment goals are to maintain a normal CVP and a urinary output above 30 ml/hour. Unfortunately, the response to a fluid challenge usually is transient, and it is necessary to increase the administration of IV fluids. In patients with severe preeclampsia this may result in pulmonary edema. These patients have increased capillary permeability and low colloid osmotic pressure and the intravenous fluids move rapidly from the intravascular into the interstitial space. When the difference between the plasma colloid osmotic pressure (usually 21–25 mmHg) and the PWP (usually 6–10 mmHg) is reduced to less than 3 mmHg, pulmonary edema may occur.

Treatment with low-dose Dopamine was commonly used in the past with the objective of decreasing renal vasospasm in patients with prerenal ARF. However, the results of a large controlled clinical trial show no differences in outcome between ARF patients treated with Dopamine and placebo (ANZICS Clinical Trials Group, 2000).

Administration of diuretics to patients in renal failure is controversial and must be limited to a few cases. Loop diuretics are used in attempts to convert oliguric to nonoliguric renal failure and facilitate patient's management. However, a study of 388 patients randomly assigned to furosemide or placebo found that although high-dose furosemide was useful in maintaining the urine output, it had no effect on patient's survival or renal function recovery (Cantarovich et al., 2004). Furosemide given in smaller doses (20–40 mg) than those used in ATN may be useful to mobilize fluids in women with prerenal failure who fail to respond to an intravenous fluid challenge because of "third spacing" formation. This is a situation that occurs mainly in severe preeclampsia where there is third space formation secondary to increased capillary permeability and decreased plasma colloid oncotic pressure.

The development of oliguria–anuria in an obstetric patient is, in the majority of cases, an indication for delivery. Delivery is beneficial for the infant, who is removed from a progressively hostile environment, and also has advantages for the mother. Patients with prerenal azotemia who had oliguria or anuria for several hours before delivery often begin to produce copious amounts of urine after delivery. This raises the possibility that compression of the ureters was present. However, in the majority of cases the diuresis that follows delivery is a consequence of better renal perfusion secondary to redistribution of the cardiac output. Approximately 25% of the cardiac output in pregnant patients is destined to fulfill the needs of the placental circulation. This need disappears abruptly after delivery and is followed by redistribution of the cardiac output and increased blood flow to the kidneys. Another advantage of delivery is that it is possible to use large doses of diuretics and perform diagnostic procedures using x-ray and radioactive isotopes without fear of causing harm to the fetus.

After the diagnosis of ATN is established (increase in plasma creatinine concentration of 0.5 mg/dl or greater, U/P osmolality ratio near 1.0, urinary sodium more than 40 mEq/L, elevated CVP, lack of response to furosemide), the role of the obstetrician is to expedite delivery, restrict the fluid intake to an amount equal to the urine output plus the insensible losses, adjust the dosing of medications that are cleared by the kidneys, and refer the patient to an institution with adequate facilities for hemodialysis. Dialysis is indicated in patients who develop cardiovascular overload during the oliguric phase of ATN, hyperkalemia (>6.0 mEq/L) that could not be controlled with the use of potassium exchange resins, severe alterations in plasma sodium concentration, pericarditis, uremic

encephalopathy, or metabolic acidosis. In obstetrical patients the medications that most commonly need doses adjustment are magnesium sulfate and gentamycin.

In patients with ATN there is a progressive increase in serum creatinine concentration of 0.3–0.5 mg/day. A slower rate of increase with up and down fluctuations is typical of prerenal disease. Serum potassium should be measured frequently, because elevations of this ion are common in the course of ARF and may reach a point at which hemodialysis becomes mandatory. The serum sodium concentration should also be measured, especially in patients who have received diuretics and large amounts of crystalloid solutions.

The most common indication for dialysis in patients with obstetric renal failure is fluid overload. Hence, fluid restriction is mandatory as soon as the diagnosis of ATN is established. It is difficult to maintain an adequate caloric intake with severe fluid restriction. One of the advantages of dialysis is that it allows a more liberal fluid intake and makes it easier to adjust the diet to an optimal caloric and protein intake.

The majority of obstetric patients with ATN recover without sequelae. Most exhibit normal creatinine clearances and blood chemistries 6–12 months later.

Hemolytic-Uremic Syndrome

HUS is a condition that is frequently included by nephrologists in the differential diagnosis of ARF secondary to HELLP syndrome. HUS is a disease independent of pregnancy which is closely related to thrombotic thrombocytopenic purpura (TTP). HUS is a rare obstetrical complication with an overall incidence of 1 in 25,000 births (Dashe et al., 1998). However, approximately 25% of all cases of TTP/HUS occur during pregnancy. The condition is characterized by the sudden onset and rapid progression of hemolytic anemia, thrombocytopenia, and renal failure usually occurring in the postpartum period. In a majority of cases hypertension is present. A flu-like syndrome usually precedes the onset of symptoms. The disease may occur at any time from 1 day to 10 weeks after delivery. HUS is a thrombotic microangiopathy secondary to exposure to enteropathic organisms, particularly E. coli serotype 0157:H7.

The essential anatomic feature in HUS is damage to the glomerular capillaries by subendothelial deposits of fibrin that separate the endothelial cells from the basal membranes. These deposits reduce the vascular lumen and cause parenchymal changes. Formation of microthrombi, especially in the afferent arterioles, is another feature contributing to renal ischemia. The formation of microthrombi is related to a decreased production of a metalloprotease named ADAMTS-13 by the endothelial cells. ADAMTS-13 normally cleaves the large multimers of von Willebrand factor, or VWF, and when its concentration is decreased the large multimers bind to platelets, causing microthrombosis. Erythrocytes and platelets are fragmented during their passage through the affected vessels, causing microangiopathic hemolytic anemia and thrombocytopenia.

Table 19-3. Differential diagnosis between HELLP syndrome, TTP, and HUS

Clinical findings	HELLP syndrome	TTP	HUS
Onset	After 28 weeks	Median 23 weeks	Postpartum
Primary manifestation	Hypertension, proteinuria	Neurologic symptoms	Renal failure
Fever	Absent	Present	Absent
Purpura	Absent	Present	Absent
VWF multimers	Absent	Present	Present

The most important differential diagnosis in patients with HUS is HELLP syndrome. This differential diagnosis is difficult but some of the criteria that may help are shown in Table 19-3. In general, patients with HUS should not have signs or symptoms of preeclampsia before delivery, at the time of delivery, or in the immediate postpartum period. Also, the diagnosis of HUS is more likely if there is a symptom-free period of several days after delivery. Persistence of symptoms and signs of HELLP syndrome beyond postpartum day 3 is another criterion that raises the probability of HUS.

The differentiation between preeclampsia and HUS is important from a prognostic viewpoint, since recovery is the rule in preeclampsia and death or chronic renal insufficiency are the usual courses for postpartum HUS (Dashe et al., 1998). The differential diagnosis is also important for management because plasmapheresis and heparin are indicated in HUS and may not be needed in HELLP syndrome. Maternal mortality in HUS has decreased with plasmapheresis but still ranges between 8 and 44%. Perinatal mortality is high, between 30 and 80%.

There is evidence indicating that plasmapheresis improves the outcome of patients with HUS (Bell et al., 1991). Also, most survivors reported in the literature have been treated with heparin. Antihypertensive drugs, anticonvulsants, antiplatelet medications, and dietary management are also important in the management of this serious condition.

In situations where the differential diagnosis between HELLP syndrome and HUS is difficult, the decision to perform plasma exchange should be based on persistence and severity of signs and symptoms rather than on personal opinion about the nature of the underlying problem. Plasmapheresis is not only lifesaving in patients with HUS but has been proven to be beneficial for patients with HELLP syndrome (Martin et al., 1995).

Renal Cortical Necrosis

This severe form of ARF is usually associated with catastrophic obstetric complications such as severe hypovolemia secondary to abruptio placenta or placenta previa, or amniotic fluid embolization. Histologically this condition is characterized by necrosis of all the elements of the renal cortex including extensive necrosis and thrombosis of the renal vessels.

Clinically, renal cortical necrosis is characterized by the sudden onset of severe oliguria or anuria in a patient with life-threatening complications of pregnancy. The urine is frankly hematuric and the urinary red cells are dysmorphic and hypochromic with the appearance of collapsed empty sacs. Hematologic abnormalities characteristic of DIC may be present. The BUN and plasma creatinine increase rapidly.

On many occasions, it is difficult to differentiate renal cortical necrosis of ATN. However, the evolution of these conditions is different and prolonged oliguria and anuria with little or no improvement of renal function is characteristic of renal cortical necrosis. Renal ultrasound demonstrates hypoechoic areas in the renal cortex and calcifications are seen in these areas several months after the onset of symptoms.

The prognosis for patients with renal cortical necrosis is poor. The majority do not recover and require chronic dialysis. Only 20–40% have partial recovery and can live without dialysis.

ARF Secondary to Obstructive Uropathy

There are a few reported cases of severe oliguria secondary to obstructive uropathy during pregnancy. Obstructive uropathy usually results from ureteral compression at the level of the pelvic brim by an overdistended uterus. This is more likely to occur in twin pregnancies and in patients with severe polyhydramnios.

Complete anuria is a frequent finding in obstructive uropathy, while in prerenal and renal oliguria urine production rarely ceases completely. Therefore, the possibility of obstructive uropathy should be considered when complete anuria develops in a patient with an overdistended uterus. In these cases interruption of the pregnancy is followed by profuse diuresis.

Nephrotic Syndrome

A nephrotic syndrome is characterized by the presence of proteinuria greater than 3 g/24 hours, serum albumin less than 3 g/dl, edema, and hypercholesterolemia. The amount of protein in the urine may be estimated by a protein to creatinine (mg/mg) ratio. Under normal conditions this ratio is less than 0.15 (protein less than 150 mg/24 hour). In patients with nephrotic syndrome the ratio will be greater than 3.5 (protein > 3 g/24 hour). Proteinuria of this magnitude almost certainly indicates the presence of glomerular damage.

Etiology and diagnosis

The most common cause of nephrotic syndrome during pregnancy is preeclampsia. Occasionally a nephrotic syndrome is seen in women with diabetic nephropathy or systemic lupus erythematous (SLE). More rare is nephrotic syndrome in the context of glomerular disease of new onset during pregnancy.

In the majority of cases the differential diagnosis between the different causes of nephrotic syndrome during pregnancy (preeclampsia, diabetic nephropathy, lupus nephritis, primary glomerular disease) is strongly suggested by the patient's clinical history. Women with preeclampsia exhibit signs and symptoms of this condition and have normal blood glucose values unless they are diabetics who have developed preeclampsia. Diabetic nephropathy causing nephrotic syndrome usually occurs in women with long-standing, poorly controlled diabetes. Patients with SLE usually have diagnosis of their condition before pregnancy and most of the time have a characteristic history of malar rash, serositis, buccal ulcers, and hematologic and serologic abnormalities. Primary glomerular disease of immunologic or infectious origin is extremely rare during pregnancy, proteinuria is not in the nephrotic range, and hematuria is usually present.

Clinical signs and symptoms are unreliable to distinguish the etiology of nephrotic syndrome during pregnancy. All conditions causing nephrotic syndrome may present with hypertension and exhibit similar laboratory alterations. Examination of the urinary sediment is useful in these cases. The presence of large, coarse granular casts is the usual finding in preeclampsia while the presence of red cells and red cell casts is diagnostic of acute glomerulonephritis. The presence of lipid droplets, cellular casts, and birefringent lipids points to chronic renal disease. Other laboratory tests useful in the differential diagnosis are the tests for autoimmune disorder (ANA titer, anti native-DNA, anti-Sm, antiphospholipid antibodies, and complement panel). A positive autoimmune serology makes the diagnosis of SLE.

Alterations in the complement panel (C3, C4, and CH50) are also useful in the differential diagnosis of nephrotic syndrome. Although there are several glomerular diseases that may cause a decrease in complement levels, this finding in a pregnant patient with nephrotic syndrome is strongly suggestive of the presence of lupus nephritis.

Renal biopsy is frequently necessary for diagnosis of patients with nephrotic syndrome. The most common indication is the presence of primary glomerular disease

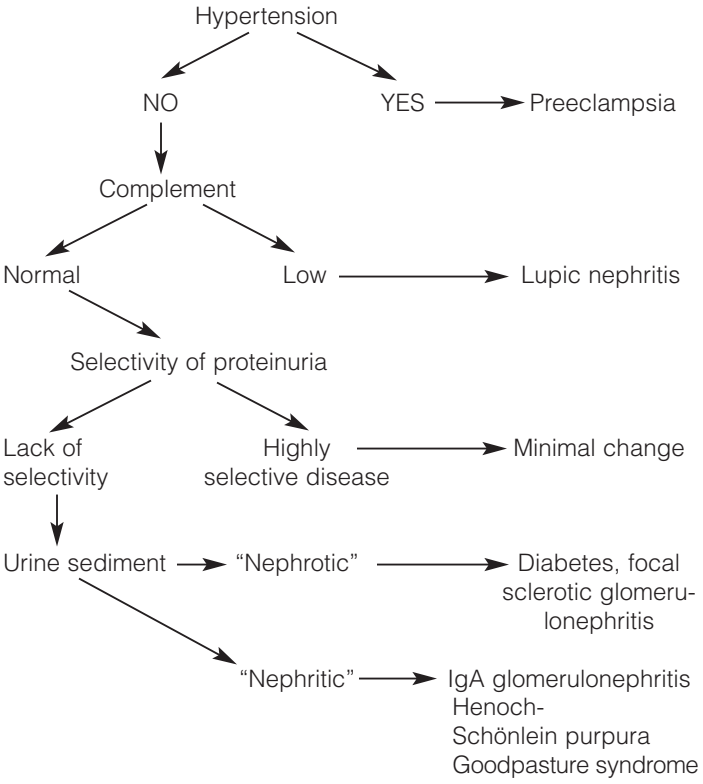

Figure 19-1. Differential diagnosis of the cause of nephrotic syndrome during pregnancy.

BOX 19-1

Differential diagnosis of nephrotic syndrome during pregnancy

1. *Preeclampsia:* elevated blood pressure, negative ANA titer, normal complement, nonselective proteinuria, benign urinary sediment
2. *Lupus nephritis:* positive ANA titer, positive DNA antibodies, low complement, nephritic sediment
3. *Diabetic nephropathy:* history of insulin-dependent diabetes of long duration
4. *Acute glomerulonephritis* (usually IgA nephropathy, minimal change disease, or focal glomerulonephritis): negative ANA titer, inflammatory urinary sediment with red cell casts

because it will determine the diagnosis and therefore the condition-specific therapy. Ultrasound-guided renal biopsy using automated biopsy instruments has decreased the complications associated with this procedure that are similar in frequency to the nonpregnant status (Packham and Fairley, 1987). Although the complications of this procedure are few in experienced hands, they are not negligible and unless the information obtained from the biopsy may significantly change the approach to therapy, it is better to postpone the procedure until the postpartum period (Chen et al., 2001).

Figure 19-1 is a summary of the diagnostic steps to be followed in the study of patients with nephrotic syndrome during pregnancy. Box 19-1 is a summary of the differential diagnosis in this situation.

Management

In the majority of pregnant patients the cause of nephrotic syndrome is preeclampsia, and the most important part of their treatment is delivery. However, in early preterm gestations (less than 32 weeks) the need to deliver should be carefully balanced against the neonatal morbidity caused by early delivery and there are situations where conservative management under strict maternal and fetal surveillance is the best option. Information about expectant management in women with severe preeclampsia may be found in the corresponding chapter of this book.

The main issues in the management of the pregnant women with nephrotic syndrome are to aggressively treat the elevated blood pressure, to provide anticoagulation therapy because of the high risk of venous thromboembolism, to decrease fluid overload with diuretics, and to treat the underlying cause of the condition if it is known. From the fetal viewpoint the main issues are assessment of fetal growth and continuous surveillance to detect and evaluate the effects of the maternal disease on fetal oxygenation.

Control of hypertension is one of the most important goals in the management of pregnant women with nephrotic syndrome. The goal of antihypertensive treatment is to maintain blood pressure below 140/90 mmHg, which is the definition of hypertension during pregnancy. For treatment of acute blood pressure elevations, the best agents are intravenous labetalol or hydralazine. Rarely, it is necessary to use intravenous sodium nitroprusside or nitroglycerin. For maintenance treatment the choices are labetalol, calcium channel blockers, hydralazine, and methyldopa. ACE-inhibitors are contraindicated during pregnancy. There is significant variation in the dose and frequency of administration of these drugs—variables that are heavily dependent on the severity of the hypertension and on individual response to therapy.

Pregnant women with nephrotic syndrome have a significant predisposition to thromboembolization. They add to the physiological hypercoagulation that characterizes normal pregnancy excessive urinary losses of antithrombin and alterations in the fibrinolytic system, resulting in as much as 40% incidence of deep vein thrombosis. A favorite target for thrombosis in patients with nephrotic syndrome is the renal vein that may be asymptomatic. Thromboembolism occurs more often in women with serum albumin levels less than 2 g/dl. Prophylactic anticoagulation is indicated in these cases, using heparin 5000–10,000 U subcutaneously twice a day or low-molecular-weight heparin 40,000 U daily. If thromboembolism actually does occur, the patient requires full anticoagulation.

The normal intravascular volume expansion of pregnancy is limited in women with nephrotic syndrome because of the significant decrease in serum albumin levels and plasma oncotic pressure with mobilization of intravascular fluid to the interstitial space and production of edema. The counter-regulatory response to the lack of effective intravascular volume is the secretion of antidiuretic hormone, resulting in fluid retention, further mobilization of fluid to the interstitial space, and more edema formation. Initially treatment is with loop diuretics and by thiazides if they develop resistance to furosemide. The effect of diuretics in plasma volume needs to be followed closely with daily determinations of the hematocrit/hemoglobin concentration.

The administration of albumin to patients with nephrotic syndrome is rarely indicated, because it is not possible to adequately compensate for urinary losses. However, if edema progresses to a state of anasarca, plasma albumin concentration is 2 g or below, and the patient is becoming oliguric, the administration of salt-poor albumin may provide temporary relief.

Causes of nephrotic syndrome during pregnancy different from preeclampsia are rare. When the cause is known it is sometimes possible to have specific treatment. Patients with lupus nephritis are usually treated with prednisone, 60–100 mg/day. Another glomerular disease that may respond to steroid treatment is focal segmental glomerulosclerosis. In these cases prednisone (1 mg/kg/day) should be given because more than 50% of these patients have a steroid-responsive glomerular process.

Pregnant patients with nephrotic syndrome are at high risk for the development of infections, particularly urinary tract infections. Therefore they should receive prophylactic antibiotic treatment. Preferred treatments are 500 mg ampicillin, 500 mg cephalosporin, or 200 mg nitrofurantoin taken at bed time.

Pregnant patients with nephrotic syndrome should be weighed daily. Their renal function should be monitored at least twice every week by measuring their BUN, creatinine, and uric acid, as well as their electrolytes. They often develop anemia unresponsive to iron therapy because of urinary losses of transferrin. They should be transfused if their hematocrit drops below 25%.

The fetus of pregnant women with nephrotic syndrome is at risk for growth restriction, preterm delivery, and antepartum fetal distress. These complications usually occur when the maternal condition worsens. The complication having the largest impact on the fetal outcome is maternal hypertension. If this occurs, the patient's management will depend on the severity of the hypertension. As a general rule, if the mother remains stable, the risk of fetal complications is small. The best methods for assessing the fetal status are serial ultrasound examinations every 3 weeks to follow fetal growth, umbilical and middle cerebral artery Doppler every week, and biweekly NSTs (nonstress tests) and fluid volume determinations.

PREGNANCY IN PATIENTS WITH KNOWN RENAL DISEASE

Pregnancy in women with preexistent renal disease is a relatively uncommon event. When a pregnant patient known to have renal disease arrives in the obstetrician's office, three main questions arise:

1. What are the fetal and maternal prognoses?
2. What are the possible complications and risks?
3. What are the basic principles of the patient's management?

The correct answers to these questions will depend on the nature and severity of the underlying renal disease, but some generalizations are valid. For instance, the general concept that maternal and fetal prognoses are directly related to the presence of hypertension and the severity of the renal condition applies irrespective of the type of renal disease affecting the individual patient. It is also generally accepted that the most common maternal and fetal complications in these patients are superimposed preeclampsia, deterioration of renal function, fetal growth restriction, and preterm birth.

Maternal and Fetal Prognoses

One important concern for a pregnant woman with renal disease is whether or not pregnancy will accelerate the progression of her condition. Most reports on this subject involve patients with moderate or mild renal insufficiency because when renal function is severely impaired, pregnancy rarely occurs. Katz et al. (1980) analyzed 121 pregnancies in 89 patients with renal disease, 26 with chronic diffuse glomerulonephritis, 12 with focal glomerulonephritis, 7 with membranous glomerulonephritis, and 21 with interstitial nephritis. Renal function declined in 16% of these pregnancies, most often in patients with chronic diffuse glomerulonephritis. Increased proteinuria occurred in 47% of these patients and in 39 pregnancies was greater than 3 g/24 hour. They concluded that in patients with normal or only mildly impaired renal function, pregnancy does not accelerate renal damage. This conclusion has been supported by two recent studies. One retrospective study of 72 patients with chronic renal disease found that approximately 15% of them had worsening of renal function during pregnancy and less than one-third recovered renal function to levels similar to those existing prior to pregnancy (Abe et al., 1985). A similar proportion of pregnant patients with renal disease had deterioration of their renal function in another study at Dallas (Cunningham et al., 1990).

Hou et al. (1985) gathered data from 25 pregnancies in 23 patients with moderate renal insufficiency as defined by a serum creatinine of 1.4 mg/dl or greater prior to pregnancy. In 14 women renal function was stable or declined at a degree consistent with the natural history of their disease, but in 7 women they found a decrease in renal function greater than expected from the natural history of their disease. This indicates that when renal insufficiency is moderate a significant number of patients will have a decline in renal function.

The fetal prognosis for women with chronic renal disease is favorable as long as they do not develop superimposed preeclampsia early in pregnancy and their renal function is not severely affected. In the study by Katz et al. (1980) neonatal survival was 94%. However, 24% were growth restricted and 20% were preterm. Patients with advanced degrees of renal insufficiency have a more obscure prognosis and their fetal survival rate is only about 50%.

The most reliable prognostic indicator of the outcome of pregnancy is the presence of hypertension. It is exceptional for patients with diastolic blood pressure of 100 mmHg or more despite treatment to undergo pregnancy without serious complications. Patients who are normotensive have better prognoses. Even patients with creatinine clearance between 20 and 30 ml/minute and serum creatinine between 2.5 and 3.5 mg/dl may have a good outcome as long as hypertension is not a part of their disease.

Second to hypertension, the most valuable prognostic index for patients with chronic renal disease and pregnancy is the degree of renal functional impairment. Patients with creatinine clearances less than 30 ml/minute, and especially less than 20 ml/minute, have a poor prognosis. The prognosis is better if the creatinine clearance is between 50 and 70 ml/minute. Patients usually have a good prognosis if their serum creatinine concentrations are 1.4 mg/dl or less, but the prognosis becomes guarded for patients with values above that level.

Another important prognostic sign is the presence or absence of proteinuria. As a general rule, if the patient has 2+ or more in qualitative tests, or 3 g or more in 24-hour urine collections at the beginning of pregnancy, the tendency will be toward increased protein losses and development of nephrotic syndrome. Patients without proteinuria at the beginning of pregnancy have better prognoses.

The histologic characteristics of the renal lesion also have prognostic value. Patients with diffuse glomerulonephritis, membranoproliferative glomerulonephritis, and focal glomerulosclerosis frequently have poor outcomes. Patients with IgA nephropathy usually have a good prognosis but some investigators have reported frequent and serious complications such as 30% incidence of fetal death, 22% incidence of prematurity, and 26% incidence of declining renal function during pregnancy (Pakham et al., 1988). Patients with diffuse mesenchymal changes and superimposed focal proliferation have much worse prognosis than patients with other histologic features.

Complications

Hypertension

The development of severe hypertension is a common and serious complication for patients with renal disease during pregnancy. The prognosis is worse when hypertension occurs before 28 weeks of gestation, and is resistant to conventional treatment. Hypertension is the most important reason for the perinatal mortality and the preterm delivery associated with renal disease during pregnancy. Maternal mortality may occur because of intracranial bleeding, abruptio placentae, or renal shutdown. Fetal mortality may occur because of decreased placental blood flow, abruptio placentae, or intrapartum hypoxia.

Fetal growth restriction

Infants born to patients with renal disease often show weight, length, and head circumference that are well below the mean for their gestational ages. This inadequate development occurs more often and is more severe in patients with high blood pressure. However, intrauterine growth restriction also occurs in normotensive patients.

Fetal growth restriction occurs in approximately 10% of normotensive and 35% of hypertensive patients with chronic renal disease. The diagnosis is made when the sonographic estimated fetal weight is below the 10th percentile for the gestational age. In addition, the ultrasound examination usually shows abnormal head to abdomen and femur to abdomen ratios and abnormal umbilical and uterine arteries Doppler.

Preterm birth

There are two main reasons for the high incidence of preterm birth in patients with renal disease. In about half of the cases, preterm birth is a necessary intervention because of maternal or fetal problems. In the other half of the cases, preterm birth is the consequence of preterm labor, usually secondary to placental vascular insufficiency.

Fetal distress

Antepartum and intrapartum fetal distress occur frequently in pregnancies complicated by intrauterine growth restriction. All patients with renal disease should have weekly NST and fluid volume estimations starting as early

as 26 weeks if their renal function is severely impaired. These fetuses may not tolerate the stress of labor.

Management

General measures

Interruption of work is necessary when complications develop and also for patients who are symptomatic from the beginning of pregnancy. In all cases, physical activity should be moderate, and periods of bed rest in the lateral supine position are beneficial. The diet should be rich in high-quality protein. Sodium intake may require adjustments if the patient is hypertensive and does not respond adequately to therapy or if there is excessive accumulation of sodium and water.

Antihypertensive treatment

If the patient is hypertensive at the beginning of pregnancy, a serious effort should be made to reduce her blood pressure to a normal range with medications. Methyldopa, hydralazine, labetalol, and calcium channel blockers should be used, and diuretics added if necessary. If the blood pressure cannot be maintained within a normal range with these drugs, the prognosis is poor and the possibility of complications is high.

Monitoring of renal function

The functional status of the kidneys should be monitored by determinations of serum creatinine every 4–6 weeks and by daily qualitative determinations of urinary protein. At the beginning of the prenatal care, a creatinine clearance determination is of value, but for subsequent checkups measurements of serum creatinine are adequate. Any elevation of serum creatinine of 0.2 mg/dl or greater requires evaluation with a creatinine clearance. The patient should be instructed to check for albumin in the first urine voided every morning and to call the obstetrician if significant changes are apparent. It is unnecessary to order periodic 24-hour urine collections for quantitative protein determinations unless there is significant proteinuria demonstrated with Albustix strips.

