Arias'

Practical Guide to HIGH-RISK PREGNANCY & DELIVERY

A South Asian Perspective

4th edition

Editors:

Amarnath Bhide

Sabaratnam Arulkumaran

Kaizad R. Damania

Shirish N. Daftary

Arias' Practical Guide to High-Risk Pregnancy and Delivery

A South Asian Perspective

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Fourth Edition

Amarnath Bhide MD, FRCOG
Consultant
Obstetrics and Fetal Medicine
St. George's Healthcare NHS Trust
London

Sabaratnam Arulkumaran PhD, DSc, FRCS, FRCOG
Foundation Professor of O&G
St. George's - University of Nicosia Medical School
Visiting Professor
Global Health, Imperial College, London
Professor Emeritus of O&G
St. George's University of London
London

Kaizad R. Damania MD, DNB, DGO, FCPS, DFP
Professor and Unit Head
Department of Obstetrics and Gynaecology
Nowrosjee Wadia Maternity Hospital and
Seth G. S. Medical College
Mumbai

Shirish N. Daftary MD, DGO, FICOG
Professor Emeritus, Former Dean and Medical Advisor
Nowrosjee Wadia Maternity Hospital
Retd. Professor of Obstetrics & Gynaecology
Seth G.S. Medical College, Mumbai
Former Jt. Associate Editor
Journal of Obstetrics and Gynaecology of India
Past President, Federation of Obstetrics & Gynaecology of India (FOGSI)

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Project Manager: Nayagi Athmanathan
Project Coordinator: Shravan Kumar
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In Loving memories of
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To our immediate and extended families,
which include our
family members, colleagues,
friends, students and patients

Preface

The third edition of this book was popular with students in training and practitioners alike. The edition had to be reprinted five times since it was first printed in 2008. It presented concisely the present-day trends in the management of pregnant women, and provided up-to-date and evidence-based guidance for the management of high-risk pregnancies. The hallmark of Medicine is advances. A newer edition was urgently required to incorporate changes in the practice of clinical medicine. The fourth edition has two new editors in addition to the previous two. Most of the chapters have been completely re-written.

Dr. Bhide left as Professor of Obstetrics and Gynaecology from Seth GS Medical College and Nowrosjee Wadia Maternity Hospital, Mumbai, and presently works as a Consultant in Obstetrics and Fetal Medicine at St George's Hospital, London. Professor Sir Sabaratnam Arulkumaran is an Emeritus Professor of Obstetrics and Gynecology at St. George's, University of London, a popular teacher, author of several peer-reviewed papers and books. He has also been the President of the Royal College of Obstetricians and Gynecologists of UK. Currently, he is the president of International Federation of Obstetricians and Gynecologists (FIGO) as well as British Medical Association. Dr. Damania is a Professor of Obstetrics and Gynaecology at the Nowrosjee Wadia Maternity Hospital and Seth GS Medical College, and has a wide clinical experience of several years. Professor Shirish N. Daftary retired as Professor of Obstetrics and Gynaecology from Seth GS Medical College and as the Dean of Nowrosjee Wadia Maternity Hospital, Mumbai. He has been practicing the art for over 40 years, and remains a very popular teacher, advisor and author.

The editors have managed to persuade leaders in the field to write for this edition. The chapters are authored by researchers working on the coal-face. Their first-hand experience, knowledge, wisdom and hard work are evident in this edition. Every attempt has been made to use current best evidence while preparing the manuscript. The contents represent state of the art reviews on common and important complications encountered in pregnancy. The addition of Indian experience lends additional information about experiences of practitioners in India, and will be useful to readers of the subcontinent.

Amarnath Bhide
Sabaratnam Arulkumaran
Kaizad R. Damania
Shirish N. Daftary

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Contributors

Amarnath Bhide MD, FRCOG
Consultant
Department of Obstetrics and Gynaecology
Fetal Medicine Unit
St. George's Hospital, London
Scientific Editor
BJOG: An International Journal of Obstetrics and Gynecology

Ameya C. Purandare MD, DNB, FCPS, DGO, DFP, MNAMS, FICMCH, FICOG, Fellowship in Gyn. Endoscopy (Germany)
Consultant Obstetrician and Gynaecologist
Purandare Hospital, KJ Somaiya Medical College, Bombay Hospital and Medical Research Centre, Masina Hospital, Naigaon Municipal Maternity Home, Mumbai

Amol P. Pawar MD, DGO, FCPS
Associate Professor
Department of Obstetrics and Gynaecology
Nowrosjee Wadia Maternity Hospital and Seth G. S. Medical College
Mumbai

Amy Coates MBBS, BSc
Fetal Medicine Unit, Academic Department of Obstetrics and Gynaecology,
St. George's Hospital Medical School, London

Ann Koschorke MRCOG
Specialist Registrar in Obstetrics & Gynaecology
Department of Obstetrics & Gynaecology,
Epsom & St. Helier University Hospitals NHS Trust,
Surrey, UK

Asma Khalil MD, MRCOG, MSc(Epi), MB, BCh
Consultant
Obstetrics & Fetal Medicine
Fetal Medicine Unit, Academic Department of Obstetrics and Gynaecology,
St. George's Hospital Medical School, London

Austin Ugwumadu PhD, FRCOG
Consultant & Sr. Lecturer
Obstetrics and Gynaecology
St. George's Hospital
London