Excessive retention of sodium and water with marked peripheral edema is a frequent problem in the pregnant patient with renal disease. If this occurs, the patient should take a low-sodium diet, decrease working time, avoid prolonged periods of standing up or sitting, and increase the daily rest in the lateral supine position. If these measures are not successful and the patient becomes uncomfortable due to her edema, diuretics may be used. The degree of intravascular volume constriction caused by the diuretic should be monitored with serial hematocrit values.

If the patient has nephrotic syndrome, she should be managed as described earlier. These patients may need intravenous albumin to partially compensate for urinary losses, mobilize fluid out of the interstitial space, and maintain the integrity of the intravascular volume.

Fetal evaluation

Fetal growth should be followed with serial ultrasound examinations. The first ultrasound should be performed at 20–22 weeks, with follow-up examinations every 4 weeks thereafter. Any deviation from normal is significant and requires initiation of additional fetal surveillance.

Delivery

The renal patient who remains stable during pregnancy may go to term and develop spontaneous labor. If the patient is unstable or symptomatic, delivery should be performed as soon as fetal pulmonary maturity is reached. If the mother becomes severely ill, immediate delivery is indicated without fetal lung maturity evaluation.

Chronic Pyelonephritis

Chronic pyelonephritis, also called reflux nephropathy, is a condition characterized by severe scarring of the kidneys as a result of persistent or recurrent infections that occurs most commonly in patients with vesicoureteral reflux. These patients may have flare-ups of renal infection during pregnancy. They should have antibiotic prophylaxis with ampicillin 500 mg, nitrofurantoin 200 mg, or cephalosporin 500 mg every night, for the duration of pregnancy.

Hyponatremia may occur in pregnant patients with chronic pyelonephritis when they receive diuretics because these agents may intensify their sodium-losing tendency. They also frequently exhibit glycosuria in the presence of normal blood sugar levels.

Pregnancy in Women with Renal Transplants

Most patients with renal transplants tolerate pregnancy well if their kidney function is adequate and if hypertension is not present (Hous, 1989). Most patients are taking azathioprine and prednisone when they become pregnant, and they should continue taking these agents during gestation. So far, no congenital malformations have been reported as a consequence of the use of these medications. Recently cyclosporin has become the most commonly used immunosuppressive agent in renal transplantation. The effects of this agent on the fetus are unknown at this time. Patients taking cyclosporin may be switched to azathioprine during pregnancy.

The most common problems with these patients are preterm labor, preeclampsia, and preterm delivery.

Rejection episodes during pregnancy are rare and difficult to diagnose. Delivery should be accomplished without delay if they develop preterm rupture of the membranes, because of the risk of infection. Vaginal delivery is the route of choice.

Pregnancy in Women in Chronic Dialysis

Patients in chronic dialysis occasionally become pregnant. Also, renal failure may occur during gestation requiring the use of dialysis. Both hemodialysis and peritoneal dialysis have been used successfully in these cases. More recently continuous hemofiltration combined or not with hemodialysis is being used for patients with end-stage renal disease. The difference between hemofiltration and hemodialysis is that in the first technique the patient's blood is filtered and water and small-molecular-weight molecules are removed. After filtration a replacement fluid is given. In hemodialysis small molecules diffuse across a semipermeable membrane until the plasma concentration of some solutes reaches normality. Hemofiltration avoids the fluctuations in plasma volume that are characteristic of hemodialysis. The majority of patients can continue their pregnancies until the baby reaches a gestational age with adequate chances of survival outside the uterus. Complications, mainly preterm labor, hypertension, hypotension, hypoglycemia, vaginal bleeding, fetal growth restriction, and placental separation are common. Increasing the number of hours of dialysis per week seems to result in better perinatal outcomes (Okundaye et al., 1998) and intensive dialysis is now the norm for pregnant women with end-stage renal disease.

INDIAN EXPERIENCE OF RENAL DISEASES IN PREGNANCY

Pregnancy is potentially hazardous in women with impaired renal function. Renal functions tend to deteriorate during pregnancy. There is enhanced risk of preterm birth, intrauterine growth restriction, pregnancy-induced hypertension, increased perinatal mortality, and an impaired obstetric outcome. Thus apart from the fetus, the mother is also prone to complications.

Observations by Indian workers reveal the following:

- The incidence of chronic renal disease in pregnancy is 0.2%. In women with mildly compromised renal functions, the obstetric outcome is generally satisfactory and the need for dialysis is low. But with increasingly compromised kidney functions, the obstetric outcome deteriorates and the need to resort to dialysis is enhanced. Women with severely compromised function should be discouraged from attempting pregnancy. In lesser affected women, strict antenatal supervision of kidney functions (proteinuria, creatinine clearance, and surveillance for urinary tract infections) is essential (Dutta, 2004). These women are best treated in institutions equipped to take care of renal problems. A nephrologist should be included in the team to monitor and treat renal problems.
- Acute renal failure is a serious complication of pregnancy. Its relationship to pregnancy-induced hypertension, abruptio placentae, and Gram-negative infections is well established. It has been observed that the frequency distribution of acute renal failure among obstetric patients is bimodal in terms of duration of pregnancy—the first peak occurring at 7–8 weeks and the second between 34 and 36 weeks (Chugh et al., 1976). Obstetric causes account for 22.1% of all cases of acute renal failure (Chugh et al., 1976).
- Renal failure was noted in 12.8% of 443 cases of septic abortion (Isaac and Hemalatha, 1976).
- In an analysis of 28 cases of acute renal failure in obstetric practice in Mumbai, it was reported that 9 were due to septic abortion, 14 had preeclampsia—of these 6 had severe hemorrhage and 4 cases were attributed to mismatched transfusion (Panwala and Sheth, 1972).
- Dialysis is recommended to maintain a blood urea level < 200 mg %. In cases of sepsis, a close watch on electrolytes is necessary (Dhall, 1986).

IMPORTANT POINTS

1. The most important changes that occur in the kidneys during pregnancy are dilatation of the collecting system, increase in RPF and GFR, and changes in the tubular reabsorption of glucose, sodium, amino acids, and uric acid.
2. The average serum creatinine concentration during pregnancy is 0.6 mg/dl. The average BUN is 9 mg/dl. The average creatinine clearance is 137 ml/minute.
3. *E. coli* is responsible for more than 80% of all acute upper urinary tract infections. The selectivity and virulence of E. coli for the urinary tract may be explained by the presence, in some strains, of fimbriae that bind to specific glycoproteins on the surface of epithelial cells.
4. Universal screening for symptomatic bacteriuria during pregnancy is not universally accepted.
5. Acute pyelonephritis during pregnancy is a serious complication. Some patients develop septic shock and pulmonary and hematologic problems.
6. Approximately 80% of all urinary stones have calcium and can be seen by x-ray in a flat plate of the abdomen.
7. Obstruction of the urinary tract by stone requires cystoscopic ureteral catheterization, dislodgment of the stone, and passage of a ureteral stent. If this is

not possible, percutaneous nephrostomy should be performed.

8. In the majority of cases ARF in pregnancy is the result of severe hypoperfusion secondary to preeclampsia or to hypovolemia caused by abruptio placenta or placenta previa.
9. Inadequate renal perfusion results in redistribution of the blood flow with production of cortical ischemia. This causes marked decrease in GFR, concentrating ability, and urinary volume. These functional changes (prerenal disease) may progress to parenchymal damage (ATN).
10. Complete anuria following an ischemic insult to the kidneys suggests renal cortical necrosis.
11. The BUN to creatinine ratio and the fractional excretion of sodium are two useful tests in the differentiation between prerenal disease and ATN.
12. The initial treatment of prerenal disease and ATN is the same and involves hemodynamic monitoring, intravascular volume expansion, furosemide, and delivery.
13. It is controversial if ATN can be prevented or ameliorated with high doses of furosemide. We believe that furosemide should be given to patients with severe oliguria unresponsive to volume expansion because the potential benefit is large and the drug has relatively few severe side effects.
14. Although many of the conditions causing nephrotic syndrome during pregnancy may cause elevation of blood pressure, the presence of this sign is strongly suggestive of the possibility of preeclampsia.
15. The finding of a decrease in complement levels in patients with nephrotic syndrome during pregnancy is strongly suggestive of the possibility of lupus nephropathy.
16. Most studies indicate that pregnancy does not accelerate renal damage in patients with renal disease and normal or only mildly impaired kidney function. However, complications will frequently occur if the patient has preeclampsia, proteinuria, or elevated serum creatinine.
17. The fetal prognosis for women with chronic renal disease is favorable if they do not develop superimposed preeclampsia before 28 weeks and if their renal function is not severely affected. Patients with advanced renal insufficiency have a more guarded fetal prognosis.

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20

Cardiac Disease and Pregnancy

CHAPTER OUTLINE

In USA 1–3% of all pregnancies are complicated by maternal cardiac disease, an association that is responsible for about 15% of all maternal deaths. The incidence of cardiac disease during pregnancy has remained stable for many years since the significant decrease in the occurrence of rheumatic heart disease in the last 40 years has been compensated by a significant increase of pregnancy in women with congenital heart disease. In developed countries survival of newborns affected by congenital heart disease is about 85%—in many cases as a result of complex surgical procedures performed in the first few months of life. As a consequence, the cardiologists and the obstetricians are today facing an increasingly large group of pregnant women with surgically corrected congenital abnormalities.

For all practical purposes, the medical management of the pregnant cardiac patient is controlled by the cardiologists or the internists. The obstetrician, however, should have adequate information about cardiac diseases during pregnancy so that he/she can function effectively as a member of the team that will be taking care of the patient. Also, he/she should be able to diagnose and in many cases initiate the management of some of the medical complications that may affect the pregnant patient with heart disease. Finally, the obstetrician should be able to recognize some of the cardiac problems that may occur during an otherwise uncomplicated pregnancy before consultation with the internist or cardiologist. In order to accomplish these functions, one should be familiar with the following topics that will be discussed in this chapter:

1. Preconceptional counseling
2. Hemodynamic changes occurring during pregnancy
3. Effects of pregnancy on maternal cardiac disease
4. Effects of maternal cardiac disease on pregnancy
5. General measures for the care of pregnant patients with heart disease
6. Management of congestive heart failure (CHF) during pregnancy
7. Management of acute pulmonary edema during pregnancy
8. Specific cardiac diseases in pregnancy

PRECONCEPTIONAL COUNSELING

Women with heart conditions who desire or anticipate pregnancy should have preconceptional counseling. The counseling session should include but not be limited to a discussion regarding the optimum time to become pregnant, the effects of the heart condition on pregnancy, the effects of pregnancy on the heart condition, the general characteristics of their care during pregnancy, the neonatal/perinatal risks, and the ways to optimize their cardiac condition before pregnancy occurs. The ideal situation for counseling would be in the early teen years because sexual activity usually starts in adolescence and in most cases is unprotected. The frequent occurrence of anxious mothers bringing their adolescent daughters with congenital or acquired heart disease to the obstetrician when they are already in the second trimester of pregnancy is distressing.

The first step in the preconceptional counseling session is to obtain a thorough history, perform a physical examination, and have available information from recent electrocardiograms and echocardiograms. This information will it make possible to obtain a functional classification and to place the patient in a risk category. The functional classification universally used is the New York Heart Association, or NYHA (Box 20-1). As shown in Box 20-2, risk categories are defined as low or minimal risk, intermediate or moderate risk, and high or major risk (Arafeb and Baird, 2006). The most important risk factors for a primary cardiac event or complication during pregnancy were analyzed by Siu and Colman (2004). These investigators recommend assigning a 5% risk for a significant cardiac event, most commonly pulmonary edema or arrhythmia, to pregnant patients with heart disease and none of the risk factors shown in Box 20-3. If one of these factors is present, the risk increases to 25%. If more than one of these factors is present the risk assigned is 75%. The evaluation of risk provides a basis to explain to the patient the need for extensive testing during pregnancy, increased frequency of office visits, need for prolonged hospitalization, and in some cases the need for surgical or medical procedures before pregnancy. Risk assessment is also useful to determine the type of facility where the patient should go for her delivery. Women with complex anatomic lesions and at moderate and high risk for complications should be counseled to deliver in tertiary centers.

Discussion of the clinical problems that women may develop during pregnancy is an important part of the preconceptional counseling. Heart failure, pulmonary edema, fatal arrhythmias, aortic dissection, and any other complications pertinent to their specific cardiac condition and their functional and risk classification should also be discussed openly. The need for early hospital admission and the possibility of critical care and central hemodynamic monitoring should be discussed as well. The need for induction of labor, shortening of the second stage of labor, methods of anesthesia used during labor and delivery, endocarditis prophylaxis, and anticoagulation therapy

BOX 20-1

New York Heart Association functional classification of cardiac disease

- Grade I—Patients have no limitations of physical exercise; ordinary activity does not cause undue fatigue, palpitations, dyspnea, or angina
- Grade II—Patients have slight limitations of physical exercise; ordinary activity results in fatigue, palpitations, dyspnea, or angina
- Grade III—Patients have marked limitations of physical activity; less than ordinary activity causes symptoms
- Grade IV—Patients have an inability to carry on physical activity without symptoms

BOX 20-2

Risk of cardiac events during pregnancy in women with heart disease

Low risk	Small left to right shunts such as ASD, VSD, and PDA Repaired lesions with normal cardiac function Mild to moderate pulmonic or tricuspid lesions Marfan's syndrome with normal aortic root Homograft or bioprosthetic valves Bicuspid aortic valve without stenosis
Intermediate risk	Uncorrected cyanotic heart disease Large left to right shunts Uncorrected, uncomplicated aortic stenosis Mechanical valve prosthesis Severe pulmonic stenosis Moderate to severe left ventricular dysfunction Previous left ventricular dysfunction now resolved (such as peripartum cardiomyopathy) Previous myocardial infarction
High risk	Pulmonary hypertension Marfan's syndrome with aortic valve involvement Cardiomyopathy Complicated aortic coarctation

BOX 20-3

Predictors of cardiac events during pregnancy

N New York Heart Association grade > II

O Obstructive lesions of the left heart
- Mitral valve < 2 cm
- Aortic valve < 1.5 cm
- Gradient peak > 30

P Prior cardiac event before pregnancy
- Heart failure
- Arrhythmia
- Transient ischemic attack
- Stroke

E Ejection fraction < 40%

BOX 20-4

Topics for discussion during preconceptional counseling

- Characteristics of the heart condition, functional and risk classifications
- Effects of cardiac condition on pregnancy
- Effects of pregnancy on cardiac condition
- Fetal and neonatal complications associated with her specific heart condition
- Need for multidisciplinary care
- Frequency of prenatal visits and need for maternal and fetal testing
- Need for anticoagulation and hemodynamic monitoring
- Timing of birth, type of hospital facility required for childbirth
- Pain control and type of anesthesia required during labor and delivery
- Potential need for cesarean delivery

should also be a part of the consult. Other important information to be shared with the patient is the projected time and the facility of choice for childbirth, and the drugs that may be used after delivery and their effects on breast-feeding (Box 20-4). Patients with Eisenmenger's syndrome, pulmonary hypertension, severe left-side obstructive lesions, and women with Marfan's syndrome and dilated aortic root should be informed of the high risk for maternal death and counseled to consider avoiding pregnancy and choose adoption or other methods to have a family.

HEMODYNAMIC CHANGES DURING PREGNANCY

Pregnancy causes significant changes in cardiovascular physiology. One of the most important studies describing the normal hemodynamic changes of pregnancy is that of Clark et al. (1989). They studied 10 healthy, primiparous patients between 36 and 38 weeks of gestation and between 11 and 13 weeks postpartum using pulmonary artery catheterization. They found that the main changes in the pregnant status were (a) decreased peripheral vascular resistance (PVR) (b) decreased pulmonary vascular resistance, (c) decreased colloid oncotic pressure, (d) increased cardiac output, and (e) increased pulse rate (Table 20-1). The most important points are that normal pregnancy significantly increases the workload of the heart, circulation is hyperdynamic, and a high cardiac output is present.

The increase in cardiac output starts at about 10 weeks into the pregnancy, reaches a maximum at about 24–28 weeks, and remains elevated until parturition (Figure 20-1). The rise in cardiac output is initially determined by an increase in stroke volume. Later, as pregnancy advances, there is an increase in heart rate of 10–15 beats/minute (bpm) that will contribute to this change. The cardiac output during pregnancy is markedly sensitive to maternal positional changes. Both echocardiographic and hemodynamic studies have demonstrated a significant decrease in cardiac output when the mother lies in the supine position. This phenomenon, which is usually observed after 24 weeks, is due to compression of the vena cava by the pregnant uterus and a decrease in the venous return to the heart.

Table 20-1. Hemodynamic changes in normal pregnancy (Clark et al., 1989)

	Nonpregnant	Pregnant
Cardiac output (L/minute)	4.3 ± 0.9	6.2 ± 1.0
Heart rate (beats/minute)	71 ± 10.0	83 ± 10.0
Systemic vascular resistance (dyne. cm. second^5)	1530 ± 520	1210 ± 266
Pulmonary vascular resistance (dyne. cm. second^5)	119 ± 47.0	78 ± 22
Colloid oncotic pressure (mmHg)	20.8 ± 1.0	18.0 ± 1.5
Colloid oncotic pressure–pulmonary capillary wedge pressure (mmHg)	14.5 ± 2.5	10.5 ± 2.7
Mean arterial pressure (mmHg)	86.4 ± 7.5	90.3 ± 5.8
Pulmonary capillary wedge pressure (mmHg)	6.3 ± 2.1	7.5 ± 1.8
Central venous pressure (mmHg)	3.7 ± 2.6	3.6 ± 2.5
Left ventricular stroke volume	41 ± 8	48 ± 6

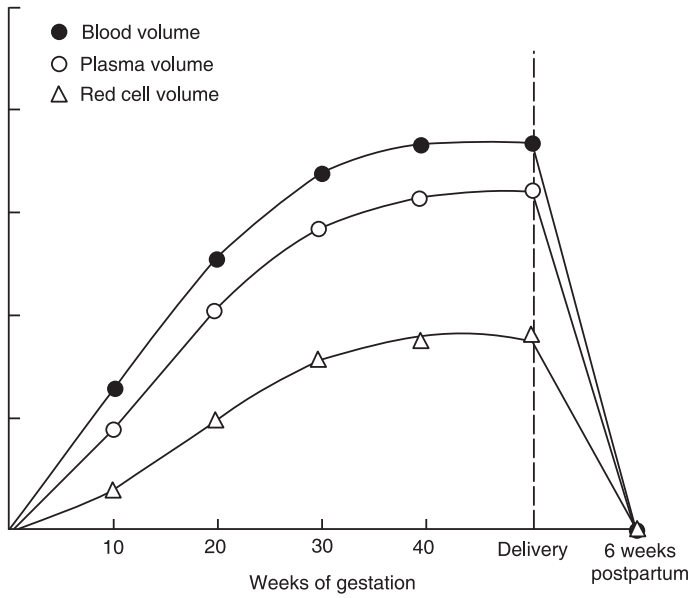

Figure 20-1. Hemodynamic changes during normal pregnancy. Expansion of plasma and red cell volume and increase in cardiac output during normal pregnancy (Redrawn from: Peck TM, Arias F. Hematologic changes associated with pregnancy. Clin Obstet Gynecol 1979; 22: 785.)

An increase in intravascular volume (IV volume) is one of the main determinants of the increased cardiac output of pregnancy. There is an increase in both red cell volume and plasma volume that starts at about 8 weeks of gestation and reaches a maximum at 32–36 weeks. In the third trimester, the IV volume has increased by approximately 50% in a singleton pregnancy, reaching a mean value of approximately 85 ml/kg. The increase in IV volume is even greater in multifetal gestations. The plasma volume increases first and then, to a lesser degree, the red cell volume increases, causing a "physiologic hemodilution" during the midtrimester of pregnancy (Figure 20-1). A good clinical marker of an expanded IV volume during pregnancy is the presence of a grade II/VI systolic ejection murmur on auscultation of the heart. This physiologic murmur appears at about 10–12 weeks into the pregnancy and disappears in the beginning of the postpartum period. Patients who do not expand their IV volumes during pregnancy (i.e., some patients with hypertension and pregnancy) do not have this murmur. The increase in IV volume fulfills the needs of the developing uteroplacental circulation and protects the mother against the potentially harmful effects of the blood loss that occurs at parturition. The increase in blood volume of pregnancy does not alter the central venous pressure that is the same as in the nonpregnant status.

Another important hemodynamic change in pregnancy is decreased peripheral vascular resistance. PVR decreases during pregnancy on the arterial and the venous side of the circulation. The mechanism for this change is not well understood but it is most likely a direct effect of placental hormones or vasodilator prostaglandins (prostacyclin) on the blood vessels. The decrease in PVR is clinically manifested by a decrease in both mean and diastolic blood pressures. This decrease is clearly observed during the second trimester, when the mean average blood pressure is 10–15 mmHg lower than in the nonpregnant state. In patients with chronic hypertension, this drop in blood pressure may conceal the diagnosis when they first present for care during the midtrimester. Most of the IV volume is contained in the capacitance vessels, and the decrease in venous resistance during pregnancy represents the adaptation of the venous vascular tree to blood volume expansion. If this adaptation does not occur, the IV volume will not expand, with serious compromise of the uteroplacental circulation.

Another physiologic change that is important, particularly for pregnant patients with Marfan's syndrome, is the increase in size and compliance of the aortic root. This tendency may facilitate aortic dissection for Marfan's patients, especially those who have dilated aortic roots before they get pregnant.

EFFECTS OF PREGNANCY ON MATERNAL CARDIAC DISEASE

The hemodynamic changes that occur during pregnancy have a profound effect on the patient with cardiac disease. All these changes increase cardiac work and their combined effect may exceed the limited functional capacity of an ailing heart. When the functional capacity of the heart is exceeded, sudden death or, more commonly, CHF and pulmonary edema will occur. As a result of the effects of pregnancy on cardiac disease, maternal mortality may be as high as 15% for all cardiac patients, although it varies widely with the severity of the cardiac problem.

There are several periods during pregnancy when the danger of cardiac decompensation is especially great. The first one is between 12 and 16 weeks of gestation when the hemodynamic changes of pregnancy begin. A second critical period is between 28 and 32 weeks of gestation when the hemodynamic changes of pregnancy peak and cardiac demands are at a maximum. About 50% of the patients who develop CHF at this stage of pregnancy are in class II or III of the NYHA classification, earlier in gestation. Another dangerous time for pregnant cardiac patients is during labor and delivery. During labor, every uterine contraction injects 300–500 ml of blood from the uteroplacental circulation into the maternal bloodstream, increasing cardiac output by approximately 15–20%. Simultaneously, during the second stage of labor, maternal pushing decreases the venous return to the heart, causing a decrease in cardiac output. These sudden and frequent variations in cardiac output during the second stage of labor may be critical for some women with underlying heart disease. Another dangerous time is immediately after delivery of the baby and placental separation when the obstructive effect of the pregnant uterus upon the return circulation to the heart disappears. At this time, there is a sudden transfusion of blood from the lower extremities and the uteroplacental vascular tree to the systemic circulation. This large and abrupt increase in blood volume is more than many pregnant cardiac patients can tolerate, and CHF occurs frequently at this time. The final dangerous time for the pregnant cardiac patient is 4–5 days after delivery. Patients with primary pulmonary hypertension, Eisenmenger's syndrome, aortic stenosis, and cyanotic heart disease may be able to go through pregnancy and labor and delivery without major complications. However, sudden death in the early postpartum period may occur. Decreased peripheral resistance with right-to-left shunting and pulmonary embolization from silent iliofemoral thrombus are two of the problems that may occur at this time.

EFFECTS OF MATERNAL CARDIAC DISEASE ON PREGNANCY

Pregnancy outcome is compromised by the presence of cardiac disease. Fetal death is usually secondary to chronic severe or acute maternal deterioration. Fetal morbidity is usually secondary to preterm delivery and fetal growth restriction, conditions that frequently occur in pregnant women with heart disease. This is probably due to their relative inability to maintain an adequate uteroplacental circulation. The frequency of these problems is related to the severity of the functional impairment of the heart and the severity of the chronic tissue hypoxia. Another fetal risk is that of congenital heart disease. If the mother has congenital heart disease, there is an increased incidence (4.5% versus 0.6% in the overall population) of fetal congenital cardiovascular anomalies.

Not long ago, the overall perinatal mortality for pregnant patients with cardiac disease was as high as 20%. The poor fetal outcome associated with maternal cardiac disease has been drastically modified with adequate prenatal care, prolonged hospitalization, and intensive care when heart failure occurs. However, fetal death still occurs in pregnant cardiac patients, mostly in mothers with cyanotic heart conditions. In these cases, the poor outcome is related to the degree of maternal polycythemia, which in turn is a result of chronic hypoxemia. Fetal death also occasionally occurs in the patients with Marfan's syndrome who have an acute aortic dissection and in cardiac patients who have significant functional impairment (class III and IV, NYHA classification).

GENERAL MEASURES FOR THE CARE OF PREGNANT PATIENTS WITH HEART DISEASE

The level of antepartum care required by pregnant women with heart disease depends on their risk classification. The care of low-risk patients (Box 20-2) may be by their primary providers, following recommendations by the maternal–fetal medicine specialist. Women in moderate- and severe-risk categories should be followed by a multidisciplinary team including the primary provider of care, maternal–fetal medicine specialists, anesthesiologists, cardiologists, and neonatologists. The role of the primary care physician and the high-risk obstetrical specialist is to monitor the fetal condition and the maternal cardiac function at frequent intervals in order to determine if the physiological changes elicited by pregnancy are exceeding the functional capacity of the heart and, in some cases, to use medications to limit the extent of these changes and improve the outcome. The anesthesiologist should be consulted early in pregnancy to assess the anesthetic risk of the patient and discuss with her the pain control that she will receive during labor and delivery. The cardiologist should see the patient on a regular basis and be available whenever the obstetrical caregiver believes that the woman is presenting signs of compromise. Early in the pregnancy and particularly if the fetus is affected by congenital heart disease the patient should see the neonatologist and, if necessary, the pediatric cardiologist to discuss possible neonatal outcomes and to find out what to expect when the baby is born. Women with cardiac lesions that place them at high risk for death during pregnancy such as Eisenmenger's syndrome and pulmonary hypertension should be advised to terminate their pregnancy and have permanent sterilization.

Monitoring Cardiac Function During Pregnancy

Evaluation of the cardiac response of the patient with heart disease to the normal hemodynamic changes of pregnancy is done mainly by clinical observation. A good method is to determine the NYHA functional classification in each prenatal visit. Easy fatigability, shortness of breath, orthopnea, and pulmonary congestion are signs and symptoms characteristic of left-sided heart failure. Weight gain, dependent edema, hepatomegaly, and increased jugular venous pressure are signs and symptoms suggestive of right-sided heart failure. All of these signs and symptoms may also occur in normal pregnant patients but in the pregnant patient with heart disease they are important and require careful evaluation.

Patients may exhibit varying degrees of biventricular failure and signs and symptoms of left or right failure may predominate, depending on the defect causing the CHF. Patients with mitral stenosis predominantly have signs of left ventricular failure, while patients with peripartum cardiomyopathy (PPCM) have signs and symptoms of biventricular failure. Shortness of breath is one of the most common complaints of left-side failure and at the same time is a dominant complaint of normal pregnant women. The "thirst for air" that occurs during pregnancy is usually not severe enough to limit the patient's activity, and normal pregnant women continue their activities despite shortness of breath. The dyspnea of left heart failure is different in that the patient is clearly limited in her level of activity and often she also complains of orthopnea and orthopneic cough. Some patients with left-side heart failure develop bronchospasm and wheezing after a few hours of sleep, i.e., "paroxysmal nocturnal dyspnea," or "cardiac asthma." In the initial phases of left-sided heart failure, tachycardia and an S3 gallop may be present on auscultation. However, the most important sign of left-sided failure is the presence of bibasilar rales. The characteristic signs and symptoms of right-side heart failure are the product of systemic venous congestion. The main manifestations are increased jugular venous pressure,

hepatomegaly, and dependent edema. The first two of these signs are not present in normal pregnancy but the last is normally present.

The obstetricians taking care of pregnant cardiac patients should search at each prenatal visit for clinical evidence suggesting the onset of CHF. Meticulous interrogation and examination of the patient is necessary. A sudden worsening of the NYHA functional classification due to increase in body weight, orthopnea, tachycardia, and hepatomegaly and the presence of pulmonary rales may point to CHF and demand further evaluation. A chest x-ray examination showing vascular redistribution with distention of the pulmonary veins in the upper lobes will provide additional evidence of pulmonary congestion. In such cases the cardiologist should be contacted and the patient admitted to the hospital for further assessment and treatment. It is necessary to avoid a superficial evaluation by ordering an electrocardiogram because this tool is insensitive to the changes caused by CHF.

Measures and Medications Frequently Used in Women with Heart Disease and Pregnancy

Antepartum

The most important measure for attenuating the impact of pregnancy upon a diseased heart is bed rest. Bed rest increases the venous return to the heart, improves renal perfusion, induces diuresis, and promotes elimination of water. Also, since bed rest reduces the metabolic needs of several organs, especially muscle, the blood flow to these organs at rest decreases markedly, ameliorating the workload on the heart.

Dietary salt restriction is a measure which helps to prevent excessive retention of sodium and water. Most pregnant cardiac patients tolerate a moderate sodium dietary restriction (4–6 g daily).

Diuretics should be given to the cardiac pregnant patient if a moderate restriction in sodium intake is insufficient to limit the normal IV volume expansion that occurs during gestation. The diuretic most commonly used is chlorothiazide. This drug acts by inhibiting sodium reabsorption in the distal tubule. For the most part, thiazides are benign drugs and their most common side effect is hypokalemia, which can be avoided by concurrent administration of a potassium-retaining agent or by increasing the dietary ingestion of potassium. Another problem with this diuretic during pregnancy is the occasional occurrence of neonatal thrombocytopenia. However, the most important concern with the use of diuretics during pregnancy is that they may decrease the plasma volume to the point that placental perfusion and fetal growth are compromised. There is evidence indicating that a decrease in IV volume during pregnancy is associated with fetal growth restriction and that the severity of the fetal growth impairment is directly related to the magnitude of the IV volume depletion. Unfortunately, one cannot accurately measure the IV volume contraction caused by diuretics in pregnant women and there is no information addressing the degree of volume restriction that is compatible with adequate fetal growth. In women taking diuretics, serial hematocrit determinations may be helpful to determine the effects of the diuretic on plasma volume and the dosage of diuretic may be adjusted to keep the hematocrit value slightly above that obtained before initiation of therapy.

Prophylactic digitalization is commonly used in pregnant patients with severe heart disease who are not in overt CHF. The objective of using prophylactic digitalization is to improve the contractility of the heart and to relieve symptoms such as easy fatigability, orthopnea, and weakness. A secondary benefit is to avoid the production of ventricular tachycardia and rapid atrial rhythms.

Women with congenital heart disease frequently require *anticoagulation* during pregnancy. The need for anticoagulation is apparent in women with artificial mechanical valve prosthesis and with chronic or recurrent arrhythmias. As it will be discussed later, the use of anticoagulation creates new risks for the mother and the fetus, increases the need for laboratory monitoring, and is a topic that needs to be discussed extensively with the mother.

During labor and delivery

In general, vaginal delivery is a better option than cesarean section for women with heart disease. The risk of bleeding, infection, and clotting complications is less and vaginal delivery is not associated with the acute shift in blood volume that happens during cesarean. However, a long labor and a difficult vaginal delivery are much more morbid than a cesarean and in many cases it is preferable to avoid the hemodynamic effects of labor and delivery by performing a quick cesarean section.

During labor it is possible to monitor and, in some cases, decrease the impact of pregnancy on an ailing heart by adopting some of the following measures:

1. The pregnant cardiac patient should always labor and even deliver in the lateral supine position in order to avoid the hemodynamic problems caused by the dorsal decubitus position.
2. The patient should have effective pain relief during labor. Pain control reduces tachycardia, myocardial work, and cardiac output. It has been calculated that pain during labor increases the cardiac output 50% above the elevation normally seen during the second stage of labor. During early labor, small doses of

intravenous morphine (2–4 mg) may be used. Later, if the patient is not anticoagulated, the anesthesia of choice is epidural blockade, administered by an experienced obstetrical anesthesiologist. Many pregnant cardiac patients will benefit from a double catheter epidural anesthesia technique. This method limits the extent of the sympathetic blockade and its effect on IV volume pooling and blood pressure. Also, it is better to administer an epidural narcotic (morphine, fentanyl) than epidural anesthetics. Because of their inability to cause sympathetic blockade, epidural narcotics may be given in situations in which there is a relative contraindication to the epidural administration of local anesthetics, such as in patients with aortic stenosis, mitral stenosis, aortic coarctation, Marfan's syndrome with dilated aortic root, or hypertrophic subaortic stenosis.

3. An important aspect of the intrapartum care of the pregnant cardiac patient is the control of the rate of intravenous fluid administration. Almost all cardiac patients in labor should be kept on the "dry" side and IV fluids restricted to no more than 75 ml per hour.
4. Cardiac patients in labor should be continuously monitored with pulse oximetry. Mild degrees of desaturation may be corrected by oxygen administration via nasal prongs rebreathing mask. Desaturation during labor that is not corrected by oxygen is suggestive of the development of pulmonary edema.
5. Patients with congenital or acquired heart lesions and with artificial valve prostheses should have antibiotic prophylaxis at the time of delivery in order to avoid subacute bacterial endocarditis. The antibiotic treatment recommended by the American Heart Association is shown in Box 20-4.
6. Pregnant cardiac patients who are not anticoagulated tend to develop thromboembolization in the postpartum period. Relative immobilization, pooling of blood in the lower extremities, and peripartum alterations in coagulation and fibrinolysis combine to produce an environment conducive to the formation of thrombi in the lower extremities. The risk of thromboembolization is approximately 2% for patients with rheumatic heart disease. To avoid this serious complication, it is necessary to initiate ambulation shortly after delivery, use pneumatic compression of the lower extremities, and give prophylactic low-dose-heparin during labor, delivery, and the immediate postpartum period.
7. Immediately following delivery, the uterus markedly decreases in size and ceases to obstruct the return circulation to the heart. At the same time, most of the blood contained in the uterine vessels is suddenly infused into the systemic circulation. These two physiologic phenomena combine to increase the blood volume to a point where it may exceed the pumping ability of the heart, resulting in acute pulmonary edema. Patients with mitral stenosis and fixed cardiac output are especially at risk for this problem, and to decrease the risk of postpartum pulmonary edema these patients should be placed in the sitting position following delivery. Sitting will increase venous pooling in the lower extremities and decrease the venous return to the heart, thereby allowing a more gradual adaptation to the postpartum hemodynamic changes. Also, if the patient is under epidural anesthesia, the anesthesiologist may raise the level of anesthesia and the sympathetic blockade. Finally, tourniquets may be used in the lower extremities.
8. At the time of delivery, oxytocin is given to make the uterus contract and to avoid intrapartum and postpartum bleeding. In the cardiac patient, it is important not to administer the medication as an intravenous bolus, because it may cause a sudden drop in PVR and the subsequent hypotension may be difficult to tolerate for some patients. Also, cardiac patients should not receive ergot alkaloids for prophylaxis or treatment of postpartum uterine atony, because these agents cause significant vasoconstriction and elevation of blood pressure, which can be deleterious as well. A summary of the measures to take in the management of the cardiac patient in labor is shown in Box 20-5.

BOX 20-5

General measures for the cardiac patient in labor

1. Labor and delivery in lateral decubitus position
2. Pulse oximetry
3. Adequate pain relief (epidural narcotics, double catheter epidural)
4. Restrict IV fluids to 75 cc/hour
5. Oxygen by rebreathing mask
6. Avoid bolus oxytocin and ergot compounds
7. Antibiotic prophylaxis
8. Thrombosis prophylaxis
9. Prevention of postpartum pulmonary edema

TREATMENT OF ACUTE CHF DURING PREGNANCY

The majority of pregnant women with heart disease are aware of their condition prior to pregnancy. Occasionally patients with a previously undiagnosed cardiac disorder present with CHF during pregnancy. In this situation, it is

necessary to define the etiology of the problem because in many cases the primary defect is amenable to surgical correction. An example would be a patient with mitral or aortic stenosis undiagnosed before pregnancy. Timely operative intervention may be lifesaving in such a situation (Esteves et al., 2006). Irrespective of the previous knowledge about their heart condition, all pregnant women presenting in CHF should have a work-up to investigate what factors are contributing to the occurrence of their heart failure. Anemia, infections, arrhythmias, noncompliance with medications or salt restriction, excessive physical activity, and administration of salt-retaining medications are the factors most frequently associated with acute CHF in the pregnant cardiac patient. Once the potentially correctable precipitating factors have been ruled out, the management of the pregnant patient in CHF consists of the following:

1. Reducing the cardiac work with bed rest
2. Decreasing the preload with diuretics
3. Improving cardiac contractility with digitalis or other agents (Dopamine, dobutamine)
4. Reducing the afterload with vasodilators

Bed rest is an essential component of the treatment of pregnant patients with CHF. The pregnant patient in CHF should be placed on bed rest so as to reduce her metabolic rate and her heart work. Unfortunately, venous thrombosis and pulmonary embolization, the most common harmful effects of bed rest, occur more frequently in pregnant than in nonpregnant patients due to the decreased fibrinolytic activity and hypercoagulability that exist during gestation. Therefore, passive leg exercises, prophylactic heparin (5000 U subcutaneously every 12 hours), and pneumatic compression stockings should be used to avoid thromboembolic complications in these patients.

Diuretics should be used with caution in the pregnant patient with CHF. One should begin treatment with low doses of furosemide or with chlorothiazide 25–50 mg daily. Diuretic therapy should be monitored with daily weight checks, as well as serial measurements of hematocrit, electrolytes, and creatinine. A rapid decrease in weight concomitant with a rise in hematocrit results from a rapid constriction of the IV volume that may be hazardous. The appearance of a low potassium value or a high serum creatinine also indicates the need for therapeutic adjustment.

Digitalis therapy is an important component of the drug treatment of patients with CHF. The digitalis preparation most commonly used is digoxin because it can be given orally, has a rapid onset of action, and a relatively short life. It is usually started with a loading dose of 1.0–1.5 mg in a 24-hour period. Maintenance dosage is usually 0.25 mg daily (0.125–0.375). Therapy is adjusted according to the patient's clinical response, the serum levels, and the electrocardiographic changes. The therapeutic serum level of digoxin is 1.0–1.5 ng/ml. Digoxin as any other digitalis drugs can be used safely during pregnancy. However, the expanded IV volume associated with pregnancy results in a lower serum level of drug compared to a nongravid patient given the same dose. Placental transfer of digoxin is poor in early pregnancy but improves with advancing gestational age. Fetal toxicity has never been described with therapeutic maternal levels. The most serious maternal side effect of digitalis therapy is cardiac arrhythmia that can be recognized by an electrocardiogram and requires rapid treatment. Discontinuation of the medication, use of antiarrhythmic medications, and correction of hypokalemia usually suffice. However, severe intoxication may require the use of digoxin-specific antibodies (Digibind).

Vasodilator therapy has become an important part of the treatment of patients with CHF. The principle behind vasodilator therapy in patients with CHF is to reduce cardiac work by lowering PVR. Several drugs may be used for this purpose. In emergency situations, the drugs most commonly used are hydralazine, nitroglycerin, and sodium nitroprusside. For maintenance therapy, hydralazine is the drug of choice. Unfortunately, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor inhibitors are contraindicated during pregnancy because they have severe fetal side effects. Hydralazine, in oral or intravenous forms, has been used for many years in patients with preeclampsia and eclampsia. Hydralazine is primarily an arterial vasodilator which is relatively safe to use during pregnancy. When hydralazine is used in large doses, a marked decrease in blood pressure may cause an alteration in placental perfusion and subsequent signs of fetal distress will appear in fetal heart rate tracings.

In acute cardiac emergencies, nitroglycerin is the vasodilator of choice for pregnant women since nitroprusside may have undesirable fetal side effects. Similarly, in cardiac emergencies, dopamine and dobutamine can be used without fear of fetal side effects. Nitrates reduce both preload and afterload, but their predominant effect is on the capacitance vessels. They decrease the venous return to the heart and are particularly useful in reducing pulmonary congestion in doses that do not markedly affect systemic blood pressure. Both nitroglycerin and sodium nitroprusside are powerful antihypertensive agents that, similar to hydralazine, may cause maternal hypotension, decreased uteroplacental perfusion, and fetal distress. The effect of peripheral vasodilators is more pronounced when the pregnant patient is supine and the weight of the uterus interferes with the venous return to the heart.

The ACE inhibitors and the angiotensin receptor inhibitors decrease PVR, pulmonary capillary wedge pressure, and heart size and they increase stroke index and exercise tolerance time. They also reduce preload by

impairing the retention of sodium and water caused by aldosterone, reduce the vasoconstriction caused by angiotensin, and block the increase in sympathetic tone mediated by the renin–angiotensin–aldosterone system. These pharmacologic properties make them ideal agents in the treatment of CHF. However, fetal growth restriction and severe fetal renal abnormalities have been described in pregnant patients taking these medications that are contraindicated at all time during pregnancy.

ACUTE PULMONARY EDEMA DURING PREGNANCY

Treatment of acute pulmonary edema during pregnancy should preferably take place in an intensive care unit. Invasive hemodynamic monitoring using Swan–Ganz catheterization is usually necessary to adequately assess the severity of the process and the response to therapy. Pulmonary edema is a life-threatening situation that occurs relatively frequently during pregnancy, making it necessary for the obstetrician to be familiar with its diagnosis and treatment. The basic problem in acute pulmonary edema is the mobilization of fluid from the pulmonary interstitial space into the alveolar space. The alveolar fluid impairs gas exchange, causing oxygen desaturation and retention of CO_2. If the condition remains uncorrected, generalized tissue hypoxia, acidosis, and death may ensue.

Pulmonary edema is caused by alterations in the forces that govern the movement of fluid in the pulmonary alveoli. Increased pulmonary capillary pressure usually due to fluid overload or CHF and altered capillary permeability due to endothelial cell injury are the most common mechanisms. Alterations in capillary pressure or permeability are aggravated by the decrease in plasma colloid oncotic pressure that normally occurs during pregnancy. The majority of cases of pulmonary edema during pregnancy are due to chorioamniotic infection, fluid overload, and administration of beta-adrenergic agents; preeclampsia and eclampsia; and CHF. The mechanism of pulmonary edema in each of these conditions is different and the management of the problem is also different.

The most common form of pulmonary edema seen by the obstetrician is associated with the treatment of preterm labor. This typically occurs in patients having a combination of chorioamniotic infection, betamimetic and glucocorticoid treatment, and large continuous intravenous infusion of crystalloid solutions. The pathophysiology of the pulmonary edema in these patients has not been completely clarified, but in the majority of them fluid overload and altered capillary permeability are the fundamental variables. Patients with exaggerated IV volume expansion, such as with multifetal pregnancies, or those with chorioamnionitis are more predisposed to develop pulmonary edema when treated with beta-mimetic agents.

Most pregnant patients who develop pulmonary edema in association with the treatment of preterm labor respond to the following treatment:

1. Discontinuation of labor-inhibiting drugs
2. Administration of furosemide (20 mg IV push initially, followed by 20 mg IV in one or more additional doses every 30–60 minutes, depending upon the response to the initial dose)
3. Administration of oxygen by mask

Another cause of pulmonary edema during pregnancy is preeclampsia. Pulmonary edema in severe preeclampsia results from endothelial cell injury, altered capillary permeability, and decreased plasma colloid oncotic pressure—factors that combine to cause mobilization of fluid into the alveolar space. In some preeclamptic patients, left ventricular failure secondary to a marked increase in PVR and fluid overload are contributory factors. Treatment of preeclamptic patients with pulmonary edema is difficult and the outcome may be poor despite the use of invasive hemodynamic monitoring. The main problem is our inability to modify with therapy the endothelial cell injury and capillary permeability problems. In this subset of patients, supportive therapy and expectant management are the favored modes of treatment.

In pregnant patients with cardiac disease, acute pulmonary edema usually results from the inability of the diseased heart to compensate for acute or chronic increases in IV volume. This may occur antenatally because of the physiologic expansion in plasma volume but it is also common after the autotransfusion that follows delivery of the fetus and placenta. Patients with stenotic valvular lesions and fixed cardiac outputs are at high risk for this complication. Treatment of acute pulmonary edema in the context of chronic heart disease requires aggressive measures aimed at decreasing preload (fluid restriction, diuretics, tourniquets), increasing the contractility of the heart (digitalis, dobutamine), and decreasing the afterload resistance (nitroglycerin, etc.).

SPECIFIC CARDIAC CONDITIONS AND PREGNANCY

The ability of a patient with heart disease to tolerate pregnancy is related to the degree of functional impairment and the specific nature of the cardiac lesion. With respect to the nature of the cardiac lesion, it is well known that some heart conditions are very well tolerated during pregnancy while others are not (Box 20-2). In this section, we will briefly describe some specific conditions that are poorly tolerated during pregnancy and that present significant problems for the cardiologists as well

as the obstetricians. It is noteworthy that termination of pregnancy is a valid legal and medical option for patients who have cardiac lesions with guarded maternal prognosis. Patients should be informed of the possibility of termination as an option in order to avoid the potential serious problems associated with their pregnancies.

Valvular Lesions

Mitral stenosis

Mitral stenosis is the most common rheumatic heart lesion and one of the most dangerous for pregnant women. In patients with mitral stenosis the obstruction to the blood flow from the left atrium to the left ventricle causes an increase in left atrial pressure that is aggravated during pregnancy because the increase in IV volume results in more blood coming to the left atrium to be pumped through the restricted outlet. In addition, the increase in heart rate that occurs during pregnancy decreases the time available for ventricular filling. The result of these two influences, increased blood volume and increased heart rate, is increased left atrial pressures and a higher risk for pulmonary edema than in the nonpregnant state. The increased left atrial pressure is transmitted to the pulmonary veins and when the pulmonary capillary pressure reaches a value above 25 mmHg, the homeostatic equilibrium between capillary pressure and plasma oncotic pressure is broken with production of pulmonary edema, which occurs in approximately 23% of pregnant women with mitral stenosis. It is not surprising that patients with mitral stenosis who are relatively asymptomatic (class I or II, NYHA classification) at the beginning of pregnancy may develop pulmonary edema when the pregnancy advances and the hemodynamic changes become more apparent.

The severity of mitral stenosis is assessed by echocardiographic measurement of the valve area that normally is 4–5 cm^2. Mild mitral stenosis corresponds to a valve area > 1.5 cm^2, moderate is between 1.0 and 1.5 cm^2, and severe < 1.0 cm^2. The incidence of maternal and fetal complications has a strong association with the valve area (Silversides et al., 2003).

Successful management of pregnant patients with mitral stenosis requires meticulous application of the measures indicated under "General management of cardiac patients during pregnancy." Bed rest, diuretics, and digitalization are the main elements of the therapy. If cardiac decompensation and pulmonary edema occur, the patient should be managed as outlined under "Pulmonary edema during pregnancy" During labor, the essentials of management include adequate pain relief, laboring and delivering in the lateral supine position, and adoption of measures to minimize the effects of the autotransfusion that follows delivery. Pregnant patients with mitral stenosis who respond poorly to medical treatment, and especially those with recurrent episodes of pulmonary edema, are candidates for cardiac surgery. The intervention of choice in most cases is mitral valvotomy. Open heart surgery and valve replacement during pregnancy have a very high fetal loss rate.

Aortic stenosis

Most cases of aortic stenosis are secondary to congenital bicuspid valve. However, in some patients the aortic valve is narrowed as a result of rheumatic heart disease. Patients with aortic stenosis develop left ventricular hypertrophy to generate the increased pressure necessary to pump blood through noncompliant valvular leaflets. Hemodynamically, these patients have fixed stroke volumes and increased left ventricular end-diastolic pressures. Eventually the left ventricular function fails to overcome the resistance to flow and the patient develops CHF. Angina and syncope frequently occur with the onset of CHF.

The severity of aortic stenosis can be assessed by measuring the valve area or the peak to peak gradient across the valve. In mild aortic stenosis the peak to peak gradient is < 36 mmHg, in moderate cases between 36 and 63 mmHg, and in severe cases > 63 mmHg. Cardiac complications during pregnancy occur almost exclusively in patients with severe stenosis (Silversides et al., 2003). Sudden death and irreversible heart failure are the most common causes of maternal death.

The cornerstone in the management of these patients is bed rest. Because of a fixed stroke volume, any activity will cause an increase in heart rate and a greater demand on the left ventricle. During labor, epidural anesthesia should be avoided because it will cause a decrease in PVR and this will increase the pressure gradient across the narrow valve. Epidural narcotics produce no sympathetic blockade and can be used in these patients. In contrast to most pregnant cardiac patients, the patient with aortic stenosis should not be restricted to 75 ml/hour of IV fluids during labor. A rate of IV fluids' administration of 125–150 ml/hour is more adequate.

Pulmonic stenosis

The prognosis in these cases depends on the degree of obstruction to flow that is assessed by the peak to peak velocity gradient across the stenotic valve. In the majority of cases, the gradient is small and pregnancy is well tolerated. When the gradient is > 50 mmHg, the stenosis is severe and consideration should be given to balloon valvuloplasty before pregnancy or after the first trimester of pregnancy.

Mitral regurgitation

Mitral regurgitation during pregnancy is usually the consequence of severe mitral valve prolapse (MVP). Pregnancy is usually well tolerated and rarely patients develop pulmonary congestion that usually responds well to diuretics. Rarely, severe mitral regurgitation causes left atrial dilatation with increased risk of atrial fibrillation.

Aortic regurgitation

This condition is usually associated with a bicuspid aortic valve or with a dilated aortic annulus in women with Marfan's syndrome. The condition is well tolerated during pregnancy and symptomatic patients usually respond well to diuretic therapy.

Mitral valve prolapse

MVP is the most common maternal cardiac condition seen in pregnant women affecting approximately 6–8% of all women of reproductive age. A reason why MVP is diagnosed frequently during pregnancy is that the incidence of minor symptomatic arrhythmias and palpitations during normal pregnancy is high. As a result, MVP is incidentally found during echocardiography performed to investigate these common cardiovascular complaints. In women with MVP, the leaflets and the chordae of the mitral valve stretch and bulge into the left atrium during systole. This, most probably, is due to a genetic defect causing abnormal collagen synthesis in the valve. The main symptoms of MVP are chest pain and cardiac arrhythmias, described by the patient as palpitations or skipped beats. Anxiety and even panic attacks may occur simultaneously with the onset of these symptoms. On physical examination, it is sometimes possible to find a midsystolic click muffled by the physiologic holosystolic murmur appearing at the end of the first trimester. The diagnosis of MVP is made by two-dimensional echocardiography, which shows systolic displacement of the mitral leaflets into the left atrium. In severe cases, Doppler will demonstrate some degree of regurgitation.

The course and the outcome of pregnancy in patients with MVP is similar to that of patients who do not have this defect. However, there are a few reported complications such as thromboembolism and endocarditis. The increase in IV volume and the decrease in PVR that occur during normal pregnancy will increase the left ventricular end-diastolic volume and, theoretically, should alleviate the signs and symptoms of MVP. This has been corroborated by clinical observations and echocardiographic studies.

Most pregnant patients with MVP do not require treatment for their symptoms. Patients with recurrent, severe arrhythmias need treatment with propanolol. Most

BOX 20-6

American College of Cardiology/American Heart Association recommendations for antibiotic prophylaxis to prevent bacterial endocarditis for uncomplicated vaginal delivery* (ACOG, 2003)

Cardiac lesion	Prophylaxis
Any congenital or acquired heart lesion in women with suspected bacteremia or active infection	Recommended
Prosthetic cardiac valves	Optional
Prior bacterial endocarditis	Optional
Complex cyanotic congenital cardiac malformations	Optional
Surgically constructed systemic pulmonary shunts	Optional
Congenital cardiac malformations**	Not recommended
Acquired (rheumatic) valvular dysfunction	Not recommended
Hypertrophic cardiomyopathy	Not recommended
Mitral valve prolapse with regurgitation or thickened leaflets or both	Not recommended
Physiological, functional, or innocent heart murmurs	Not recommended
Previous Kawasaki disease without valvular dysfunction	Not recommended
Previous rheumatic fever without valvular dysfunction	Not recommended
Cardiac pacemakers and implanted defibrillators	Not recommended
Prior coronary bypass surgery	Not recommended

*No recommendations were made for women with heart lesions undergoing cesarean delivery.

**Except repaired atrial septal defect, ventricular septal defect, patent ductus arteriosus, isolated secundum atrial defect.

BOX 20-7

American College of Cardiology/American Heart Association recommended endocarditis prophylaxis regimens (Bonnow et al., 1998)

High-risk patients	Ampicillin 2.0 g IM/IV plus gentamycin 1.5 mg/kg (not to exceed 120 mg) within 30 minutes of starting procedure. Six hours later ampicillin 1.0 g IM/IV or amoxicillin 1.0 g po.
High-risk patients allergic to penicillin	Vancomycin 1.0 g over 1–2 hours plus gentamycin 1.5 mg/kg (not to exceed 120 mg). Complete infusion within 30 minutes of starting the procedure
Moderate-risk patients	Amoxicillin 2.0 g po 1 hour before procedure or ampicillin 2.0 g IM/IV within 30 minutes of starting the procedure
Moderate-risk patients allergic to penicillin	Vancomycin 1.0 g IV over 1–2 hours. Complete infusion within 30 minutes of starting the procedure

patients do well with doses between 10 and 40 mg four times daily. Propanolol is safe for both mother and fetus. There is no need for antibiotic prophylaxis at the time of delivery for patients with MVP (Box 20-6). The risk of bacterial endocarditis following delivery in these patients is very low. The recommended antibiotics and their dosages in situations where antibiotic prophylaxis is indicated are shown in Box 20-7.

Women with prosthetic heart valves

Prosthetic heart valves have been used for many years in the treatment of congenital and acquired disorders. For this reason, pregnancy in women with artificial heart valves is not rare. The pregnancy outcome in these patients will depend on the type of valve (mechanical, porcine, human allograft), the site and the number of valves that were replaced, and the functional capacity of the heart following surgery. In general, these patients suffer from thromboembolization, complications derived from their anticoagulant regimen, valve dysfunction, endocarditis, and heart failure.

The type of valve is important in that porcine and human allograft valves do not require anticoagulation while it is absolutely necessary in patients with metallic valves. The site of valve replacement is important because patients with prosthetic mitral and tricuspid valves have a fixed cardiac output, while patients with aortic valves can respond to the physiologic needs of pregnancy with increases in cardiac output. Finally, prognosis is better if only one valve is abnormal and if the patient belongs to NYHA class I or II.

The most frequent complications in patients with prosthetic valves result from anticoagulation therapy. When they are not pregnant, these patients are anticoagulated with coumadin and have relatively few problems. Unfortunately, coumadin is a teratogenic agent and these patients need to be switched to heparin, which is not as effective as coumadin in the prevention of thromboembolization. The same dilemma occurs for other pregnant patients who need anticoagulation for conditions such as mitral stenosis, atrial fibrillation, deep vein thrombosis, pulmonary embolization within 3 months of pregnancy, and PPCM in the third trimester. Coumadin has well-known teratogenic effects when it is administered early in pregnancy. Its use in the early part of the first trimester may result in fetal abnormalities such as nasal hypoplasia, hypertelorism, prominence of the frontal bone, short stature, abnormalities of the central nervous system, mental retardation, and stippling of the epiphyses of long bones (chondrodysplasia punctata). The most common of these defects are nasal hypoplasia and stippled epiphyses that occur in approximately 4.6% of the patients and abnormalities of the central nervous system that occur in 2.6% of the cases. It is also associated with spontaneous fetal intracranial bleeding and fetal death when it is taken in the second and third trimesters of pregnancy. In view of the adverse effects of coumadin, many authorities recommend switching to heparin therapy. Heparin should be administered subcutaneously every 8–12 hours in a dose adequate to maintain the PTT (partial thromboplastin time) two to three times the basal value 6 hours before the next dose. The frequency and discomfort of injections and the frequent laboratory testing are reasons for noncompliance, inadequate anticoagulation, and subsequent thromboembolization. These problems may be obviated with the use of a heparin lock for self-intravenous administration, but this method requires close attention for the possibility of infection. Another potential side effect of heparin is that it may cause osteoporosis, a complication that occurs mainly in patients who receive 20,000 or more U/day for more than 6 months. Heparin-induced thrombocytopenia may also occur but usually the platelet count remains above 10,000/mm^3. Unfractionated heparin has a longer half-life and can be administered every 12 hours with less discomfort and fewer hematomas at the injection sites. Some investigators recommend that patients with prosthetic valves be anticoagulated with heparin during the first 12 and the last 4 weeks of pregnancy and with coumadin in the interim months. However, there is no adequate evidence to support this plan of management.

At the time of labor and delivery, anticoagulation must be reversed. The patient on unfractionated heparin will have normal clotting 4–6 hours after discontinuing the medication. Maternal effects of coumadin can be easily reversed with the administration of fresh frozen plasma but the fetus needs 1–2 weeks after discontinuing coumadin to reverse anticoagulation. This is why patients on this drug should be switched to heparin several weeks before the anticipated delivery time.

Left to Right Shunts

In general, lefts to right shunts are well tolerated during pregnancy. The main problem is that these shunts may cause pulmonary hypertension with reversal of the shunt and production of cyanosis. For this reason, all patients with left to right shunts should be evaluated by echocardiogram before pregnancy or as soon as the pregnancy is discovered to rule out pulmonary hypertension. As it will be described later in this chapter, pulmonary hypertension is a serious condition associated with poor maternal and perinatal prognosis.

Atrial septal defects

The outcome of pregnancy in women with atrial septal defects, or ASD, is usually benign. This defect is usually found in association with MVP, and complications

associated with this defect are rare in women less than 40 years' old.

Ventricular septal defects

VSD during pregnancy are uncommon because most of them close spontaneously or are surgically corrected during childhood. If a VSD is detected during pregnancy or the woman has a history of a VSD corrected during adulthood, it is important to obtain an echocardiogram to investigate if pulmonary hypertension is present. Pulmonary hypertension is a common consequence of delayed closure or no closure of a VSD and the outcome of pregnancy in women with pulmonary hypertension is poor.

Patent ductus arteriosus

Patent ductus arteriosus, or PDA, is rarely seen during pregnancy because most to them are surgically corrected during childhood. Similar to VSD the outcome is determined by the presence or absence of pulmonary hypertension.

Right to Left Shunts

These shunts are characterized by the passage of deoxygenated blood into the systemic circulation with production of cyanosis. These conditions usually require surgical treatment during childhood to permit survival. A significant number of patients born with right to left shunts have the defect repaired during childhood, are no longer cyanotic, and are getting pregnant. Fortunately, as long as their ventricular function is normal they tolerate pregnancy well (Zuber et al., 1999). However, some of them may have progressive right ventricular failure and cardiac arrhythmias. The right to left shunt most frequently seen by the obstetrician is corrected tetralogy of Fallot. Others are transposition of the great arteries, Ebstein abnormality, double-outlet right ventricle, single ventricle, and tricuspid atresia.

The outcome of pregnancy in women with uncorrected right to left shunts is not good (Presbitero et al., 1994). Thirty-two percent of them develop cardiovascular complications including heart failure, stroke, supraventricular tachycardia, and endocarditis. The live birth rate is 43%. The main determinants of the live birth rate are the arterial oxygen saturation and the hemoglobin concentration. Women with oxygen saturation less than or equal to 85% have a live birth rate of 12% as compared with 92% for those with oxygen saturation equal to or greater than 90%. Women with prepregnancy hemoglobin concentration of at least 20 g/L have an 8% rate of live births (Presbitero et al., 1994).

The type of surgical correction in congenital cyanotic heart disease varies with the nature of the heart defect. In many corrected defects the right ventricle becomes responsible for the systemic circulation and the outcome of pregnancy will depend on the ejection fraction of this ventricle (Davlouros et al., 2006). Systemic right ventricular function may deteriorate during pregnancy with resulting CHF. As a general rule, an ejection fraction equal or larger than 40% in the right systemic ventricle is associated with good outcome. The study by Khairy et al. (2006) demonstrated the importance of the right ventricular function in the outcome of the pregnancy in women with congenital heart disease. These investigators found that pulmonary edema and CHF were associated with subpulmonic ventricular dysfunction and/or severe pulmonary regurgitation, independent of the subaortic ventricular systolic function.

Women with corrected tetralogy of Fallot do quite well during pregnancy as long as the systemic ventricular function is good and there is no significant right outflow obstruction with severe pulmonic regurgitation and right ventricular dysfunction (Veldtman et al., 2004). Women with surgically corrected transposition of the great vessels usually have the systemic circulation supported by the right ventricle and may develop CHF during pregnancy. They also may have some degree of obstruction of the pulmonary veins and develop atrial arrhythmias due to their extensive atrial surgery. Women with a single functional ventricle (hypoplastic left or hypoplastic right heart) usually are corrected with a Fontan type of operation where the ventricle is used to support the systemic circulation but there is no pumping organ for the pulmonary circulation. This situation makes it difficult to increase cardiac output that will depend on the systemic venous pressure. Therefore, pregnancy will not be tolerated well and will be frequently complicated by CHF and arrhythmias that respond poorly to treatment. The rate of fetal loss is 30%.

Myocardial Conditions

The myocardial conditions most commonly seen during pregnancy are PPCM and ischemic heart disease. In the majority of these cases the maternal and fetal prognosis is guarded.

Peripartum cardiomyopathy

Every obstetrician should be familiarized with this form of congestive cardiac failure, which is intimately related to pregnancy. This disease occurs in 1 out of 2500–15,000 live births. The initial description of the syndrome suggested that it appears after parturition and so it was named "postpartum cardiomyopathy" or "puerperal heart failure." Today we know that the signs and symptoms of this disease may appear at any time in the last month of pregnancy and up to 5 months after delivery, and hence the name "peripartum cardiomyopathy" is

being used more frequently. Peripartal cardiomyopathy is responsible for an elevated proportion of maternal deaths, particularly in Black women (Whitehead et al., 2003). Risk factors include advanced maternal age, multiparity, multifetal gestation, obesity, and Black race.

Some investigators doubt that PPCM is a distinct clinical entity and consider it to be a form of the same dilated cardiomyopathy that is prevalent in older patients. This position is supported by the similarity in pathologic findings, clinical expression, and hemodynamic changes between patients with PPCM and those with dilated cardiomyopathy. However, the epidemiologic evidence suggests that PPCM is a distinct entity because there is a strong association between cardiomyopathy and pregnancy and it is exceptional to observe dilated cardiomyopathy unrelated to childbearing in young women. Also the disease tends to recur in subsequent pregnancies. These facts suggest that PPCM is a unique form of myocardiopathy, probably of viral origin or immune-mediated (Felker et al., 2000). This hypothesis is supported by investigations, demonstrating evidence of myocarditis in heart biopsies of a high number of patients with PPCM. Other authors disagree, and Cunningham et al. (1986) found that 21 (75%) out of 28 patients had associated cardiovascular diseases that could be the underlying etiology of their PPCM.

The diagnostic criteria for postpartum cardiomyopathy (Demakis and Rahimtoola, 1971) are as follows:

1. Development of heart failure in the last month of pregnancy or up to 5 months postpartum
2. Absence of an identifiable cause for the cardiac failure
3. Absence of recognizable heart disease before the last month of pregnancy
4. Left ventricular dysfunction demonstrated by echocardiographic criteria

The echocardiographic criteria for the diagnosis of PPCM (Hibbard et al., 1999) are the following:

1. Ejection fraction less than 45% or M-mode fractional shortening less than 30% or both
2. End-diastolic dimension more than 2.7 cm/m^2

The majority of patients with PPCM are 20–35-year-old and present in the 2nd or 3rd postpartum month with weakness, shortness of breath, orthopnea, cough, paroxysmal nocturnal dyspnea, and palpitations. Physical examination will reveal tachycardia, cardiac arrhythmias, pulmonary rales, and peripheral edema. Chest x-ray examination will show an enlarged heart and pulmonary vascular redistribution. Echocardiography and right heart catheterization will demonstrate enlargement of all chambers of the heart, predominantly the left ventricle. The left ventricular wall motion ejection fraction and the cardiac output are decreased and pulmonary wedge pressure is increased. Some patients with PPCM will develop deep vein thrombosis and pulmonary embolization.

Bed rest, digitalis, diuretics, and anticoagulant therapy are the most important interventions in the management of patients with PPCM. Immunosuppressive therapy can be considered if the myocardial biopsy indicates myocarditis and there is no improvement after 2 weeks of standard therapy (Pearson et al., 2000). The prognosis for these patients is guarded and is especially poor in those with low left ventricular ejection fraction. Patients who have dilated hearts 6 months after the onset of symptoms have very high mortality. Patients who have normal-sized hearts 6 months after the initiation of therapy usually have good prognoses. Also important in the prognosis is the time from the onset of symptoms to the initiation of therapy and when therapy is delayed more than 6 months from the initiation of symptoms the prognosis is poor.

Women who recover from PPCM are at high risk for recurrence in subsequent pregnancies. The risk of recurrence is approximately 21% in women in whom the left ventricular function returns to normal and 44% in those who have persistent left ventricular dysfunction (Elkayam et al., 2001). Women with persistent ventricular dysfunction should be advised to avoid pregnancy. The problem is how to advise the 70–80% of women who seem to have a complete recovery of left ventricle size and function. In an attempt to clarify the prognosis in these cases, women with a history of PPCM had a dobutamine stress echocardiographic study to assess their left ventricular contractile reserve (Lampert et al., 1997). The results indicated that women with recovered PPCM and normal echocardiogram had significantly less left ventricular contractility reserve than a group of normal matched controls. These findings are of concern and suggest prudence in counseling about pregnancy women with apparently recovered left ventricular function.

Ischemic heart disease

Acute myocardial infarction (MI) during pregnancy is extremely rare, approximately 1 in 10,000 pregnancies. Equally rare is pregnancy in women with a history of MI before pregnancy. The most common causes of MI during pregnancy are coronary atherosclerosis and coronary thrombosis but it may also occur following coronary spasm and in association with the administration of ergonovine, prostaglandins, and tocolytic agents. Acute MI carries a substantial risk for mother and fetus. Hankins et al. (1985) reported a maternal mortality of 35%. A more recent large series (Roth and Elkayam, 1996) reported a maternal mortality of 21% and fetal mortality of 13%.

Most pregnant women having an MI exhibit characteristic chest pain, nausea, dyspnea, and diaphoresis. The

diagnosis is made by electrocardiography and by determination of the serum troponin A level. Most of the cases occur in the third trimester when the risk of death is higher than in the second or first trimesters of pregnancy. Death occurs more frequently immediately following the MI or within the first 2 weeks following the heart attack. Treatment is similar to that in the nonpregnant patients and streptokinase and tissue plasminogen activator can be used despite case reports of abruption and neonatal intracranial bleeding, because maternal recovery is the most important factor for fetal well-being. Similarly, there is no contraindication to cardiac catheterization because the fetal radiation exposure is minimal. If at all possible, delivery following a MI should be delayed for a minimum of 2 weeks to allow the myocardium to heal. Vaginal delivery is usually preferred.

The risk for future pregnancies in women who had an MI is guarded. CHF, angina, and severe arrhythmias may complicate the course of a future pregnancy in as many as 50% of these patients (Avila et al., 2003). Episodes of arrhythmia in the third trimester of pregnancy are of concern because they may be the precursors of a fatal ventricular arrhythmia.

OTHER CARDIAC CONDITIONS OF IMPORTANCE DURING PREGNANCY

Aortic Coarctation

Aortic coarctation is rarely seen during pregnancy because the majority of women affected with this condition have been diagnosed and surgically treated during childhood. In most cases the narrowing of the aorta is distal to the left subclavian artery, resulting in isolated hypertension in the right arm. Determining the arm–leg blood pressure gradient, which is abnormal when greater than 20 mmHg, assesses the severity of the coarctation.

Uncorrected aortic coarctation is a lesion with poor prognosis during pregnancy and maternal mortality is between 2 and 9.5% depending on the severity of the constriction. Mortality increases to 15% with the development of hypertension during pregnancy. These women are predisposed to aortic dissection and ruptured aneurysms and some experts recommend cesarean delivery to avoid the fluctuations in blood pressure that occur during the second stage of labor. This recommendation is not based on facts, and it is possible that vaginal delivery under epidural anesthesia has equal results. Management during pregnancy consists of frequent monitoring to detect the development of hypertension and delivery when this diagnosis is confirmed. These patients need prophylaxis for bacterial endocarditis at the time of delivery.

Eisenmenger's Syndrome

Patients with Eisenmenger's syndrome have pulmonary hypertension with right to left or bidirectional shunt through an open ductus, an ASD, or a VSD. In these patients, increases in pulmonary pressures or decreases in PVR may cause right to left shunting and arterial blood oxygen desaturation.

The outcome of pregnancy in patients with Eisenmenger's syndrome is very poor. Maternal mortality is approximately 52% and total fetal wastage approximates 41.7%. Despite the best medical and obstetrical care, these patients often die in the postpartum period from irreversible cardiovascular collapse. Because of this poor prognosis, every pregnant patient with significant ventricular, atrial, or ductus defects should have cardiac catheterization to determine the status of her pulmonary pressure.

In addition to the general measures for pregnant cardiac patients described above, anticoagulation with heparin to avoid the formation of microthrombi in the pulmonary circulation should be used for Eisenmenger's syndrome. Epidural narcotics can be used for pain relief during labor. To maintain PVR above that of the pulmonary artery and to avoid right-to-left shunting, it may be necessary to use intravenous fluids and peripheral vasoconstrictors during delivery and the puerperium.

Primary Pulmonary Hypertension

This uncommon abnormality is characterized by an increase in thickness of the pulmonary arterioles. The development of intimal fibrosis and fibroelastosis as well as the production of a typical "onion skin" configuration of the vessels can be seen on microscopic examination. The consequence of this lesion is a marked increase in pulmonary vascular resistance that results in pulmonary hypertension. There is dilatation of the right-side chambers of the heart and a low, probably fixed, cardiac output. The cause of this disease is unknown.

Pregnancy is deleterious to patients with primary pulmonary hypertension. The maternal mortality is approximately 40% and the fetal outcome is also poor with frequent spontaneous abortions and fetal demises secondary to maternal deaths. Most maternal deaths occur in the last trimester and in the postpartum period as a result of sudden cardiac collapse.

Pregnant patients with primary pulmonary hypertension should be on hospital bed rest, once they reach 20 weeks of gestation. At this time, anticoagulation with heparin should be instituted. Also, vasodilator therapy with hydralazine (75–150 mg daily) may be beneficial. Epidural anesthesia may be used for pain control during labor.

Marfan's Syndrome

Patients with Marfan's syndrome have defective connective tissue secondary to an alteration in protein synthesis that affects mainly the collagen and elastic tissues. The abnormality is manifested in alterations of the skeletal tissues, the heart, and the eye. The main sites of cardiac involvement are the mitral valve and the ascending aorta. Most of these patients have MVP and in some cases mitral regurgitation is present. Dilatation of the aortic root sinuses is often seen as well.

Marfan's syndrome is inherited as an autosomal dominant condition and mothers should be informed of the 50% risk of transmission to their offspring. In addition, there is the risk that pregnant patients with Marfan's syndrome may develop serious cardiovascular complications during pregnancy. The most important of these complications is acute aortic dissection. In the old literature, this was considered to occur in approximately 50% of all pregnant patients with Marfan's syndrome. In more recent reviews it has become apparent that pregnancy is relatively safe for these patients unless they have marked dilatation of the aortic root or other severe cardiac problems.

Ideally, a patient with Marfan's syndrome contemplating pregnancy should have a preconceptional echocardiogram to determine the diameter of the aortic root. If it is greater than 4.0 cm, she is at significant risk for aortic dissection and she should be offered surgery. If the patient is in early pregnancy, she should be informed that termination of pregnancy is an option. Once the pregnancy is advanced, the probability of a favorable outcome will depend on her response to bed rest and to beta-adrenergic blockade.

Aortic dissection is initiated by an intimal tear. This is followed by a separation of the medial layer of the vessel by blood being propelled from the left ventricle. The dissection advances a variable distance, following the course of the blood flow. The outer wall of the dissection is made up mainly by the adventitial layer of the vessel and the frequency of rupture is very high, resulting in extravasation of blood into the pericardial space or the mediastinum. It is widely accepted that hormonal influences on the connective tissue during pregnancy weaken the medial layer of the aorta and increase the possibility of aortic dissection in women with Marfan's syndrome.

The main symptom of aortic dissection is severe, excruciating precordial or interscapular pain that radiates to the back, shoulders, or abdomen. Characteristically, the blood pressure is normal despite the shock-like state of the patient. Symptoms of pericardial tamponade or internal bleeding may also be present if the adventitia is ruptured. Other symptoms occur if there is obstruction of one or more of the aortic branches, and may include stroke, MI, and paralysis or ischemia of the upper limbs. Chest x-ray usually shows widening of the mediastinal area and left pleural effusion. CT angiogram and thoracic aortography are the main tools for confirmatory diagnosis.

Patients with aortic dissection should be treated and stabilized in an intensive care unit before having corrective surgery. Pharmacologic treatment is directed toward decreasing PVR and left ventricular ejection velocity with beta-blockers and vasodilators to avoid progression of the dissection. Surgical treatment varies depending on the extension of the dissection and the presence of complicating factors. In all cases the objective is to graft the ascending aorta obliterating the entry and, if present, the outflow of the dissecting channel. The operative mortality rate for acute proximal dissection is approximately 7–8%.

Cardiac Arrhythmias During Pregnancy

Significant maternal arrhythmias during pregnancy are rare. Minor transient arrhythmic episodes occur frequently but they are harmless and require no therapy. The cause of the increased frequency of minor dysrhythmias, usually premature beats, may be related to the adaptation of the heart to the physiological hemodynamic changes of pregnancy.

One of the arrhythmias that the obstetricians occasionally observe is paroxysmal supraventricular tachycardia (PST). PST is characterized by a rate between 150 and 250 bpm, usually below 200 bpm. The patient is often aware of her tachycardia and may sense palpitations or feel anxious, short of breath, and lightheaded. An EKG will show narrow QRS complexes. In 90% of the cases, the etiology of the PST is atrioventricular node reentry. In these cases, the ventricle and the atria are activated simultaneously and no "p" wave is seen. To convert a hemodynamically stable patient with PST to a normal sinus rhythm, the first treatment is carotid sinus massage. The patient should be supine with IV fluids running and continuously monitored with EKG. The right carotid sinus should be massaged first for about 10 seconds. If there is no response, try the left side for 10 seconds. The two sinuses should never be massaged simultaneously. The patient may attempt a Valsalva's maneuver during the carotid massage to increase the effectiveness of the procedure. If there is no response, the drug of choice is adenosine. The dose is 6 mg IV given over 1–2 seconds. If there is no response, give 12 mg IV after 1– 2 minutes. The 12 mg dose may be repeated if necessary. Another useful drug is Verapamil, 5–10 mg as an IV bolus in 1–3 minutes. This dose may be repeated 15–30 minutes later if there is no response. The main side effect of Verapamil is hypotension, which is transient and responds easily to IV fluids. Adenosine is another excellent drug for the treatment of supraventricular arrhythmias. Cardioversion is

rarely necessary but it can be used if there is no underlying cardiac lesion and no evidence of hemodynamic instability. Digitalis and quinidine are used for prophylaxis and chronic maintenance therapy. In patients with CHF, the treatment of choice for PST is digoxin rather than Verapamil. The management of this situation should be left to the cardiologist.

Atrial flutter, atrial fibrillation, and ventricular tachycardia are rarely seen during pregnancy. These dysrhythmias should be diagnosed and treated by the cardiologist. The drugs used for these conditions, as well as electrocardioversion, are innocuous for the fetus.

INDIAN EXPERIENCE OF HEART DISEASE COMPLICATING PREGNANCY

Heart diseases complicate about 0.5–1.0% of all pregnancies. These include those that exist prior to the onset of pregnancy and those developing during the course of pregnancy, delivery, or during the postpartum period. Cardiac disorders may be congenital or acquired structural abnormalities and arrhythmias. In India, rheumatic heart disease still accounts for the majority of cardiac lesions detected during pregnancy. In the Western World, the incidence of rheumatic heart disease has declined significantly; also a great number of women of congenital heart lesions corrected in infancy are now presenting with pregnancy.

Table 20-2 presents the incidence of heart disease complicating pregnancy reported in India.

Table 20-2 shows that almost 85–90% of cardiac lesions encountered in pregnancy are rheumatic in origin. The commonest valve involved is the mitral valve and the commonest lesion is mitral stenosis followed by mitral regurgitation and aortic stenosis. Congenital lesions account for 3–10% of the lesions; the rest include syphilis, atherosclerosis, myocarditis, and others.

The functional classification of cardiac disease in pregnancy helps to determine prognosis. Joint management with a cardiologist and hospitalization whenever necessary have helped to control the disease better and prevent complications. However, the maternal morbidity is high, and in the absence of proper care, the patient often deteriorates rapidly. The maternal mortality in severely affected women tends to be around 10%.

Table 20-2. Contribution of rheumatic heart disease in pregnancy in India

Authors	Year	Incidence (%)
Devi and Subhadra	1957	87.8
Masani	1957	87.7
Punjabi	1966	83.0
Parvathi and Anjanyelu	1976	90.0
Ananthasubramaniam et al.	1980	83.0
Sikdar	1980	93.2
Chadha et al.	1981	90.3
Allahbadia et al.	1989	88.0

Adapted from Daftary SN, Desai SV. Heart disease complicating pregnancy. In: Daftary SN, Desai SV, eds. Selected Topics in Obstetrics and Gynecology (2nd edn). New Delhi: BI Publications, 2006: 35.

Surgical intervention has helped to save lives (Pandole et al., 2000). A series of 23 cases of tight mitral stenosis complicating pregnancy treated with mitral valvotomy was reported from Ahmedabad with successful outcome in 20 cases (Yajnik et al., 1977). In a report from New Delhi of 61 cases of transventricular mitral commissurotomy (TVMC) performed. Most patients who had undergone TVMC prior to pregnancy tolerated the hemodynamic burden of pregnancy satisfactorily and had a satisfactory perinatal outcome. TVMC could be undertaken until the second trimester of pregnancy (Amudha et al., 2001). In another interesting case of double heart lesions, treated with double heart valve replacement (mitral and aortic) following surgery, a successful pregnancy and delivery took place (Minocha et al., 2001).

The improved outcome of pregnancy in women with heart disease jointly managed by a cardiologist and obstetrician in a well-equipped center is illustrated by the following cases.

1. A rare case of congenital rubella syndrome with a Fallot's tetralogy was successfully delivered through joint efforts and team work (Deshpande et al., 2001).
2. Eisenmenger's syndrome is a dreaded complication in pregnancy; generally a termination of pregnancy is advised. However, as per an interesting case report from New Delhi, a case of Eisenmenger's syndrome was successfully managed jointly by the cardiologist and obstetrician with intensive monitoring (Suneja et al., 2002).
3. In a rare case of Epstein's anomaly in pregnancy from Coimbatore, the patient was delivered successfully, but she required readmission after 6 weeks for cardiomyopathy and popliteal vessel embolism (Chitra et al., 2002).

Peripartum cardiomyopathy (Tank and Paghdiwalla, 2001): The combined stress of pregnancy and the accompanying structural and functional changes might be responsible for its occurrence. The best diagnostic test is echocardiography, which shows dilatation of the left ventricle and atrium and impaired myocardial contractility. Management consists of rest, limiting physical activity, salt restriction, diuretics, and digitalization and afterload reduction with hydralazine, captopril, or prazosin helps to improve myocardial performance. Heparin is prescribed to prevent thromboembolic episodes. It generally

resolved over a period of time in about 50% cases, but is known to recur in subsequent pregnancy and delivery. Hence future pregnancy is contraindicated. If no improvement occurs in a year's time, the long-term prognosis is guarded. Shukla et al. (Mumbai; 2003) reported the incidence of peripartum cardiomyopathy of 1:4000–1:5000 live births. It is followed by high maternal mortality rate. Of these patients 50–60% recover spontaneously. The rest suffer persistent ventricular dysfunction and die early or require cardiac transplantation (Shukla et al., 2003).

It may be concluded that the outcome of pregnancy in women with cardiac lesions has improved a great deal ever since the inclusion of a cardiologist in the team looking after these patients in need of special care. Cardiac surgery has improved the outlook for many a case of congenital heart disease, enabling them to live fuller lives and by reducing the hazards of childbearing; also, acquired valvular diseases can be treated and the cardiac function improved. India is marching on with the times, what could not be achieved a few years ago is now a present day reality.

IMPORTANT POINTS

1. In normal pregnancy, circulation is hyperdynamic. There is a high cardiac output and decreased peripheral and pulmonary vascular resistance.
2. The increase in IV volume that occurs during normal pregnancy fulfills the need of the developing uteroplacental circulation and protects the mother from the potentially harmful effects of the blood loss that occurs at parturition.
3. The hemodynamic changes that occur during normal pregnancy increase the cardiac work. This effect may exceed the functional capacity of an ailing heart.
4. The danger of cardiac decompensation during pregnancy is greatest between 28 and 32 weeks, when the hemodynamic chances of pregnancy peak, but is also increased during labor and delivery and in the postpartum period.
5. Immediately after the placental separation, the obstructive effect of the pregnant uterus on venous return disappears and there is a sudden transfusion of blood from the lower extremities and the uteroplacental circulation into the systemic circulation. A patient with heart disease may not tolerate this increase in blood volume.
6. The pregnant cardiac patient should have effective pain relief during labor and should labor in the lateral supine position. In the majority of cases the anesthesia of choice is epidural blockade administered by an experienced obstetric anesthesiologist.
7. The most frequent fetal complications in patients with heart disease are preterm birth and growth restriction.
8. Almost all cardiac patients in labor should be kept "dry" and their IV fluids restricted to no more than 75 cc/hour. An exception to this rule is the patient with aortic stenosis.
9. The principal measures in the management of the pregnant patient in CHF are (a) decrease the cardiac work with bed rest, (b) decrease the preload with diuretics, (c) improve the cardiac contractility with digitalis, and (d) reduce the afterload with vasodilators.
10. The prognosis for a patient with PPCM is poor if she has significantly reduced left ventricular ejection fraction and if her heart remains dilated 6 months after initiation of therapy.
11. Patients with Marfan's syndrome contemplating pregnancy should have an echocardiogram to assess the diameter of the aortic root and if it is greater than 4.0 cm, there is a high risk for aortic dissection.
12. Patients with surgically corrected congenital abnormalities of the heart frequently have the right ventricle supporting the systemic circulation. CHF happens more commonly in a systemic right than in a systemic left ventricle and assessment of the systemic right ventricle ejection fraction is an important prognostic index of cardiac complications during pregnancy.

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Section III

TROPICAL DISEASES IN PREGNANCY

21

Tropical Diseases in Pregnancy

CHAPTER OUTLINE

Many developing countries located in tropic and subtropics of Asia and Africa, South America, and the Caribbean Islands are subject to diseases that are related to poverty, poor housing and sanitation, lack of education, parasitic infestations, and lack of drive on the part of health authorities to control the prevailing environmental conditions. Many of these illnesses affect pregnant women adversely and influence the obstetric outcome.

In this chapter, five common conditions of significance in India will be discussed: malaria in pregnancy, dengue fever, intestinal parasitic infestations, hepatitis complicating pregnancy, and pregnancy and tuberculosis.

MALARIA IN PREGNANCY

Malaria has been recognized through centuries, it is a parasitic disease caused by the protozoon of the genus *Plasmodium*. The common varieties encountered in India belong to the *P. vivax* and *P. falciparum* types. These are transmitted through the bite of the vector, recognized as the female anopheles mosquito. Parts of India where malaria is endemic include northeastern states, Bihar, Orissa, Andhra Pradesh, and Chhattisgarh. However, the problem exists in other parts of India as well. Worldwide efforts (1960s) helped to control epidemics of malaria during the last century (1960), but it has resurged in over a 100 countries around the world. Europe, North America, and the Pacific Islands are comparatively free from the disease, but India has witnessed a resurgence of a more aggressive form of the disease, which is attributed to emergence of drug-resistant strains, poor vector control programs, and increased endemicity. Malaria affects more than a billion people worldwide (WHO, 2000) and is responsible for more than a million deaths. Pregnant women with their lowered immunity are highly susceptible and vulnerable to the disease. Fetal transmission is known, often leading to an adverse obstetric outcome. Abortions, preterm births, intrauterine fetal growth retardation, and stillbirths have been reported. In the mother, the ill-effects of hyperpyrexia, severe hemolytic anemia, and adverse effects on the vital organs in turn contribute to enhanced maternal morbidity and mortality. Early diagnosis and prompt treatment help in controlling the hazards of this disease.

The Malarial Parasite

Four subspecies of the genus *Plasmodium* have been recognized to cause malaria in humans; these include *P. vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*. Of these, the first two are prevalent in India. The entire Indian population is now deemed at risk for malaria. Following the bite from an infected female anopheles mosquito, sporozoites are injected into the human host along with its saliva. These are present in the peripheral blood for a short time and then they enter the tissues. Further development takes place in the liver parenchyma (exoerythrocytic stage) where the parasites multiply asexually (*schizogony*). In about a week's time, the hepatic cells burst to release *merozoites* into the circulation which invade the host erythrocytes and multiply in it. The infected erythrocytes burst cyclically at 48–72-hour intervals to release fresh *merozoites* into the circulation; in this way waves of *merozoites* keep infecting erythrocytes repeatedly. The older *merozoites* leave the peripheral circulation to get sequestered into capillaries of internal organs to complete schizogony. If the infected host is bitten by the female anopheles mosquito, then the parasites in these infected RBCs enter the sexual phase of *gametocytes* which mature in the stomach lining of the mosquito. The male and female *gametocytes* mature and conjugate. The fertilized female forms the *oocyst*. It is filled with *sporozoites* which, on release, enter the salivary glands of the mosquito and through its bite enter the human host to complete its asexual cycle. The duration of the extrinsic incubation period in the mosquito (vector) varies with atmospheric temperature, rainfall, and humidity and the *Plasmodium* species involved. Optimum temperature is 98° F. Higher temperatures are unfavorable to the vector and the parasite. The differences in species tolerance explain why *P. vivax* predominates in temperate climates and both *P. vivax* and *P. falciparum* are prevalent in the tropics and sub-tropics. *P. ovale* is restricted to West Africa and *P. malariae* is generally restricted to a few localities. *P. falciparum* is capable of multiplying rapidly and causing high-intensity parasitemia. Hence it is the cause of the most severe form of the disease. The erythrocytic cycles continue until therapeutic intervention occurs or the host develops immunity.

Pathology

The basic pathological process is hypoxia. It is most marked in *P. falciparum* infection. Hypoxia (tissue anoxia) results from intracapillary collection of sludge teaming with parasitized cells which cause sluggish/obstructed circulation, leading to hypoxia in its earlier stages, which is reversible, followed by anoxia, leading to degeneration and necrosis of the tissues of the reticuloendothelial system. Continued phagocytosis of damaged erythrocytes, parasites, and malarial pigments results in cellular hypertrophy of the reticuloendothelial system. Fibrosis, infarction, necrosis, and pigment deposition ultimately lead to clinical hepatosplenomegaly. The brain may appear darker following pigment deposition. Thrombosis, infarction, and necrosis may also affect other organs like the suprarenals, gastrointestinal tract, heart, and lungs. Involvement of the kidneys causes blackwater fever following a sudden bout of intravascular hemolysis. During

pregnancy, any localization of the parasites into the placental sinuses at the fetomaternal interface may lead to miscarriage or congenital fetal malaria and its sequelae.

Clinical Features

Pregnancy is known to cause immunosuppression. Hence pregnant women are more susceptible to malaria and vulnerable to its consequences. Severity of the disease depends on the species of invading *Plasmodium* parasite, the intensity of the parasitemia, the extent of host resistance, the speed of diagnosis, and implementation of effective therapy. All the earlier mentioned factors will influence the obstetric outcome.

The typical attack is characterized by three distinct stages, provided that no antipyretics have been prescribed earlier. The three stages are "the cold stage, the hot stage, and the sweating stage." It is followed by another similar attack in 24–48 hours. Falciparum malaria often runs an unpredictable course. Other symptoms besides fever with rigors include headache, malaise, nausea and vomiting, delirium, hemolytic jaundice, anemia, and cachexia. Splenomegaly is usually present. Immunity is gradually acquired following repeated exposures. On average it takes 5–10 years to develop immunity in endemic areas. In immune pregnant women the clinical features are generally less dramatic and may be restricted to asymptomatic parasitemia with occasional placental involvement. In nonimmune women, prophylaxis with effective antimalarial drugs and observance of rigid control measures against exposure to mosquitoes is the best course of action.

Incidence of placental involvement during pregnancy in women living in endemic areas varies between 16 and 60%, but congenital transfer of malaria is uncommon. Passive transfer of maternal IgG antibodies across the placenta helps protect the fetus. In nonendemic areas, the nonimmune mother is more likely to suffer from manifestations of acute illness and there is an enhanced risk of congenital malaria. There is poor correlation between hemoglobin levels and parasitic index during pregnancy (Giles et al., 1969). Parasitemia peaks during the second trimester of pregnancy followed by peak occurrence of anemia (McGregor, 1993).

Life-threatening complications of malaria include cerebral malaria, seizures, algid fever with persistent vomiting and diarrhea, circulatory collapse causing a cold clammy skin, blackwater fever, hypoglycemia, severe anemia, jaundice, and other causes.

Diagnosis

It is based on strong clinical suspicion, backed up by following investigations.

- Giemsa-stained thick blood smear from peripheral blood preferably obtained during an attack
- Detection of PCR-based *Plasmodium* DNA in peripheral blood
- Fluorescent microscopy
- Rapid malaria test

Effects of Malaria During Pregnancy

Pregnant women are more susceptible due to attenuation of their immunity to malaria. This immunity is regained toward the end of pregnancy but is lost once again during subsequent pregnancies (Playfair, 1992; Brabin, 1993). During pregnancy, the ability to limit the parasites is lost. There is a progressive increase in immunity status with rising parity. Hence primigravidae are at maximal risk (Vleguels et al., 1987). Ibeziako et al. (1990) reported the transplacental transfer of maternal malaria IgG antibodies which provides immunity to the fetus and the newborn for 3–6 months during infancy. Malarial parasites, especially *P. falciparum*, have an affinity for the placenta (McGregor, 1993). He further suggested that the affinity of the malarial parasites for the placenta may be due to establishment of a new vascular system, which provides a safe haven away from the host–effector defense mechanism, permitting free and unhindered replication of the parasite. This is especially true of *P. falciparum*, which has the capacity to sequester deep into tissues during schizogony and thereby escapes immune attacks.

Maternal effects

- Hyperpyrexia
- Hemolytic anemia
- Lactic acidosis
- Folate deficiency
- Bleeding disorders including DIC (disseminated intravascular coagulation)
- Hypoglycemia
- Acute renal failure
- Acute pulmonary edema
- Cerebral malaria: seizures, delirium
- Circulatory collapse
- Fluid and electrolyte imbalance
- Jaundice
- Blackwater fever
- Death

Fetal and perinatal effects

- High risk of abortion
- Higher incidence of preterm delivery
- Intrauterine growth retardation (IUGR)
- Low birth weight
- Intrauterine fetal demise

- Congenital malaria
- Failure to thrive
- High perinatal morbidity and mortality

Effects of Pregnancy on Malaria

- Pregnancy is an immunocompromised state; therefore the hazards of malaria increase.
- Frequency of infection is high during advanced pregnancy.
- Severity of infection is higher in primigravidae.
- There is higher morbidity because of complications following malaria during pregnancy.

Prognostic Parameters

In a pregnant woman suspected to be suffering from malaria, treatment should be aggressive, along with close watch on following parameters to judge severity of condition, to implement timely corrective measures, and to assess response to treatment.

- Parasitemia > 5%
- Packed cell volume < 30%
- Hemoglobin < 7.1 g%
- Hypoglycemia: blood glucose < 40 mg%
- Low levels of glucose in cerebrospinal fluid
- Raised venous lactic acid, >60 m.mol/L
- Low levels of antithrombin III
- Peripheral schizontemia
- Increased plasma S-nucleotides
- Serum creatinine > 3.0 mg%
- Blood urea > 60.0 mg%

Management

Selection of the antimalarial drug, its route of administration, safety profile in pregnancy, supportive treatment, and assessment of response to treatment (clinical and investigational) form the sheet anchor of management. Often a team of experts and intensivists are necessary to provide optimum care. In spite of intensive care, the prognosis is often guarded.

1. Not all antimalarials are safe during pregnancy. Drug selection depends on the severity of attack and drug sensitivity of the parasite. In some areas, there has been a proliferation of chloroquine-resistant infections—where it may be more prudent to opt for a more effective antimalarial drug from the outset. Antimalarials commonly prescribed during pregnancy include chloroquine and quinine.
2. Treatment of uncomplicated malaria: chloroquine is prescribed as 10 mg base/kg po at 24 hours and 5.0 mg base/kg at 48 hours. For radical care, primaquine is prescribed after delivery. Alternatively, consider prescribing quinine 10 mg/kg po every 8 hours for 7 days.
3. Treatment of complicated malaria: chloroquine 10 mg base/kg intravenous over 8 hours, followed by 15 mg base/kg over 24 hours. Alternatively, consider quinine salt 20 mg/kg intravenous infusion over 4 hours every 8 hourly until oral intake becomes permissible. Complete 7 days treatment in all.
4. Parenteral therapy may be necessary in severely ill patients as stated above.
5. Antimalarial drugs not used or contraindicated in pregnancy include doxycycline, artemesinine, pyrimethamine, halofantrine, atovaquone, maloprim, paludrine, and mefloquine (Dixit and Bhargava, 1999).
6. Patients with severe anemia (Hct < 20) require packed cell transfusions.
7. Associated complications such as hyperpyrexia, respiratory distress, renal failure, metabolic acidosis, hypoglycemia, and electrolyte imbalance require urgent correction.
8. Obstetric complications can be dealt with in usual manner.

Preventative Treatment

Women who live in areas with endemic malaria and who are pregnant for the first or second time are more likely to be infected with *P. falciparum* malaria than nonpregnant women of a similar age. This infection contributes to antenatal anemia and slows fetal growth, which may harm the mother and baby. Drugs have been widely used to prevent infection or its consequences. From the 1980s, prophylaxis to prevent, suppress, or eradicate malaria parasites with a variety of drugs has been tested. From the 1990s, one of its modification, called intermittent preventive treatment (IPT) has been used, wherein women are treated for malaria presumptively at fixed times during the pregnancy, usually with drugs with a long half-life, such as sulfadoxine–pyrimethamine. There remains debate as to whether the mechanism of IPT actually differs a lot from prophylaxis, but the regimens are very different. IPT requires just two or three doses during pregnancy, compared to prophylaxis regimens that may be daily (e.g., with proguanil) or weekly (e.g., with chloroquine). Prophylaxis and IPT are in addition to good care during pregnancy, which includes prompt treatment of women when they present clinically with fever or anemia.

A Cochrane review concluded that chemoprophylaxis or IPT reduces antenatal parasite prevalence and placental malaria when given to women in all parity groups. They also have positive effects on birth weight and possibly on perinatal death in low-parity women. Chemoprophylaxis was given using chloroquine (weekly), pyrimethamine (weekly or monthly), proguanil (daily), pyrimethamine–dapsone (weekly), and mefloquine (weekly).

Sulfadoxine–pyrimethamine (three times in pregnancy) and chloroquine (two or three doses in pregnancy) were used for IPT. It was not possible to assess any potential impact on drug resistance.

Congenital and Neonatal Malaria

Vertical transmission can be detected on testing the blood of the newborn for parasitemia within first 7 days of life. Generally neonatal protection is provided by transplacental passage of maternal IgG antibodies. Congenital malaria is more likely to affect babies of nonimmune mothers during times of epidemics. Clinical features include fever, irritability, feeding difficulties, anemia, hepatosplenomegaly, and jaundice. Unless the parasites are detected in heel prick smears, the possibility of other TORCH infections or syphilis cannot be ruled out. The diagnosis is missed, because it is not considered in the differential diagnosis of neonatal pyrexia of unknown origin.

DENGUE FEVER IN PREGNANCY

Dengue is a mosquito-borne virus infection, endemic worldwide in the tropics and subtropics. Dengue fever is caused by a flavivirus spread by the vector mosquito *Aedes aegypti.*

Causative Organism

Flavivirus is a single-stranded RNA virus with four subtypes: DEN-1, DEN-2, DEN-3, and DEN-4. The vector for all the subtypes is the mosquito *A. aegypti.* The mosquito typically breeds near human habitation in relatively fresh water pools or collections (Peters, 1998).

Pathology

Following the mosquito bite of an infected *A. aegypti*, the clinical manifestations become apparent after an incubation period of 2–7 days. All the four subtypes of the dengue virus (DEN) cause similar clinical syndrome. The usual presenting symptoms are fever, headache, retro-orbital pain, severe backache, myalgia and hyperesthesia, anorexia, nausea and vomiting, abdominal pain, epistaxis, and bleeding from mucosal surfaces. Clinical examination reveals a macular rash, adenopathy, palatal vesicles, scleral congestion, and scattered petechiae (Qureshi et al., 1997). Rarely a second superimposed infection with a different subtype can lead to a fulminant, life-threatening form described as "dengue hemorrhagic fever (DHF)" or "dengue shock syndrome (DSS)," comprising a constellation of findings based on vascular instability and decreased vascular integrity. The induction of vascular permeability and shock triggered by the immune response depends on the infecting subtype, and DEN-2 is the most likely offender.

Clinical Features

- Fever of recent acute onset or persisting for 4 or more days
- Macular rash, intense congestion of eyes, and retro-orbital pain
- Backache, myalgia, and hyperesthesia
- Anorexia, nausea and vomiting
- Abdominal pain with hepatomegaly
- Sudden severe headache is suggestive of an intracranial bleed
- In severe DHF, there is evidence of petechial bleeding and bleeding from mucosal surfaces
- Circulatory collapse, hypotension, rapid, thready pulse
- Cold, clammy skin
- Death

Diagnosis

It is based on following investigations interpreted along with the clinical picture.

- Leukopenia
- Hemoconcentration (Hct above 20% for the expected age)
- Rise in hemoglobin level
- Thrombocytopenia (<100,000/cc)
- Elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase (Peters, 1998)
- ELISA test: antigen detection by enzyme-linked immunosorbent assay
- Reverse transcription polymerase chain reaction (RT-PCR)
- Isolation of virus from blood using mosquito inoculation or mosquito cell culture
- During recovery, IgM ELISA or paired serology

Maternal Risks

- Risks during pregnancy are comparable to the non-pregnant state.
- Deranged liver functions in dengue fever (thrombocytopenia) may mimic HELLP syndrome.
- DHF is associated with high maternal mortality unless treated promptly and aggressively.

Fetal Risks

- No evidence of teratogenicity, abortion, or IUGR following dengue infection during pregnancy
- Evidence of vertical mother-to-fetus transmission present (Thaithumyanon et al., 1994; Chye et al., 1997). This results in thrombocytopenia, fever, and hepatomegaly in the newborn. In grave infection, the newborn may show coagulopathy and multiorgan failure, particularly if the mother has suffered from dengue in the week prior to delivery (Chong and Lin, 1989).

Management

- Treatment should be prompt and aggressive
- Symptomatic treatment
- Intravenous fluids
- Broad spectrum antibiotics
- Blood transfusions and blood component therapy
- Monitor maternal vital parameters
- Monitor serum electrolytes
- Monitor blood coagulation profile

INTESTINAL PARASITIC INFESTATIONS IN PREGNANCY

In this section, the gastrointestinal tract parasitic infestations commonly encountered in Indian women during pregnancy will be discussed. In clinical practice, the obstetrician is often called upon to treat pregnant women suffering from amebiasis, giardiasis, and helminthiasis. The symptoms that they produce and their effects on pregnancy need recognition and treatment.

Amebiasis in Pregnancy

Definition

It has been defined by WHO as the condition of harboring the protozoon *Entameba histolytica* with or without clinical manifestations. Brumpt (1925) proposed that there were two separate but morphologically indistinguishable species of *E. histolytica*, one that was capable of causing disease (*E. dysenteriae*) and the other a harmless commensal (*E. dispar*). Ellen and Samuel (1996) estimated on the basis of the new taxonomy that 10% of those reported to be suffering from amebiasis suffer from the invasive form of *E. histolytica*, accounting for 50 million persons with a mortality rate between 0.5 and 1.0%.

Pathology

Amebiasis is primarily a disease of the large intestine. It involves the caecum, ascending colon, rectum, sigmoid colon, appendix, and lower ileum in descending order of frequency. It is transmitted through exposure to contaminated water or food, food handlers, orofecal contamination, oroanal sexual contact and through vectors like flies, cockroaches, and rodents. The ingested cysts of *E. histolytica* disintegrate in the small intestine and release trophozoites, which are carried into the large intestine where they invade the crypts of the glands or invade the gut wall with proteolytic enzymes to cause inverted flask like ulcers. Transmission through the portal venous system permits them access to the liver where they may cause abscess formation. The abscess (generally in the right lobe) may burst into the pleura or peritoneal cavity, with grave outcome. Amebiasis is aggravated by high-carbohydrate, low-protein diet, malignancy, alcoholism, steroid and immunosuppressant medications, pregnancy, and puerperium. It is not an opportunistic infection in AIDS.

Clinical features

The clinical features appear about 2–4 weeks after acquiring infection. The symptoms range from asymptomatic to fulminant bloody mucus diarrhea, intestinal perforation, and peritonitis and bleeding.

Patients with low-grade disease suffer from anorexia, acidity, irritable bowels, flatulence, anorexia, malaise, debility, cramping pains, and recurrent diarrhea. Visceral spread may be accompanied by high fever, epigastric pain, enlarged tender liver, cough, weight loss. Amebic ulcers of the genital area in females have been recorded. During pregnancy, vomiting, anorexia, indigestion, flatulence, increasing malnutrition, failure to gain weight, anemia, and IUGR may follow recurrent diarrhea.

Diagnosis

Microscopic examination of fresh sample of stools may reveal the hematophagus trophozoites of *E. histolytica* (Figure 21-1) and their cysts. ELISA kits, PCR amplification of rRNA genes for the detection and differentiation of different species of *E. histolytica*, DNA hybridization and counter-current electrophoresis, and stool cultures are methods for detecting *E. histolytica* infection; however, in routine practice, microscopic examination of a fresh sample of stools constitutes the most common method employed in clinical practice in India.

Maternal effects

- Malnutrition: protein vitamin and mineral deficiency
- Poor weight gain
- IUGR
- Chronic ill-health

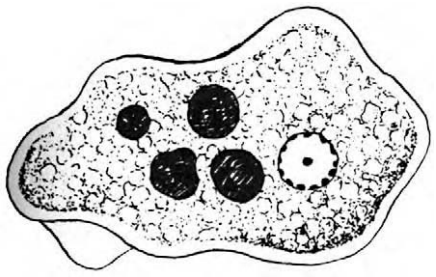

Figure 21-1. Trophozoites of *E. histolytica*.

Fetal effects

- Low birth weight
- IUGR

Treatment

WHO (1986) recommendation is that asymptomatic patients should require no treatment. Medications may be avoided during pregnancy. For women with gastrointestinal symptoms, a luminal amebicide diloxanide furoate 500 mg twice daily for 10 days can be prescribed safely during pregnancy. In more severe cases, metronidazole 750 mg along with diloxanide furoate three times daily is effective with few side effects. Diiodohydroxyquin is contraindicated in pregnancy. Sanitary precautions (boiled water, freshly cooked food, avoiding fried and seasoned food) should be observed to prevent reinfection.

Giardiasis in Pregnancy

Definition

Giardiasis is an intestinal infection caused by a flagellate *Giardia lamblia*. It is widely prevalent in the tropics.

Pathology

This parasitic infection is acquired through consumption of contaminated water and food and through oroanal or even vaginal sexual contact. The ingested cysts undergo excystment in the duodenum and the trophozoites colonize, multiply, and cause acute or chronic intermittent or persistent bulky, greasy, foul-smelling diarrhea. *G. lamblia* can cause morphological damage to the small intestine, causing partial villus atrophy resulting in malabsorption of fat, other nutrients, and vitamins A and B_{12}. The mechanism causing alteration of mucosal architecture is possibly immune mediated (Vinayak, 1992). Bacterial overgrowth is responsible for fat malabsorption. Nodular lymphoid hyperplasia of the small intestine with IgA immunoglobulin deficiency is a common association (Ament and Rubin, 1972).

Clinical features

Patients suffering from intestinal giardiasis complain of intermittent or persistent diarrhea, typically the stools are bulky, greasy, and foul smelling. Other accompanying symptoms include cramping abdominal pain, bloating, flatulence and belching, chronic fatigue, and malabsorption. Pregnant women may suffer from an exaggerated form of hyperemesis gravidarum, flatulence and diarrhea, reflux acidity, diarrhea, inadequate weight gain, and signs of anemia, vitamin deficiency, and clinical features of intestinal malabsorption.

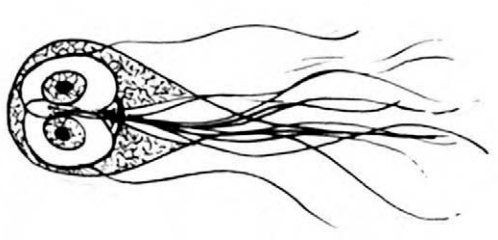

Figure 21-2. Trophozoites of *G. lamblia*.

Diagnosis

Routine stool examination commonly reveals cysts and occasionally trophozoites of *G. lamblia* (Figure 21-2). The stools usually show no RBCs or pus cells. Thus, a simple stool examination helps to establish the diagnosis in 75–85% cases. The parasite can be identified on examination of duodenal aspirates and brush cytology scrapings obtained during upper gastrointestinal endoscopy. Enterotest on feces of suspected patients reveal the presence of specific antigiardia IgG antibodies and IgM antibodies during an acute infection. Immunodiagnostic tests for *G. lamblia* antigens are highly specific (90–100%). Sensitive ELISA tests and indirect fluorescent serological tests using cultured *G. lamblia* have also been developed.

Maternal effects

- Malnutrition
- Poor weight gain
- IUGR
- Chronic gastrointestinal upset

Fetal effects

- Low birth weight
- IUGR

Treatment

In most healthy immunocompetent individuals, *G. lamblia* is a self-limiting disease due to host defense mechanism. Tinidazole 500 mg twice daily for 3–5 days is recommended. The single-dose therapy of 2.0 g is not recommended in pregnancy. It may be a wise precaution to avoid its use during the first trimester of pregnancy, although no teratogenic effects have been reported. Oral therapy with metronidazole 250 mg three times daily for 5 days has been extensively tried out with satisfactory results. Furazolidone 100 mg four times daily for 7 days has also been used. Drinking boiled water and strict observance and maintenance of personal hygiene help to break the fecal–oral cycle to prevent recurrence.

Helminthiasis in Pregnancy

In this section will be discussed *intestinal nematodes*, *cestodes*, *trematodes*, and *tissue nematodes*. According to a WHO estimate, the annual estimates of death rates from intestinal nematodes are as follows: deaths due to hookworm (*Ancylostoma duodenale*) infection are 65,000, due to roundworm (*Ascaris lumbricoides*) are 60,000, and those due to whipworm (*Trichuris trichiura*) are 10,000. Others like threadworm (*Enterobius vermicularis*), pinworm (*Strongyloides stercoralis*), and whipworm (*T. trichiura*) also cause irritating symptoms.

WHO recommends antenatal (after the first trimester) deworming for pregnant women who live in areas where the prevalence of hookworm infection exceeds 20–30%. However, deworming has not been included in antenatal care packages in most developing countries. The evidence for substantial public-health benefits and reductions in global burden of disease from deworming is overwhelming. Moreover, there are simple, effective, safe, and cheap treatments already available. The challenge is to get the treatments to those who need them.

Hookworm infestation

Background

1. Causative organisms
- *A. duodenale* (old world hookworm)
- *Necator americanus* (new world hookworm)
- *Ancylostoma ceylanicum* (rare infestation)

2. Magnitude of the problem
- About 900 million people affected globally
- About 200 million affected in India

3. Distribution of disease
- *N. americanus* found in moist tropical regions of North America, South America, and south India
- *A. duodenale* common in drier and colder climates of north India, Middle East, China, and Japan
- Few cases of *A. ceylanicum* have been reported from Kolkata in West Bengal

4. Transmission
- Direct barefoot exposure to contaminated soil (farmers and land workers)
- Ingestion of food containing larvae (raw farm products)
- Transplacental and transmammary transmission of *A. duodenale* reported from China (Yush Jiang and Hu, 1995)

5. Life cycle: Barefoot exposure for 5–10 minutes to contaminated soil allows the filariform larvae to penetrate the skin between the toes. These enter the circulation to reach alveoli. From there they enter the trachea, and swallowed larvae from the trachea pass through the pharynx to enter the gastrointestinal tract. In the duodenum and upper jejunum, below the ampulla of Vater, the adult *A. duodenale* (about 1 cm in length) lays about 15,000–20,000 eggs daily for 6–8 years. The *A. duodenale* sucks about 0.2 ml of blood daily. The *N. americanus* lays fewer eggs (6000–10,000/day), sucks less blood (0.03 ml daily), and survives for 2–4 years. The eggs are passed out in the feces and germinate in moist soil to begin a fresh life cycle.

Clinical features

- At the site of larval penetration, an erythematous maculopapular rash with itching and a local blister is observed.
- When the larvae migrate from the pulmonary alveoli to the trachea, the patient may experience wheezing, breathlessness, cough, and fever.
- During the phase of intestinal colonization, the patient often suffers from dyspepsia and gastroenteritis.
- In the well-established infestation, the patient suffers from the ill-effects of chronic blood loss leading to progressively increasing anemia. The patient manifests clinical features of iron deficiency anemia and hypoproteinemia, leading to lethargy, fatigue, pallor, edema, and in advanced cases there may be clinical features of high-output heart failure.
- For epidemiological assessment, the intensity of infection is judged on the basis of Chandler's (1927) worm index. The amount of blood loss is estimated as 2.0 ml/day for 1000 eggs/g of feces. The evidence of 5 or more eggs per low-power microscope field indicates approximately 5000 eggs/g of feces.
- During pregnancy and lactation, the enhanced demand on the mother aggravates the iron and protein deficiency. There is also a concomitant deficiency of folate and vitamin B_{12}.

Diagnosis

- It is based on microscopic examination of stools, revealing the typical four- to eight-celled hookworm morula (Figure 21-3).
- Routine hemogram will show presence of hypochromic microcytic anemia, characterized by low levels of hemoglobin.
- There will be lowered levels of serum ferritin and a high iron-binding capacity.

Effects on the mother

- Causes anemia and its sequelae
- Hypoproteinemia
- Risk of preterm delivery
- IUGR
- Chronic ill-health

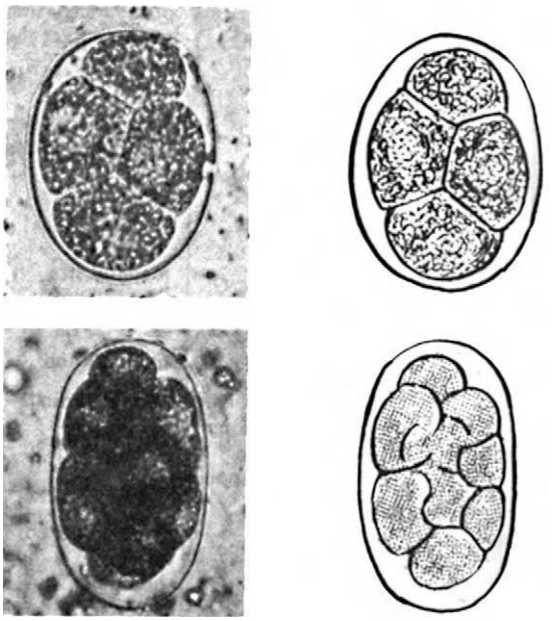

Figure 21-3. Four- to eight-celled hookworm (*A. duodenale*) morula.

Effects on the fetus

- Prematurity
- Low birth weight
- Transplacental and transmammary transfer cause infantile disease
- Increased mortality in affected infants (Yush Jiang and Hu, 1995)

Treatment

- In mild cases, treatment should be deferred until completion of the first trimester.
- Anthelmintics of choice include Pyrantel pamoate as a single oral dose of 10 mg/kg body weight to a maximum of 1.0 g.
- Mebendazole and albendazole should be avoided in the first trimester of pregnancy (de Silva, 1997).
- Supportive treatment consisting of supplementary oral iron, folic acid, vitamin B_{12}, and high protein diet.
- Blood transfusion in cases of threatened preterm labor or incipient heart failure.
- Both mebendazole and albendazole have been used in pregnancy, and these could be effective in reducing maternal anemia and improving birth weight and infant survival in hookworm-endemic regions (de Silva et al., 1997; Christian et al., 2004).

Ascariasis (Roundworm infection)

Background

1. **Causative organism:** The nematode *A. lumbricoides* (roundworm)
2. **Magnitude of the problem:** About 25% of the world's population is infested with *A. lumbricoides*.
3. **Distribution of the disease**
   - The prevalence is higher in rural tropical areas with warm and humid climate.
   - Poor sanitation and hygiene predispose to its occurrence.
4. **Transmission:** Ingestion of food contaminated with embryonated eggs of *A. lumbricoides*
5. **Life cycle:** Each female worm in the gut releases about 24,000 eggs (both in fertile and infertile forms) daily for a period of 6–18 months. The expelled eggs in the feces become infective after soil incubation for 2–3 weeks and remain infective up to about 6 years. After oral ingestion of embryonated eggs, the larvae are liberated in the small intestine. The larvae then penetrate the gut wall and migrate via the circulation to the liver and lungs. After 10 days, they travel to the bronchi and trachea up to the epiglottis; from there the larvae are swallowed to reach the intestine and thereafter mature into adult worms over a period of 60 days.

Clinical features

Due to extensive migration of the larvae and adult worms, the patients may suffer from a wide variety of symptoms.

- Asymptomatic carrier
- Upper respiratory symptoms of persistent cough
- Bronchopneumonia
- Intestinal cramps
- Vomiting
- Chronic indigestion
- Protein, carbohydrate, and vitamin deficiency
- Malnutrition
- Volvulus, intestinal obstruction
- Intussusception
- Biliary colic
- Appendicular colic
- Liver abscess

Diagnosis

- Blood count may reveal eosinophilia during the stage of larval invasion.
- Stool examination reveals fertile and nonfertile eggs (Figure 21-4).
- Radiography after ingestion of radio-opaque meal may reveal filling defects, but is not advisable during pregnancy.
- Chest x-ray shows patchy infiltration (Loeffler's syndrome).
- Ultrasonography may reveal a coiled up mass of worms.
- Other tests include Ascaris complement fixation and precipitation and cutaneous hypersensitivity tests.

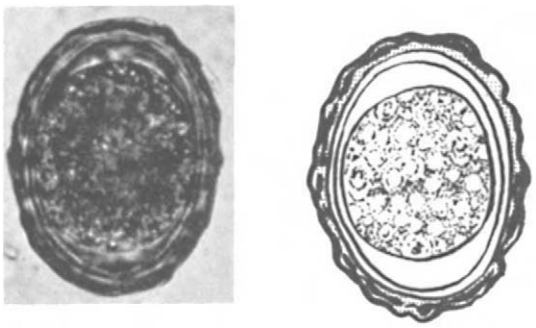

Figure 21-4. Fertile and nonfertile eggs of *A. lumbricoides.*

Effects on the mother

- Chronic malnutrition and suboptimal health
- Chronic indigestion
- Abdominal cramps
- Rarely acute abdomen

Effects on the fetus

- Low birth weight
- Preterm birth

Treatment

- Piperazine citrate is not preferred because of toxicity.
- Pyrantel pamoate is preferably delayed until the end of the first trimester; it is administered in dose of 10 mg/kg body weight as a single dose. The drug paralyzes the worms, which are then expelled.
- Albendazole and mebendazole should be avoided in the first trimester of pregnancy.
- Surgical intervention may be called for in case of acute abdomen—often following roundworm obstruction.

Enterobiasis (E. vermicularis; threadworm, pinworm, and oxyuria infection)

Background

1. **Causative organism:** The infection is caused by *E. vermicularis.*
2. **Magnitude of the problem:** About 300 million people worldwide suffer from enterobiasis.
3. **Predisposing factors**
   - Poor personal hygiene
   - Oroperineal contact
4. **Life cycle:** The E. vermicularis adult worm measures 8–133 × 0.5 cm. Infective eggs when ingested become larvae in the duodenum and mature into adult forms in the gut lumen. Fertilized female worms remain in the caecum, appendix, and the adjacent gut until they are full of eggs; thereafter they migrate through the anal canal at night to deposit their eggs (about 10,000) on the perianal skin before they die. These eggs become infective within a few hours of deposition. Autoinfection is widespread and spreads rapidly amongst other family members or institutional inmates. There is no multiplication of worms inside the body. The average lifespan of adult worms is about 2 months.

Clinical features

- Anal and vulval pruritus is the leading complaint.
- These symptoms are further aggravated in pregnancy.
- Occasionally the adult female worms migrate into the vagina, causing vaginitis.
- In nonpregnant subjects, pelvic inflammatory disease secondary to enterobiasis has been reported.
- Disturbed night sleep.

Diagnosis

- Microscopic examination of perianal scrapings and scotch tape on slides or swabs and examination of scrapings from the undersurface of fingernails reveal the typical eggs of *Enterobius vermicularis* (Figure 21-5).
- Gross examination of stools may reveal presence of adult worms.

Effects on the mother

Generally no significant ill-effects are observed in pregnant mothers.

Effects on the fetus

No significant ill-effects are reported.

Treatment

- Defer treatment until after the end of the first trimester if feasible.
- Oral Pyrantel pamoate 10 mg/kg up to a maximum of 1.0 g.
- Treat all members of the family simultaneously.
- Bedding and clothing to be washed in hot water with added bleach.
- Careful hand washing with soap and water before meals and after using the toilet.

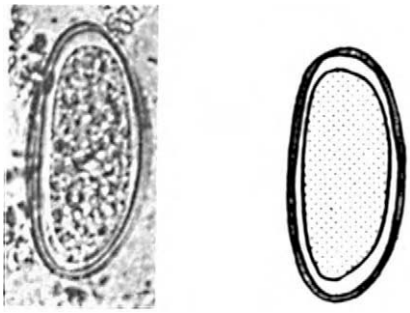

Figure 21-5. Eggs of *E. vermicularis.*

Strongyloides (S. stercoralis)

Background

1. **Causative organism:** The infection is caused by *S. stercoralis*.
2. **Magnitude of the problem**
   - About 80 million people affected worldwide
   - Prevalent in warm climates
3. **Predisposing factors**
   - Poor sanitation and hygiene
   - Autoinfection
   - Immunocompromised individuals (corticosteroid therapy, pregnancy, AIDS-affected individuals, malignancy, and malnutrition) are susceptible and suffer from severe symptoms
4. **Life cycle:** The filariform larvae (2–2.5 mm wide × 30–50 mm long) penetrate the skin to enter the circulation, reach the lungs, escape from the alveoli to ascend the tracheobronchial tree, and thereafter be swallowed to reach the gut. In the duodenum and jejunum, the adult worm lays its eggs. These hatch quickly to release the rhabditiform larvae which, after being expelled in feces, become infective filariform larvae. Besides the host–soil–host cycle, there are alternative modes of spread like autoinfection by developing into filariform larvae in the gut and sexual reproduction in the soil. Transmammary migration in nursing mothers has been reported.

Clinical features

- Asymptomatic if parasitic load is low
- In patients suffering from heavy infestation, there may be evidence of malabsorption, protein-losing enteropathy, iron-deficiency anemia, intestinal symptoms of indigestion, flatulence, and belching
- Upper respiratory symptoms of cough, pulmonary symptoms of breathlessness
- Cutaneous manifestations like urticaria, petechiae, and ulcers

Diagnosis

- Examination of fresh sample of stool
- Examination of duodenal aspirates
- Jejunal biopsy
- Sputum examination may reveal larvae
- ELISA larval antigen test is positive in 85% patients

Maternal effects

- Malnutrition
- Anemia
- Poor weight gain
- Gastrointestinal upsets

Fetal effects

- Low birth weight
- IUGR
- Drug effects (albendazole, mebendazole)

Treatment

- Thiabendazole 25 mg/kg twice daily for 2–3 days after delivery
- Albendazole 400 mg twice daily for 3 days may be used during pregnancy

Trichuriasis (T. trichiura; whipworm infestation)

Background

1. **Causative organism**
   - The infection is caused by *T. trichiura*.
   - The *T. trichiura* worm is about 30–50 mm in length
2. **Magnitude of the problem**
   - *T. trichiura* infection is prevalent worldwide.
   - About 500–800 million people are affected.
   - It affects more people living in hot moist tropical climates.
3. **Predisposing factors**
   - Poor sanitation and public hygiene
   - Poverty
   - Ignorance and lack of education
   - Poor personal hygiene
4. **Life cycle**
   - Ingested embryonated eggs hatch in the small intestine and migrate to the large bowel without any extra intestinal migration and stay confined in the caecum and appendix. .
   - The entire cycle takes 3 months to complete.
   - Each female worm lays about 5000 eggs/day.
   - The worms survive for many years.

Clinical features

- Malnutrition
- Anemia
- Gastrointestinal symptoms like flatulence, diarrhea, tenesmus, and vomiting
- Severe dysentery may follow

Diagnosis

- Feces examination may reveal presence of adult worms, and typical barrel-shaped eggs (Figure 21-6).
- Proctoscopy may reveal presence of adult worms.
- Blood count often shows eosinophilia.

Maternal effects

- Nil in mild cases

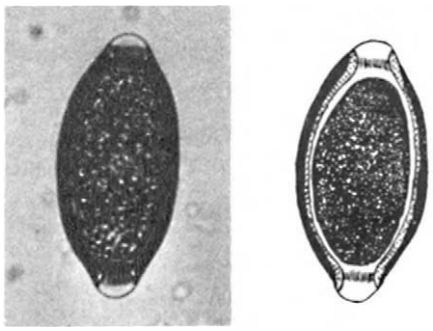

Figure 21-6. Barrel-shaped eggs of *T. trichiura.*

- Malnutrition
- Anemia

Fetal effects

- Low birth weight

Treatment

- Pyrantel pamoate 10 mg/kg up to a maximum of 1.0 gm. Is recommended in pregnancy, preferably after completion of the first trimester.
- Albendazole and mebendazole 400 mg may be prescribed after the first trimester in pregnancy.

Cestode (Tapeworm infestations)

Cestodes or tapeworms have been recognized as human parasites. These are difficult to treat and recurrence rates are high.

Background

1. Causative organisms
- *Taenia saginata* (beef tapeworm)
- *Taenia solium* (pork tapeworm)
- *T. saginata asiatica*
- *Diphyllobothrium latum* (fish tapeworm)

2. Magnitude of the problem: Worldwide estimates not known

3. Predisposing factors
- Consumption of nonvegetarian food
- Consumption of raw or undercooked food

4. Life cycle
- *T. saginata*: the adult worms measure 5–10 m, with 1000–2000 proglottids (segments). The *T. saginata asiatica* has been more recently discovered in Asian communities. *T. solium*: the adult worm measures 2–3 m, with less than 1000 proglottids. The *D. latum*: adult worm measures about 10 m. *Hymenolepis nana* (dwarf tapeworm) is the smallest and most common of the cestodes. The adult worm measures 25–40 mm in length.
- Man is both a definitive and intermediate host for *T. saginata* and *T. solium.*

Clinical features

- Large tapeworms are generally asymptomatic.
- Gastrointestinal symptoms of nausea and diarrhea may occur.
- Rarely, the proglottids may cause obstruction of the bile duct, pancreatic duct, or the appendix.
- In case of infection with the larval stage of *T. solium* (cysticercosis), ectopic parasitism occurs with involvement of the central nervous system, striated muscles, eyeball, and rarely other tissues.
- *D. latum* is known to cause abdominal discomfort, diarrhea, or constipation and megaloblastic anemia because of competitive utilization of available folic acid and vitamin B_{12}.
- Infestations with the small tapeworms cause abdominal pain, anorexia, nausea and vomiting, weight loss, and irritability.

Diagnosis

- Finding gravid proglottids in clothing or bedding
- Proglottids may rarely be found in fresh stool samples
- Perianal cellophane tape test reveals eggs (Figure 21-7)
- Enzyme electrophoresis of glucose phosphate isomerase helps in species differentiation

Maternal effects

- None to those arising out of concomitant nutritional deficiencies and anemia

Fetal effects

- Secondary to maternal health status

Treatment

- Praziquantel 10 mg/kg single dose and niclosamide 2.0 g is the treatment of choice for *T. saginata*, *T. solium*, *D. latum*, and *H. nana.*
- Moderate purgative 2–3 hours after treatment is required for *T. solium.*
- Niclosamide is safe in pregnancy. No teratogenic effects are reported.
- Praziquantel is more effective for treatment of *H. nana.*
- Supplementation with folic acid and vitamin B_{12} is recommended in *D. latum* infection.

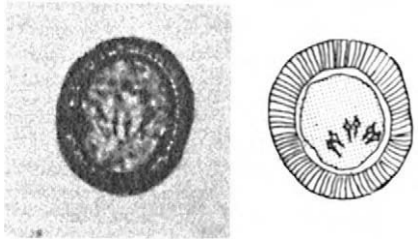

Figure 21-7. Eggs of *T. saginata.*

- Albendazole 15 mg/kg/day in two to three divided doses for 8–28 days is recommended for cysticercosis (it be avoided in the first trimester of pregnancy unless clinical situation is grave).
- Care should be exercised in observing strict personal hygiene and disposal of feces and used toilet papers.

Hydatid disease (Echinococcosis)

Hydatid disease is an infestation generally affecting the rural shepherd community.

Background

1. **Causative organisms:** Commonly implicated organisms causing human hydatid disease include the following:
   - *Echinococcus granulosis* (cystic hydatid disease)
   - *Echinococcus multilocularis* (alveolar hydatid disease)
2. **Magnitude of the problem:** Rural farming and shepherds are likely to be affected.
3. **Predisposing factors:** Close association with animals
4. **Life cycle**
   - Human echinococcosis results from infection by the larval stage by the above-mentioned parasites.
   - Echinococcosis is a zoonosis in which humans are the intermediate host for the larval stage of the parasite.
   - The hydatid cyst may persist in the host for many years.
   - Common sites for hydatid cysts include liver (65%) and lungs (25%) and the rest of the sites include the brain, kidney, bones, skeletal muscles, and pelvic organs. Bickers (1970) described hydatid cyst in the pelvis.

Clinical features

- Liver cysts remain symptomatic for about 10–20 years or even longer. These symptoms are the result of mechanical pressure on surrounding structures, causing obstructive jaundice, cholangitis, reactive hepatitis, hepatic cirrhosis, and portal hypertension.
- Pulmonary echinococcosis may present with fever, cough, breathlessness, chest pain, and occasionally hemoptysis.

Diagnosis

- Eosinophilia
- Plain x-ray chest may reveal a thin eggshell calcification
- CT scan/MRI/USG (ultrasound) are safer during pregnancy
- Casoni skin test (less specific; Kumar, 1990)
- Immunoblot test is 98% specific and 91% sensitive for liver cysts
- Indirect hemagglutination test is positive in 60–90% cases
- ELISA, immunofluorescence are useful screening tests
- The arc-5 test is diagnostic (except for cross-reactivity with cysticercosis)
- Aspiration of cyst—considered risky earlier—is being increasingly resorted to under USG guidance under cover of albendazole and intracystic instillation of scolicidal solution

Maternal effects

- Malnutrition
- Dystocia in case of pelvic cysts

Fetal effects

- Negligible in asymptomatic mothers
- Low birth weight
- Preterm birth in sick mothers
- Drug-induced toxicity

Treatment

- Surgical treatment, aiming at operative removal of hydatid cysts constitutes definitive treatment.
- Medical treatment consists of albendazole 800 mg daily in divided doses for 1–3 months.
- Mebendazole 50 mg/kg daily in three divided doses for 3 months.
- Albendazole and mebendazole should be used with caution in the first trimester and restricted for acute emergency situations only.

Trematodes (Schistosomiasis)

Background

1. **Causative organisms**
   - *Schistosoma haematobium*
   - *Schistosoma japonicum*
   - *Schistosoma mansoni*
2. **Magnitude of the problem**
   - Schistosomiasis infects about 200 million people worldwide
   - Annual death toll 200,000
   - Egypt and East African countries are mainly affected
3. **Life cycle**
   - Schistosomes are flat worms that parasitize humans, and snails serve as intermediate hosts. Exposure to contaminated water initiates the infection.
   - The adult worms of *S. japonicum* and *S. mansoni* localize in the mesenteric and hemorrhoidal veins and involve the liver and gastrointestinal tract. Adult *S. haematobium* localizes and matures in the pelvis and bladder venous plexus, affecting the pelvic

organs, bladder, and lower gastrointestinal tract. *S. japonicum* and *S. mansoni* involve the same organs. However, *S. japonicum* (1400–3500 eggs/day) is more virulent than *S. mansoni* (250–350 eggs/day).

Clinical features

- *S. japonicum* and *S. mansoni* cause mucous diarrhea and hepatosplenomegaly, and later in the course of the disease produce colonic polyposis or Banti's syndrome. These patients are often carriers of chronic salmonella.
- *S. haematobium* causes hematuria, hepatosplenomegaly, and at times mucus diarrhea, bladder polyposis, and carcinoma.
- Pelvic organs are often involved by eggs of *S. mansoni* and *S. haematobium*, causing salpingo-oophoritis, infertility, and ectopic pregnancy. Involvement of the cervix causes abortion, and vulval and vaginal involvement cause dyspareunia and dystocia.
- Schistosomiasis (bilharziasis) during pregnancy predisposes to malnutrition, proteinuria, hematuria, recurrent UTI, and anemia. Placental involvement with IUGR has been reported.
- Female genital schistosomiasis is a risk factor for the transmission of HIV (Fieldmeier et al., 1994).

Diagnosis

- Microscopic examination of urine, stools, and vaginal discharge for eggs (Figure 21-8)
- Biopsy from bladder, rectum, or liver
- Plain X-ray abdomen in nonpregnant mothers often reveals calcification
- Intravenous pyelography
- Cystoscopy—"sandy patches" ulceration
- Barium enema—spiculating ulcers
- CT scan may reveal pathognomonic turtleback calcification in *S. haematobium*
- Immunoblot (western blot) is very accurate
- Earlier skin test is no longer recommended

Maternal effects

- Chronic proteinuria causing weakness, edema, and anemia
- Malnutrition

Fetal effects

- Low birth weight
- IUGR

Treatment

- Praziquantel 40 mg/kg in a single dose is the treatment of choice
- Metrifonate for *S. haematobium* 7.5–10 mg/kg (do not exceed 600 mg) once only

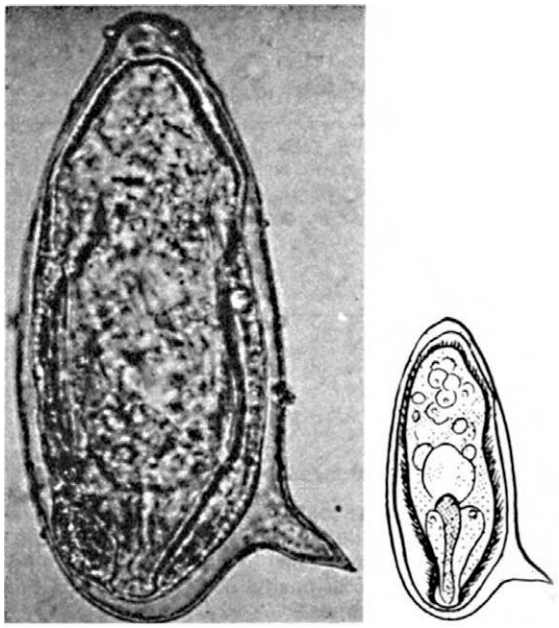

Figure 21-8. Eggs of *S. mansoni.*

- Oxamniquine 12–15 mg/kg for *S. mansoni.* Contraindicated in pregnancy as it is known to be mutagenic and embryotoxic
- Surgical excision of obstructing granulomas during delivery
- Surgical excision of polyps causing obstructive uropathy

Tissue nematodes (Filariasis)

Background

1. Causative organisms
- *Wuchereria bancrofti* found in India
- *Brugia malayi* common in Southeast Asia

2. Magnitude of the problem
- More than 80 million people suffer from lymphatic filariasis.
- In India about 15 million people are affected.
- The parasitic index is three to four times higher.
- Prolonged exposure for 3–6 months in endemic areas causes infection.
- The distribution is centripetal (central city), whereas Malaysian filariasis is centrifugal (outskirts).

3. Life cycle
- Adult worms (females) are 8–9 cm × 0.2–0.3 mm in size.
- Following a mosquito bite, microfilariae inhabit lymphatics and lymph nodes, causing acute and chronic obstructive reactions followed by fibrosis, granulomatous tissue reaction, and irreversible lymphedema.
- In endemic areas, people gradually acquire immunity.

Clinical features

- Initially the patient may suffer from fever with rigors and acute lymphangitis.
- Chronic disease is characterized by obstructive lymphatic outcome.
- Usually, the lower limbs, upper limbs, abdomen, pelvic organs, and external genitals may be affected, leading to sexual difficulties, infertility, and difficulty during labor—necessitating resort to cesarean section.
- Nonpitting edema and elephantiasis of limbs, vulva abdominal wall, etc.
- Other manifestations include chyluria, chylous ascites, and hydrothorax.
- Usually the fetus remained unaffected.

Diagnosis

- The diagnosis is essentially based on clinical findings.
- Microfilariae are usually detected in venous blood ideally drawn between 9.00 PM and 1.00 AM in a wet preparation of dehemoglobinized thick/thin smear.
- Knott's concentration technique of examining the centrifuge deposit may be more rewarding.
- Diethylcarbamazine (DEC) provocation test is performed on venous blood collected half an hour after oral administration of 100 mg of DEC.
- Venous blood can be filtered through a fine mesh filter membrane and stained for microfilariae to obtain a high yield.
- An x-ray may reveal calcified worms in lymph nodes.
- Intradermal test and complement fixation tests help to exclude the diagnosis.
- Indirect fluorescence and ELISA tests can detect antibodies (IgG and IgE) in 95% of active cases and 70% of established elephantiasis.
- Immunological tests and high eosinophilia are suggestive of filariasis.
- A PCR test from antimicrofilaramic person from blood and urine sample is available.
- USG can detect worms in lymph nodes.

Maternal effects

- Difficulty during labor if lower genital tract and vulva are involved
- A case report by Toll (1979) described presence of microfilariae in amniotic fluid from a patient suffering from hydramnios

Fetal effects

- The fetus usually remains unaffected.

Treatment

- Defer treatment until after delivery unless there are compelling reasons to act otherwise.
- DEC in dose of 5.0 mg/kg in three divided doses for 14–21 days.
- Concomitant administration of steroids or antihistaminic helps to control allergic reactions.
- Sensitivity can be tested by administering a single dose of 25–50 mg DEC for worm eradication.
- WHO recommends a dose of 75 mg/kg for *W. bancrofti* and 30–40 mg/kg for *B. malayi.*
- Other drugs like mebendazole 30 mg three times per day for 3 weeks and levamisole 50–150 mg have been found to be useful for adult and larval forms of *W. bancrofti.*
- Antibiotics should be administered to control bacterial infections.
- Cesarean section may be necessary for obstructive vulval growths.
- Ivermectin, a microfilaricide, is under evaluation, but not recommended during pregnancy.

HEPATITIS IN PREGNANCY

Clinical jaundice is found as a complication in 1:1000 pregnancies in India (Rao,1982). The frequency is higher whenever there is an outbreak of epidemic hepatitis. In Asian countries, jaundice claims many maternal lives during pregnancy. The incidence of total deaths due to jaundice in pregnancy reported from India ranged from 10 to 20% (Bhatia, 1990; ICMR, 1990; Bera and Sengupta, 1992; Jayaram, 1992). Of these 90% were attributed to viral hepatitis (Lahiri, 1976).

Liver has a dual blood supply (hepatic artery and portal vein). It is therefore most vulnerable to viral infections. But other causes like bacterial (leptospirosis), parasitic infections (amebiasis), as well as exposure to drug toxicity and idiosyncrasies can also contribute to liver damage and jaundice. Fortunately, the liver has a large functional reserve.

Jaundice in pregnancy can be caused by many factors like cholestasis, hyperemesis, severe preeclampsia and eclampsia, gall stones, viral infections, and drugs. However, hepatitis is the most common and serious offending cause. It is associated with high morbidity and mortality. Hepatitis may be caused by specific hepatitis viruses (A to E), Epstein Barr virus, echovirus, cytomegalovirus, and yellow-fever virus.

Clinical manifestations due to these liver disorders depend on the extent of parenchymal hepatic necrosis. In mild infections, the patient may remain anicteric followed by recovery. On occasions, however, severe liver damage may be followed by cirrhosis. Rarely malignancy may ensue.

In patients who are malnourished, immunocompromised, and pregnant or whenever the infection is fulminant, hepatic failure is likely to set in, leading to cholemia,

coma, and even death. Mothers in advanced pregnancy acquiring viral hepatitis are most vulnerable.

Hepatitis A Virus (Infectious Hepatitis) in Pregnancy

Background

1. Epidemiology
- Hepatitis A virus (HAV): it is an RNA enterovirus (picornavirus)
- Resistant to environmental factors

2. Transmission
- Spreads by the fecal–oral route
- Ingestion of contaminated food and water, shellfish collected from sewage contaminated water
- Infected serum

3. Incubation period
- It ranges 2–7 weeks with average of 28 days
- Virus is present in blood, bile, and stools; therefore the person remains infective during the above period

Clinical Features

1. Presenting symptoms and clinical course

The patient may present with varying clinical features.
- General symptoms of weakness and fatigue, fever, and malaise
- As gastroenteritis—nausea and vomiting, anorexia, or loose motions
- As viral respiratory infection
- It is often a mild self-limiting illness and confers immunity on the subject

2. Long-term consequences
- Chronic infection with HAV does not occur, and hence there is no carrier state.

Laboratory Diagnosis

- Detection of the presence of anti-HAV IgM in serum

Prevention

- Improved sanitation
- Strict personal hygiene
- Frequent hand washing with soap and water
- Active immunization of health workers, day-care personnel, those who travel to endemic areas, sewage and waste water workers, and veterinarians dealing with nonhuman primates
- Passive postexposure immunization with immune globulin (0.02 ml/kg) can protect persons exposed to HAV against clinical illness. It is most effective if administered within 48 hours of exposure, but is helpful even up to 2 weeks into the incubation period
- Patients at risk should receive active immunization with the HAV vaccine

Pregnancy

- Incidence during pregnancy is 1:1000.
- It is not transmitted to the fetus in utero.
- It may be transmitted to the neonate during delivery or postpartum period (fecal–oral route).
- Infants born to mothers infected with HAV during the third trimester of pregnancy should receive postexposure prophylaxis with immunoglobulin.

Management

- Routine antenatal care
- General supportive measures
- Take care of nutrition and correct anemia
- Avoid exposure to infected individuals
- Observe strict personal hygiene
- Neonate should receive postexposure immunoprophylaxis
- Severely ill patients (encephalopathy, deep jaundice, coagulopathy) should be hospitalized
- Observe all precautions—barrier nursing
- Correct fluid and electrolyte imbalance
- Fresh blood transfusion, cryoprecipitate, blood component therapy
- Administration of inactivated-virus vaccine if available

Hepatitis B Virus in Pregnancy

Infection of the liver with hepatitis B virus (HBV) occurs in many people, but it is often asymptomatic. Chronic HBV infection affects over 350 million people worldwide and about 1 million die annually of HBV-related chronic liver disease. Nevertheless many people achieve eventually a nonreplication status. The prolonged immunologic response to infection leads to the development of cirrhosis of the liver, liver failure, or liver cancer in about 40% patients. In endemic areas where carrier status is < 5.0%, most individuals are infected perinatally by vertical transmission or in early childhood (Wright, 2006).

Background

1. Epidemiology
- HBV is found worldwide, but is endemic in certain areas like India.
- It belongs to the class of DNA virus.
- There are 200–400 million carriers worldwide.
- The carrier rates approximate 35% in Asia and Africa.
- It accounts for about a million deaths annually related to viral-hepatitis-induced liver diseases.

2. Transmission
- HBV is transmitted via body fluids (blood, semen, vaginal secretions, saliva, and breast milk).
- Mother-to-infant transmission accounts for 40% of all chronic HBV carriers.

3. **Types of infection**
   - Asymptomatic—about 75%
   - Acute hepatitis following HBV accounts for 300,000 cases of acute hepatitis annually in the USA. Estimates in India are not known
   - Chronic hepatitis—about 10% of infected adults develop chronic hepatitis, which leads to serious consequences
   - Approximately 80% of infected infants develop chronic hepatitis
4. **Incubation period:** It ranges from 30 to 180 days.
5. **Sequelae of chronic HBV infection**
   - Chronic hepatitis
   - Cirrhosis of liver, which can ultimately cause liver failure, accounts for about 4000 deaths annually in USA. Indian figures are not known
   - Hepatocellular carcinoma. Following HBV infection, liver cancer risk mounts 40-fold. It accounts for 800 deaths annually in the USA. HBV is second only to tobacco among human carcinogens

Prevention

- Active immunization with three doses of recombinant DNA-HBV vaccine.
- A booster dose after 5–10 years is recommended.
- Neonates born to HBV positive mothers should receive passive immunization with HBV immune globulin in addition to active immunization.

Clinical Features

Following an average incubation period lasting about 70 days, the patient enters the prodromal or preicteric phase characterized by gradually increasing anorexia, malaise, and fatigue. As the liver gets inflamed, the patient experiences right upper quadrant pain. The liver enzymes register a rise with onset of fever, resembling serum sickness with arthralgia, urticaria, and rash. With rising fever, about 50% enter the icteric phase. The liver becomes enlarged and tender, and jaundice becomes evident. Other symptoms include nausea and vomiting, pruritus, darkening of the urine, and the stools getting lighter in color. From then onwards, the majority will steadily improve, about 10% deteriorate to suffer from chronic persistent hepatitis, and a few fulminant patients will deteriorate further to hepatic failure and death. Patients with chronic HBV hepatitis are prone to long-term sequelae stated earlier.

Diagnosis

- All pregnant women should be routinely screened for HBV antenatally.
- High-risk groups should be rescreened at 28 weeks—these include Asians, patients at occupational risks, those exposed to HBV carriers, mentally challenged individuals, those attending to patients undergoing hemodialysis, patients with history of multiple blood transfusions, patients with repeated sexual exposures to different partners, and IV drug users.

Pregnancy

Acute infection with HBV occurs in 1–2 per 1000 pregnancies. Additionally 0.5–1.5% of pregnant women are carriers. In the tropics, widespread malnutrition worsens the prognosis.

There is no evidence of transplacental transmission, but perinatal infection of the neonate occurs during delivery and the postpartum period. These neonates should receive both passive and active immunization. This policy helps to prevent 95% of mother-to-infant transmission of HBV.

Effects on the Mother

Women who are suffering from chronic HBV present with the following:

- Gastrointestinal symptoms are more pronounced.
- Chronic carriers are more likely to suffer from cirrhosis, esophageal varices, and liver failure.

Effects on the Fetus

- There is no increased risk of abortion or preterm birth, IUGR, or stillbirth in acute infections, unless malnutrition is present.
- Since HBV has no teratological effects, there is no risk of teratogenic effects on the fetus in women with acute disease.
- Avoid using scalp electrodes during labor.
- HBV is not transmitted transplacentally to the fetus.
- Gentle resuscitation after birth—avoid mucosal trauma to the pharynx.
- With appropriate immunoprophylaxis, including hepatitis B immune globulin and hepatitis B vaccine, breastfeeding of infants of chronic HBV carriers poses no additional risk for the transmission of the HBV. Neonatal death may follow perinatal infection.

Management

- All HBsAg-positive carriers should be screened for liver involvement.
- All family members should be screened and immunization offered as necessary.
- Neonates of affected mothers should be offered both passive and active immunization, preferably within 12 hours of birth.
- All HBsAg-negative mothers should be offered active immunization soon after delivery.
- Passive immunization should be offered to nonimmune mothers at high risk for hepatitis B.

Hepatitis C Virus in Pregnancy

Hepatitis C virus (HCV) is the most common cause of non-A, non-B (NANB) hepatitis worldwide. However, HEV (hepatitis E virus) is the most important cause of NANB hepatitis in developing countries like India.

Background

1. **Epidemiology**
   - Hepatitis C is a single-stranded RNA virus.
   - It affects about 0.6% of the population (Ohto et al., 1994).
   - Predisposing factors are same as those for hepatitis B infection.
2. **Transmission:** HCV is transmitted parenterally, perinatally, and sexually. By blood product screening, transfusion-related viral transmission has been virtually eliminated, and maternal fetal transmission is now one of the most important modes of transmission.
3. **Incubation period:** It varies from 15 to 150 days.

Prevention

- There is no vaccine available against HCV.
- Immune globulin has not been proven to prevent infection.
- In fact, immunoglobulin administration has been associated with HCV infection.
- Ensure prevention of infected blood, organs, semen from entering the donor pool.

Clinical Features

- After an incubation period of 5–150 days, symptoms develop 5–12 weeks following exposure.
- Symptoms are similar to those of HBV infection.
- Almost 80% patients are asymptomatic and fail to develop jaundice.
- Acute fulminant infection can lead to hepatic failure and aplastic anemia.
- About 50–80% become chronic infected with HCV. Of these, 29–76% develop chronic active hepatitis or cirrhosis.
- Chronic infection is strongly linked with the development of hepatocellular malignancy over time—say about 30 years.

Laboratory Diagnosis

- HCV infection is confirmed with serologic assays—antibodies to HCV (anti-HCV).
- Molecular tests for diagnosis virus particles.
- The third-generation assays for anti-HCV are more sensitive and specific.
- Qualitative PCR assay for the presence of viral particles is the most specific test for detection of HCV before antibodies have developed.

Pregnancy

- The most significant clue in history taking is the history of substance abuse.
- Vertical transmission of HCV does occur, but its precise incidence is not known.
- HIV-positive women with HCV have a higher risk of vertical transmission.
- Risk of mother-to-child transmission for HCV is about 5%, but this rises to 15% for those with combined HCV and HIV infections.
- There is at present insufficient evidence to recommend cesarean delivery or to recommend avoidance of breast-feeding.
- There is at present no currently effective intervention to prevent mother-to-child transmission of HCV.

Effects on the Mother

- She may be asymptomatic.
- She may have symptoms similar to HBV infection.
- Fulminant infections may lead to liver failure and death.

Effects on the Fetus

- Generally none
- Risk of vertical transmission estimated to be 5%
- If the mother has concomitant HIV infection, the risk of mother-to-child transmission rises threefold (Silverman et al., 1995)
- Most infected children remain well but are at high risk of developing chronic liver problems during adulthood

Management

- Test all pregnant mothers in high-risk group for HCV, antenatally.
- Ensure adequate nutrition and prescribe hematinics to prevent anemia.
- Monitor fetal growth.
- Obstetric interventions should be undertaken for obstetric indications only.
- Role of elective cesarean section to minimize risk of vertical transmission is not yet established, hence not recommended.
- No HCV vaccine is available so far for protecting neonates.
- Treatment with interferon alpha produced improvement in 28–46% of patients with chronic HCV. However, 50% of these showed relapse within 6 months of cessation of therapy—pregnant women were excluded from the study (Davis et al., 1989).

Hepatitis D Virus in Pregnancy

Hepatitis D requires HBV for replication and expression and so it occurs only in those people who are already

infected with hepatitis B. In acute hepatitis B, once HBsAg clears the blood stream, so does hepatitis D. About 20–25% of chronic HBV carriers ultimately are coinfected with hepatitis D virus (HDV) (Rizzetto, 1983; Hoofnagle, 1989).

Background

1. **Epidemiology**
   - Hepatitis D is an incomplete virus.
   - It requires the presence of HBV to replicate.
   - Hence HDV develops only in HBsAg-positive patients.
2. **Transmission**
   - Similar to HBV
   - Perinatal transmission rare
3. **Incubation period:** Approximately 35 days

Prevention

Since HDV affects only HBV positive patients, therefore effective immunization against HBV holds the key to HDV prevention.

Clinical Features

- After the incubation period, patients of HBV coinfected with HDV tend to run a more severe course. About a third of these coinfected patients go on to develop fulminant hepatitis.
- Chronic HBV patients coinfected with HDV rapidly progress to develop subacute and chronic HDV infection and a more rapid progression to cirrhosis.
- Although 15–30% of HBV-positive individuals ultimately progress to cirrhosis and portal hypertension, the incidence rises to 70–80% in individuals coinfected with HDV. Mortality due to hepatic failure approaches 25% (Hoofnagle, 1989).

Laboratory Diagnosis

- Detection of D antigen in serum or hepatic tissue
- Identification of the IgM antibody to hepatitis D virus in the serum

Pregnancy

- Effects are same as in HBV infection—only more severe in these coinfected individuals.
- Perinatal transmission is rare.

Management

- It is based on similar lines as that for HBV infection.
- Treatment with interferon alpha produced improvement in 28–46% of patients with chronic HCV. However, 50% of these showed relapse within 6 months of cessation of therapy—pregnant women were excluded from the study (Davis, 1989).

Hepatitis E Virus in Pregnancy

HEV is the primary cause of enterically transmitted NANB hepatitis; most outbreaks occur in developing countries. Poverty, crowding, poor sanitation and hygiene, and lack of education serve to precipitate epidemics.

Background

1. **Epidemiology**
   - Epidemiologic features similar to those of hepatitis A.
   - It is endemic in India and is the primary cause of enterically transmitted NANB hepatitis.
   - Most epidemic outbreaks occur in poor underdeveloped countries of the tropics.
   - Maternal mortality during epidemics has been alarmingly high.
2. **Transmission**
   - Essentially through consumption of contaminated food and water
   - Vertical transmission has been reported (Khuroo et al., 1995)
3. **Incubation period:** Incubation period ranges from 2 to 9 weeks with an average of 45 days.

Prevention

- No vaccine is available.
- Administration of immune globulin does not prevent development of clinical disease.

Clinical Features

- HEV produces an acute self-limiting disease similar to HAV.
- Fulminant disease occurs in about 10% cases.
- It is associated with a mortality rate of 10–18% (Bradley and Maynard, 1986).
- It does not result in a chronic carrier state (Bradley and Maynard, 1986).
- Vertical transmission has been reported (Khuroo et al., 1995).

Laboratory Diagnosis

- Demonstration of virus-specific antibodies

Pregnancy

- The disease is more severe during pregnancy.
- It is associated with a high mortality rate (10–18%).
- Vertical transmission is known to occur.

- Perinatal transmission frequency is as yet undetermined.

Maternal Effects

- HEV runs a more severe course during pregnancy
- Preterm births common
- Risk of postpartum hemorrhage high due to prothrombin deficiency
- High risk of fatality

Fetal Effects

- Vertical transmission known
- Perinatal transmission also likely to occur
- Prematurity
- Low birth weight
- Higher perinatal morbidity and mortality

Management

- Similar to patient suffering from HAV

Hepatitis G in Pregnancy

Hepatitis G infection is more likely in patients suffering from HBV, HVC, HIV infections or IV drug users (Velasquez et al., 1990). The vertical transmission risks during pregnancy are high. Hepatitis G probably does not cause chronic active hepatitis or cirrhosis. Diagnosis is based on the detection of virus-specific antibodies. Management is similar to that for HBV/HCV.

Indian Contribution to Hepatitis in Pregnancy

In India, the experience of the prevalence and behavior of hepatic in pregnancy has been briefly recounted below.

1. HBV is still a major concern with a positivity of 4–6% of HBsAg among the population. HEV is the major cause of NANB hepatitis, while HCV is not a major cause of acute viral disease (Kar et al., 1997).
2. Sunita Mittal et al. (1996) reported the frequency of HBsAg positivity of 4.6% by RPHA (reverse passive hemagglutination assay) and 6.3% by micro-ELISA method. These authors detected HBeAg in 18% of HBsAg-positive patients.
3. Mittal et al. (1996) estimated that 1.17–1.64% among infants born out of 24 million annual births in women of India would be infected with HBV. In other words, every year in India, 2.6–3.9 lakh infants are infected by HBV perinatally.
4. Gill et al. (1996) conducted a study on 2000 pregnant women. They investigated the prevalence of HBsAg and further tested all the positive patients for HBeAg. They reported an incidence of 5 and 12%, respectively. These authors recommended the routine screening of all pregnant women in the third trimester for HBsAg and to implement the policy of offering immunoprophylaxis to all newborns soon after birth.
5. In a general study by Ahmad et al. (2001), the overall HBsAg prevalence was 12.8%. The highest was in renal transplant patients (21.7%), followed by patients with acute hepatic disease (15.3%), pregnancy with jaundice (9.4%), chronic renal failure (8.8%), and nephritic syndrome (3.1%), whereas the prevalence rate in control group was 2.4%.
6. Sharma et al. (1996) conducted a small study on 150 pregnant mothers. They reported an overall prevalence of HBsAg in these mothers of 10% and an HBsAg positivity of 5% in the cord blood of newborns in the series. Transplacental transmission was 50%. Anti-HBc was present in 75% of HBsAg-positive mothers, and of these 58% neonates acquired HBsAg infection. Eighty-eight percent of newborns of the HBsAg-positive mothers were alive and healthy; there was 1 stillbirth and 1 baby with congenital anomalies.
7. Gupta et al. (1992), investigating the problem of vertical transmission in 15 affected mothers, observed that the babies born to HBeAg-positive mothers were at greatest risk (73%) of acquiring the infection by 12 months. If the mothers were only HBsAg positive, the risk was lower (17%) and if the mother was anti-HBe–positive, the risk was lowest (9%).
8. Nayak et al. (1989) mentioned that although in the developed world acute HBV in pregnancy runs a similar course to that in nonpregnant women, it is not so in developing countries, where rampant nutritional deficiencies and other tropical diseases make the prognosis much worse. The maternal mortality rate was 28.5%. The obstetric outcome in NANB hepatitis in pregnancy was equally bad as in HBV infection during pregnancy.
9. Khuroo et al. (2003) reported that the obstetric outcome in pregnancy was much worse in women with HEV. Maternal age > 40 years, low prothrombin time, or onset of coma was indicative of a grave prognosis.
10. Patra et al. (2007) studied 220 pregnant women with hepatitis. Infection with HEV caused acute viral hepatitis in 60% of included women. Fulminant hepatic failure was more common and maternal mortality was greater in HEV-infected women than in non-HEV-infected women. Antepartum hemorrhage, intrauterine death, preterm delivery, and poor fetal outcome were all more common in women infected with HEV.

TUBERCULOSIS COMPLICATING PREGNANCY

Tuberculosis has once again drawn worldwide attention. Increase in migration of people caused by changing world socioeconomic scenario, breakdown of joint family support systems, homelessness, overcrowding and poverty, poor sanitation in rapidly growing cities, and the emergence of drug-resistant organisms coupled with shrinking health care access have led to a resurgence of tuberculosis. It is a well-recognized health hazard in India and the developing neighboring countries of the subcontinent. Tuberculosis kills more adults in India as compared to any other infectious disease.

Background

1. Magnitude of the problem
- Worldwide about 15–20 million people are affected.
- Of these about 12–15 million live in developing countries.
- About 3 million deaths from tuberculosis occur annually worldwide.

2. Causative organism
- *Mycobacterium tuberculosis* (human type and bovine type)

3. Predisposing factors
- Poverty
- Malnutrition
- Poor hygiene and sanitation
- Overcrowding and overwork
- Consumption of nonpasteurized milk
- Exposure to infected untreated contacts
- Immunocompromised status—HIV positive status, pregnancy

4. Changing incidence
- Effective chemotherapy led to decline in tuberculosis worldwide until 1986.
- Recent dramatic upsurge in young urban adults attributed to drug resistance and spread of HIV.
- The Indian National Tuberculosis Control Programme was initiated in 1962.
- The epidemiological programme needs a greater push; the epidemiological curve has registered a decline, but it has plateaued far above the acceptable level.
- The highest incidence of pulmonary tuberculosis occurs in the age group of 17–35 years. This corresponds to the childbearing years in a woman's life.
- The prevalence rates are lower in women as compared to men.
- A study of "Tuberculosis during Pregnancy" was carried out in Mumbai (from 1991 to 1995). Mumbai (Saraiya et al., 2001) reported the highest incidence in the age group of 20–25 years. Primigravidae accounted for 20% of the affected patients. In the above study, pulmonary tuberculosis accounted for 85%, abdominal tuberculosis for 6%, genital tuberculosis for 1%, and the rest accounted for 8% (lymph nodes, bone, etc.). Anemia was common in affected women.

Clinical Features

- Enquiry of past history of tuberculosis or contact with a tuberculosis patient is often present in about a third of these cases.
- Early cases of tuberculosis may often be asymptomatic. But on close enquiry, many do admit to loss of appetite, lassitude, sleep sweats, and evening rise of temperature. With more advanced disease, they often complain of cough with expectoration, hemoptysis, and weight loss. Pleurisy is associated with chest pain and breathlessness. Abdominal pain is common in ileocecal tuberculosis. Patients with genital tuberculosis are generally infertile and suffer from menstrual disturbances, commonly oligomenorrhea. In case of conception, the risk of abortion and preterm delivery is high.
- Clinical examination often reveals presence of enlarged nontender lymph nodes. Chest examination may reveal presence of post-tussive rales, pleural rub, and signs of pleurisy.

Investigations

- Chest radiography (shielding of abdomen during pregnancy is important)
- CT scan of chest preferred—greater accuracy (miliary tuberculosis, mediastinal lymph nodes, cavities, areas of consolidation) and it gives less radiation. May be undertaken during the third trimester
- CBC (complete blood count), ESR (erythrocyte sedimentation rate) are of limited value
- Tuberculin test, Mantoux test (limited value as BCG inoculation is common)
- Sputum examination for acid-fast *M. tuberculosis*
- Sputum culture
- Serological tests
- PCR testing

Diagnosis

It is based on the composite information, including the following:
- History and clinical findings
- Investigations as detailed above
- Response to treatment

Effect of Pregnancy on the Disease

- With effective chemotherapy, the outlook has improved remarkably.
- Pregnancy does not worsen the course of the disease.
- There is a higher risk of relapse during the puerperium.

Effects on the Mother

- Pregnancy may worsen the maternal outcome in drug-resistant patients.
- Consider MTP (induced abortion) in selected cases not responding to therapy.
- Incidence of preterm delivery has come down following effective chemotherapy.

Effects on the Fetus

- Modes of transmission of *M. tuberculosis* to the fetus and newborn are discussed in Table 21-1.

Table 21-1. Mode of spread of tuberculosis from mother to fetus

Maternal focus	Mode of spread
Placentitis	Hematogenous
Amniotic fluid	Aspiration
Cervicitis	Direct spread
Pneumonitis	Airborne (postnatal)

- Effective chemotherapy has reduced the incidence of low birth weight.
- There is no evidence of increase in congenital fetal abnormalities ever since the stoppage of use of streptomycin in the treatment of tuberculosis. Streptomycin use was associated with congenital deafness.

Prevention

- BCG vaccination in childhood
- Isolation of open cases of tuberculosis and their prompt treatment
- Screening of all close contacts of tuberculosis-affected patients

Management

1. Rest
2. Nutritious diet
3. Medical management: during pregnancy, it is recommended that the patient should be jointly managed with a physician well versed in the care of tuberculosis. During the first trimester, nausea may pose a problem (Table 21-2).
4. Dosage of antituberculosis drugs are given in Table 21-3.

Table 21-2. Choice of medication during various phases of tuberculosis

	Intensive phase (first 2 months)	Continuation phase (next 4 months)
Sputum-positive pulmonary tuberculosis or Severe form of extrapulmonary tuberculosis	Isoniazid Rifampicin Pyrazinamide Pyridoxine supplement	Isoniazid Rifampicin Ethambutol Pyridoxine supplement
Sputum-negative pulmonary tuberculosis or Extrapulmonary tuberculosis which is not severe	Isoniazid Rifampicin Pyrazinamide Pyridoxine supplement	Isoniazid Rifampicin

Table 21-3. Dosage of antituberculosis drugs in daily and twice weekly regimes

Drugs	Daily dose (mg/kg/day)	Twice weekly dose (mg/kg/day)	Maximum daily dose (mg/kg/day)
Isoniazid	10	20	300
Rifampicin	10–20	10–20	600
Ethambutol	15–25	50	2500
Pyrazinamide	25–35	50	2500

5. If mother is sputum positive, observe neonatal care as follows:
   - Use of face mask while nursing the neonate and frequent hand washing.
   - If congenital tuberculosis is present, treat the neonate with triple drug therapy.
   - In absence of congenital tuberculosis, oral isoniazid 10 mg/kg/day for 3 months.
   - Chest X-ray and Mantoux test: if both are negative, advise BCG vaccine; if Mantoux test is positive and chest x-ray is negative, advise isoniazid for further 9 months. If chest x-ray is also positive, initiate three-drug regimen for 1 year.
6. Obstetric management: Joint management with physician is recommended.
   - (i) Monitor signs of drug side effects. It is advisable to monitor liver involvement and platelet count in each trimester. (ii) Monitor fetal growth from mid-pregnancy onwards. (iii) Monitor fetal health. (iv) All obstetric interventions should be based on obstetric indications. (v) During vaginal delivery, cutting short the second stage with outlet forceps

assistance is the practice in India. (vi) Neonate to be under care of neonatologist. (vii) Puerperium is the period of anxiety and stress when relapse may occur. Therefore ensure adequate rest to the mother.

- It is noteworthy that incomplete treatment not only is insufficient, but also increases the risk of emergence of multidrug resistant tuberculosis. Direct observed therapy can be used to improve the compliance.

IMPORTANT POINTS

1. Malaria has staged a resurgence in India. It affects a billion people worldwide and accounts for more than a million deaths annually. The common infecting agents are the *P. vivax* and *P. falciparum*. These are acquired through the bite of the female anopheles mosquito. Human beings are the intermediate host for asexual multiplication of the parasite. Pregnant women have lowered immunity and are therefore more vulnerable. The basic pathology of malarial infection is hypoxia as a result of the intracapillary obstruction caused by sludge composed of parasitized and damaged erythrocytes. This leads to hemolysis and anemia and a response from the reticuloendothelial tissues, causing splenomegaly and liver damage. Dissemination to other organs follows in severely affected subjects. Placental parasitization (6–10% in endemic areas) can lead to abortion, preterm delivery, or congenital fetal malaria. Clinical attack typically consists of fever with rigors consisting of the cold stage, the hot stage, and the sweating stage. These tend to recur every 48–72 hours. With passage of time, immunity develops. Life-threatening complications include cerebral malaria, seizures, algid fever, circulatory collapse, severe anemia, blackwater fever, jaundice, hypoglycemia, and other causes. Diagnosis is established on the basis of identification of parasitized erythrocytes in a peripheral blood smear, PCR testing of peripheral blood for *Plasmodium* DNA, fluorescent microscopy, and rapid malaria test. Primigravidae are more vulnerable, and pregnant women living in endemic areas fare better than others because of immunity developed over time. Chloroquine and quinine are the most commonly used drugs to treat malaria.
2. Dengue is a mosquito-borne virus infection. The virus is a single-stranded RNA virus. It causes high fever, body ache, gastrointestinal symptoms, bleeding tendency, and circulatory collapse which may lead to fatality if not aggressively treated. Vertical transmission to the fetus has been recorded.
3. Amebiasis is common in the tropics. It is caused by the protozoon *E. histolytica*. Amebiasis causes intestinal symptoms of indigestion, belching, flatulence, and diarrhea, leading to malnutrition and cramping abdominal pain. Hepatic involvement is a serious complication. Diagnosis is generally established by microscopy of fresh stool sample. Treatment includes use of diloxanide furoate to treat luminal disease. Metronidazole and related derivatives are effective, but it is advisable to prescribe these drugs after the first trimester.
4. Giardiasis is caused by the protozoon *G. lamblia*. Infection is acquired through consumption of contaminated water and food. It causes abdominal discomfort and flatulence, with passage of large greasy stools. These women often suffer from deficient weight gain and protein vitamin deficiency. Diagnosis is established by examination of fresh sample of stool for evidence of trophozoites and cysts of *G. lamblia*.
5. Helminthiasis is common in tropical developing countries. Poverty, overcrowding, illiteracy, poor sanitation, and defective hygiene predispose to parasitic infection.
6. Hookworms are a common cause of anemia during pregnancy. Diagnosis is based on demonstration of typical four- to eight-celled morula of *A. duodenale*. Treatment of choice is with Pyrantel pamoate.
7. Roundworm infestation is often asymptomatic. However, malnutrition is not infrequent. Upper respiratory symptoms and colics following obstruction of appendicular lumen, biliary duct or pancreatic duct. Diagnosis is based on stool examination, revealing fertilized and nonfertilized eggs of *A. lumbricoides*. Medications recommended include Piperazine citrate and Pyrantel pamoate.
8. Oxyuris infection is common. It is transmitted by oroperineal contact and poor personal hygiene. It causes pruritus (anal and vulval), disturbed night sleep. Diagnosis is based on microscopic examination of anal scrapings. Pyrantel pamoate is the drug of choice.
9. *S. stercoralis* is common in warm, humid tropical countries. Poor sanitation and hygiene help spread of disease. Autoinfection is known to occur. Stool examination is the first line of investigation. Thiabendazole is the drug of choice.
10. *T. trichiura* infection is common in tropics. It causes gastrointestinal upsets, indigestion, malnutrition, and generally poor health. Feces examination reveals typical barrel-shaped eggs. Eosinophilia is common. Pyrantel pamoate is the treatment of choice.
11. Tapeworms are associated with consumption of raw or undercooked nonvegetarian food (beef, pork, fish). Stool examination reveals the characteristic eggs and at times proglottids. Tapeworms cause malnutrition and megaloblastic anemia. Praziquantel is the drug of choice.

12. Hydatid cysts are uncommon, found in animal-rearing communities.
13. Filariasis is yet another parasite spread by mosquito bite. Elephantiasis of the vulva can cause dystocia. DEC is the drug of choice.
14. Hepatitis during pregnancy can have grave consequences. The commonest types encountered are HAV, HBV, and HBE. Vertical/postnatal transmission occurs in 50% of affected mothers. The incidence of HBsAg positivity in the Indian population is 4–6%. Approximately 1.5% of babies born in India are HBsAg positive and in need of immunization (active and passive) of neonate at birth. Outbreaks of epidemics of HAV and HEV cause infectious hepatitis. These are associated with fatality rates of 15–20%. Perinatal mortality is high due to low birth weight, prematurity, and vertical transmission of disease.
15. There has been a resurgence of tuberculosis in India. Large-scale population migration from rural areas to urban slums, poverty, overcrowding, poor sanitation, malnutrition, and the appearance of drug-resistant strains of *Mycobacterium* has led to the upsurge of the disease. In addition, with the spread of HIV infection the incidence of tuberculosis has increased concomitantly. Pregnant women are more susceptible. Diagnosis is based on clinical assessment coupled with investigations like sputum examination and culture, Mantoux test, chest x-ray, serological tests, PCR testing. The three-drug regimen (isoniazid, rifampicin, and pyrazinamide along with pyridoxine) has been found to be effective. In occasional patient in early pregnancy who does not respond to therapy, pregnancy termination may need consideration. Vertical transmission has been well documented.

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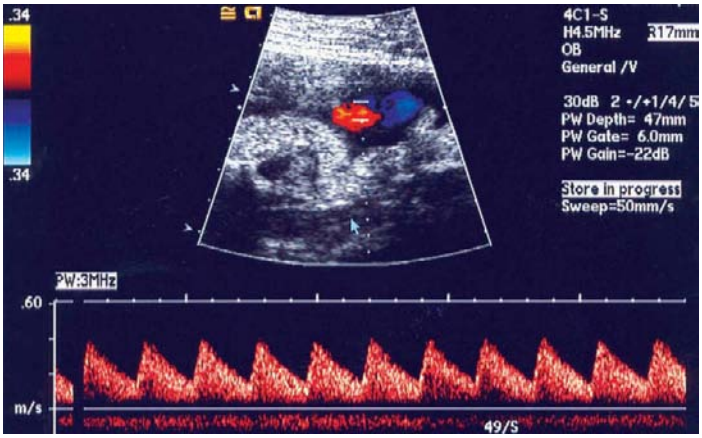

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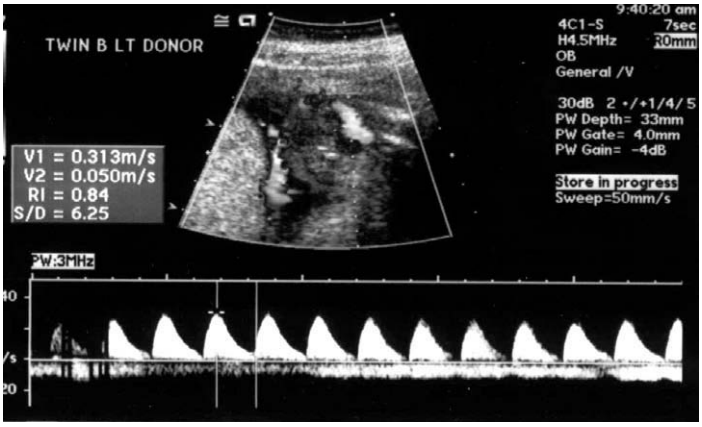

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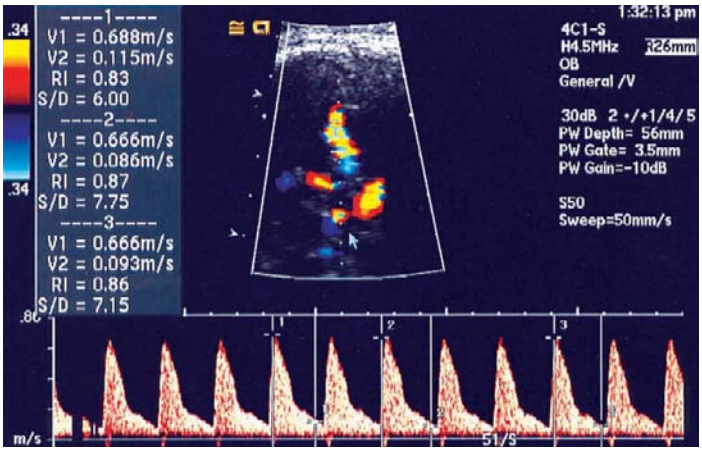
Figure 1-7. Normal and abnormal umbilical artery waveforms. **A**, Normal umbilical waveforms: normal diastolic flow. **B**, Abnormal umbilical waveforms: decreased to absent diastolic flow.



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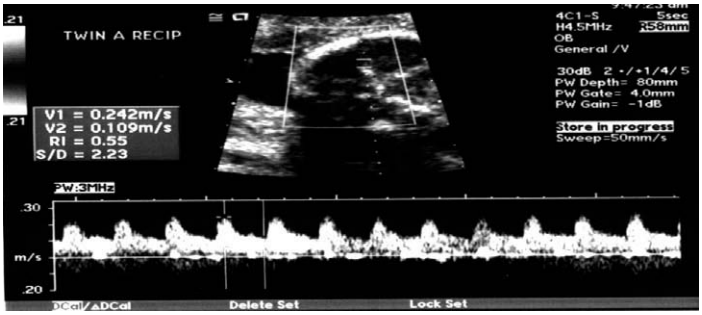

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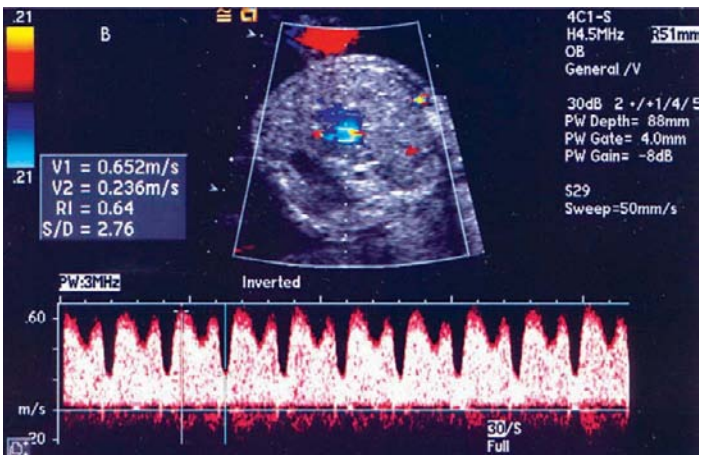
Figure 1-8. Changes in middle cerebral artery diastolic flow reflecting centralization of flow. **A**, Normal MCA Doppler waveforms showing high resistance to flow. **B**, Abundant diastolic flow in the middle cerebral artery waveforms indicating low resistance and centralization of flow.



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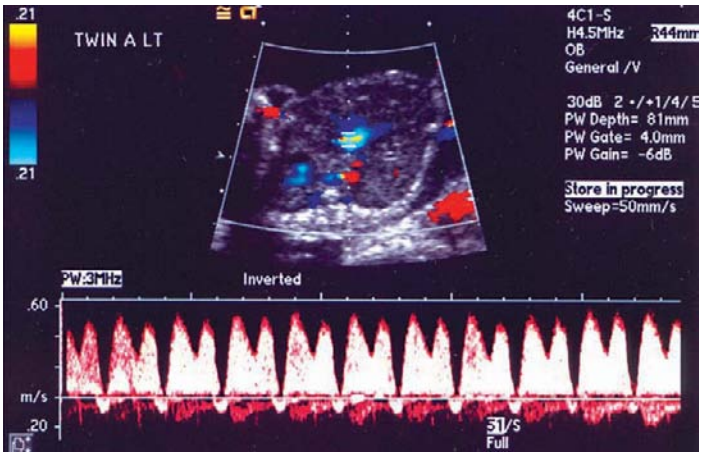

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Figure 1-10. Normal and abnormal ductus venosus waveforms. **A**, Normal ductus venosus waveforms. **B**, Abnormal ductus venosus waveforms showing interrupted and reversed forward flow during atrial systole.

COLOR PLATES

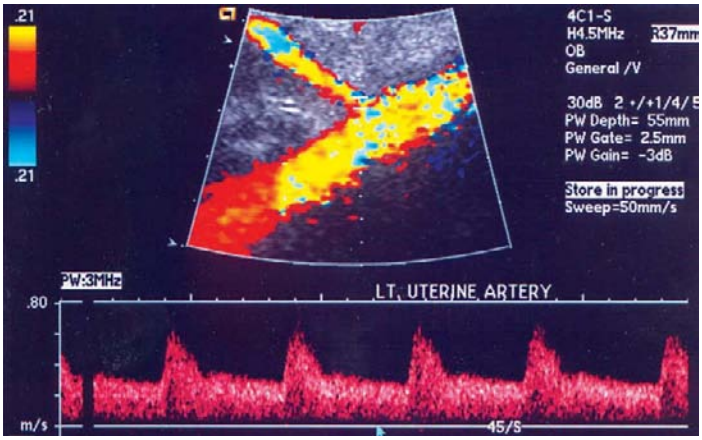


Figure 1-11. Normal uterine artery Doppler waveforms.

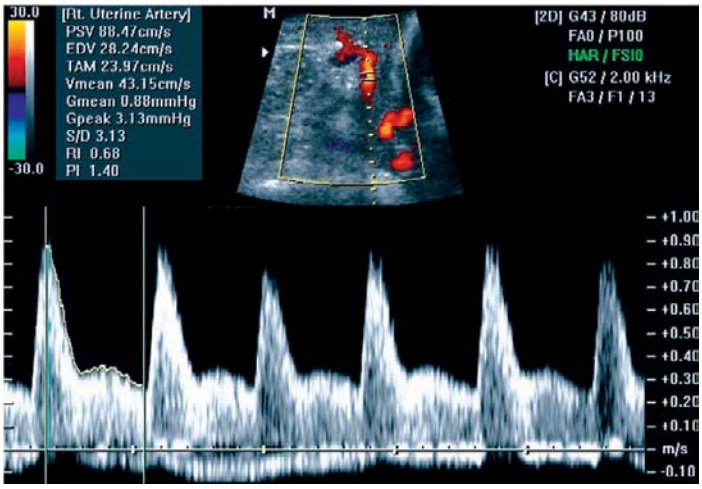
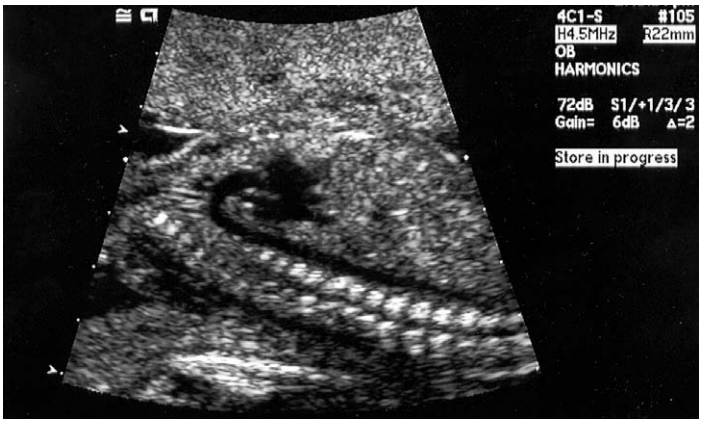


Figure 1-12. Uterine artery waveforms showing early diastolic notching.



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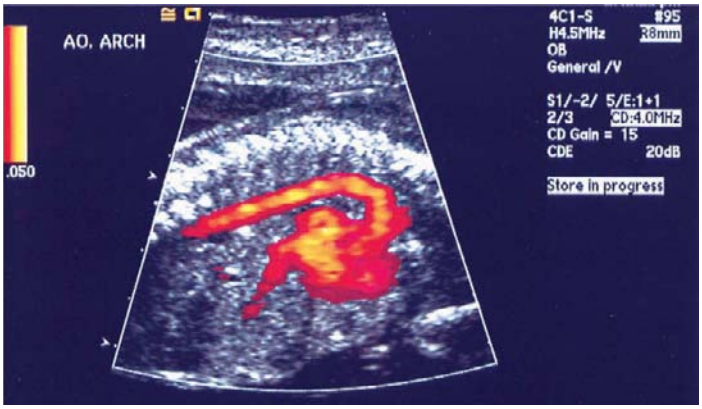

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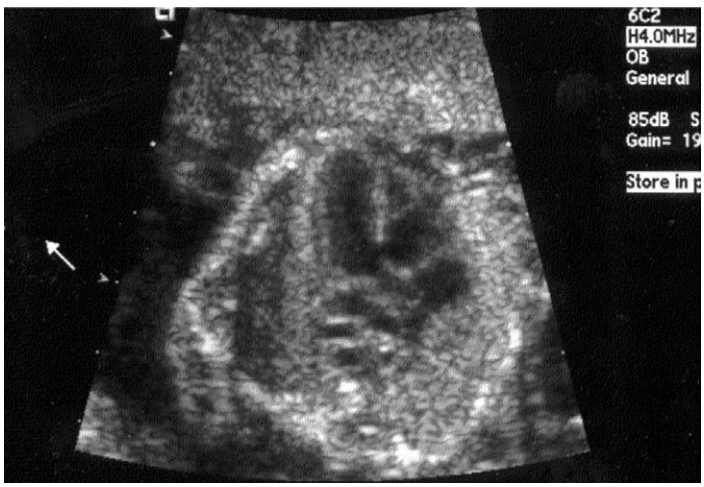
Figure 3-11. A, Aortic arch. B, Color Doppler view of the aortic arch.



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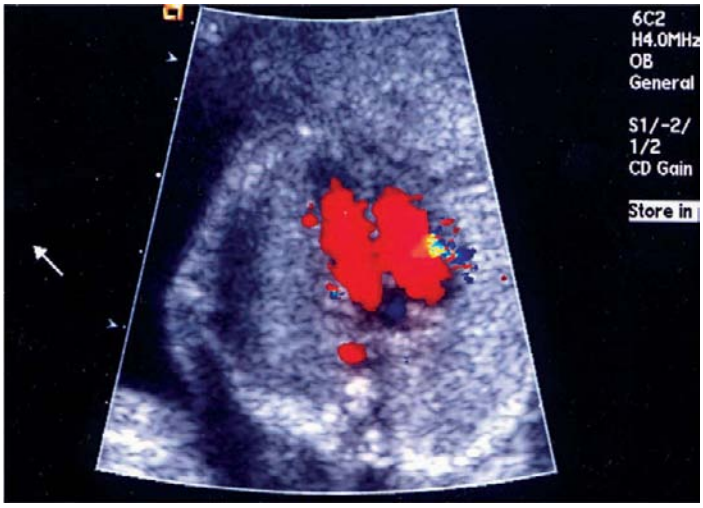

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Figure 3-16. A, Ventricular septal defect. B, Color Doppler image of ventricular septal defect.

COLOR PLATES

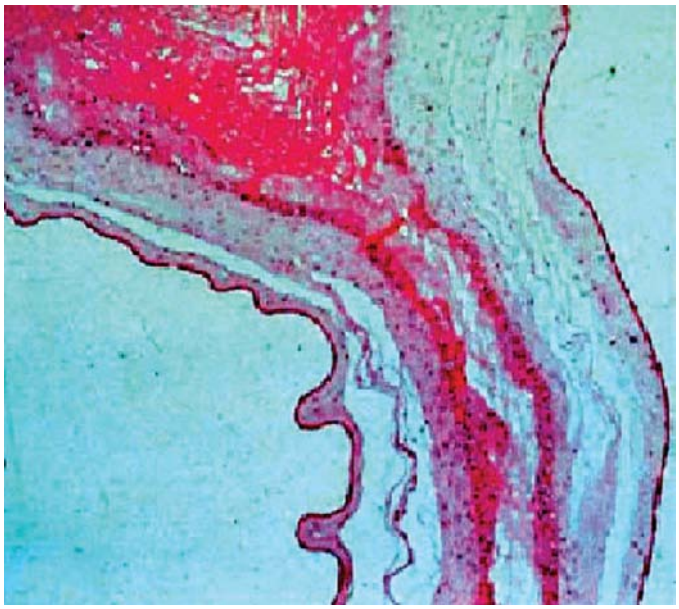

Figure 12-1. Histology of dichorionic pregnancy.

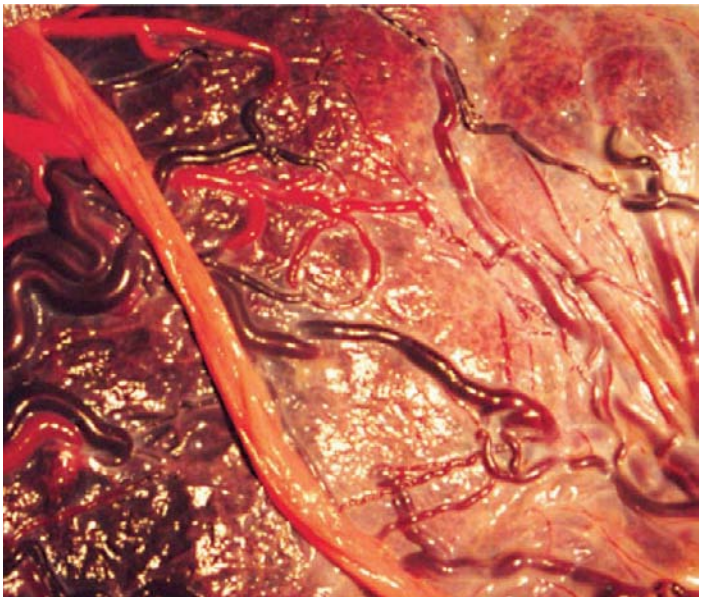

Figure 12-3. Deep arteriovenous anastomosis. An artery and a vein run in opposite direction on the surface of a placental cotyledon.

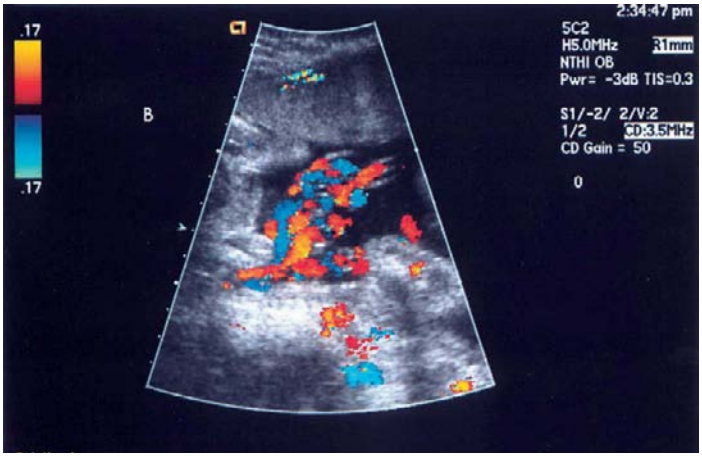

Figure 12-4. Color Doppler ultrasound image of entangled umbilical cords in monoamniotic twin pregnancy.

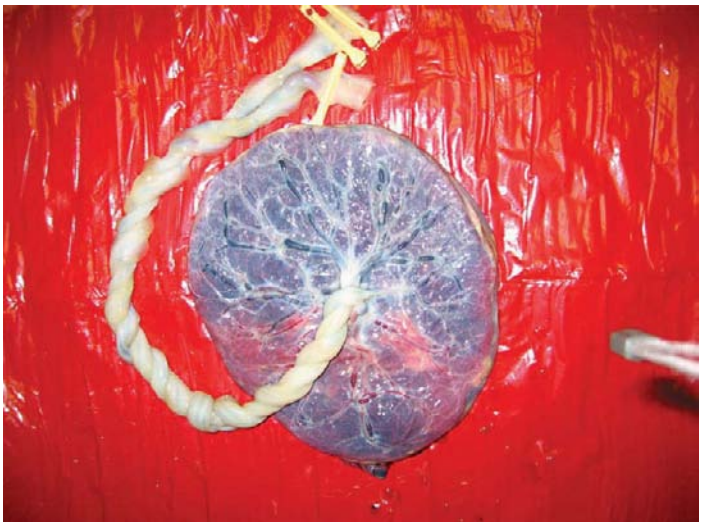

Figure 12-5. Severe entanglement of the umbilical cords in monoamniotic twin pregnancy.