Avinash Bhatt MD, MRCOG (UK)
Consultant
Obstetrics and Gynaecology
Dr Bhatt's Hospital, Mumbai

Edwin Chandraharan MBBS, MS (Obs & Gyn), DFFP, DCRM, MRCOG
Consultant Obstetrician and Gynaecologist
St. George's Healthcare NHS Trust
London

Francesco D' Antonio MD, PhD
Clinical Research Fellow
Fetal Medicine Unit
St. George's Hospital, London

Gargee Pandit MS
Registrar
Seth GS Medical College and Nowrosjee Wadia Maternity Hospital
Mumbai

Giorgio Pagani MD
Consultant
Obstetrics and Fetal Medicine
University Hospital Breschia, Italy

Hemantha Senanayake MBBS, MD, FRCOG
Professor and Head
Department of Obstetrics and Gynaecology
Faculty of Medicine, University of Colombo
Colombo, Sri Lanka

Kaizad R. Damania MD, DNBE, FCPS, DGO, DFP
Professor and Unit Head
Department of Obstetrics and Gynaecology
Nowrosjee Wadia Maternity Hospital and Seth GS Medical College
Mumbai

Kim Hinshaw MBBS, FRCOG
Consultant Obstetrician and Gynaecologist
City Hospitals Sunderland NHS Foundation Trust
Sunderland, Tyne and Wear, UK

Lilian Alabi-Isama MBBS, DFRSH, MRCOG
Specialist Registrar in Obstetrics and Gynaecology
St. George's Hospital
London

Michael Egbor PhD, MRCOG
Consultant Obstetrician & Gynaecologist
Department of Obstetrics & Gynaecology,
Epsom & St. Helier University Hospitals NHS Trust
Surrey, UK

Milind S. Phadke MD, DM (Cardiology)
Asst. Professor
Department of Cardiology
GS Medical College and KEM Hospital, Mumbai
Consultant Cardiologist
Pulse Cardiac Center, Mumbai

Muhunthan K MBBS, MS, FSLCOG, MRCOG
Sr. Lecturer & Consultant
Head of Obstetrics and Gynaecology
University of Jaffna
Sri Lanka

Nirmala Chandrasekharan MRCOG, FRCP
Fellow
Maternal and Fetal Medicine
Department of Obstetrics & Gynaecology
Mount Sinai Hospital, Toronto, Canada

Parikshit Dahyalal Tank MD, DNB, FCPS, DGO, DFP, MNAMS, MICOG, MRCOG
Honorary Clinical Associate
Nowrosjee Wadia Maternity Hospital
Consultant
Ashwini Maternity and Surgical Hospital, Center for Endoscopy and ART
Mumbai

Rohana Haththotuwa MBBS, FSLCOG, FRCOG
Visiting Consultant Obstetrician and Gynaecologist & Director
Ninewells Hospital for Women
Colombo, Sri Lanka

Sabaratnam Arulkumaran PhD, DSc, FRCS, FRCOG
Professor Emeritus
Dept. of Obstetrics and Gynecology
St. George's Hospital and University of London
London

Sadia Muhammad MBBS, MRCOG
Clinical Fellow in Obstetrics and Gynaecology
St. George's Healthcare NHS Trust,
London

Sara Kenyon PhD, MA, RM
Sr. Lecturer
Public Health Building
School of Health and Population Sciences
Edgbaston Campus, University of Birmingham
Edgbaston, UK

Shirish N. Daftary MD, DGO, FICOG
Professor Emeritus, Former Dean and Medical Advisor
Nowrosjee Wadia Maternity Hospital
Retd. Professor of Obstetrics & Gynaecology
Seth G.S. Medical College, Mumbai
Former Jt. Associate Editor
Journal of Obstetrics and Gynaecology of India
Past President, Federation of Obstetrics & Gynaecology of India (FOGSI)

Tessa Homfray FRCPCH
Consultant Clinical Geneticist
Medical Genetics
St. George's Healthcare NHS Trust
London

Tiran Dias MRCOG (UK), MD-Research (London), Dip (Fetal Med.) UK
Consultant Obstetrician and Gynaecologist
District General Hospital
Ampara, Sri Lanka

Vandana Bansal MD, DGO, DNB, MRCOG, FNB (High-risk pregnancy and perinatology)
Associate Professor
Department of Obstetrics and Gynaecology
Nowrosjee Wadia Maternity Hospital & Seth GS Medical College
Mumbai

Vedrana Caric MRCOG
Consultant Obstetrician & Gynecologist
James Cook University Hospital
Middlesborough, UK

Vikram Sinai Talaulikar MD, MRCOG
Clinical Research Fellow
University College Hospital
London

Vinay Jaiswal MD (Med.), DM (Cardio.)
Sr. Registrar
Department of Cardiology
GS Medical College and KEM Hospital
Mumbai

Contents

Chapter 1

Prenatal Diagnosis of Chromosomal Abnormalities

Asma Khalil and Amy Coates

Chapter Outline

INTRODUCTION

Chromosomal abnormalities arise when the normal complement of 46 chromosomes that produces a karyotype is altered, usually during cell division, either by an increase or reduction in the number of chromosomes. Many chromosomal abnormalities are not compatible with life and often result in spontaneous miscarriage. Some chromosomal abnormalities are compatible with life and produce very distinct syndromes. Approximately 1% of children born in the UK each year have a chromosomal abnormality or genetic disorder.[1] The role of health care professionals is to provide education and counselling about screening and diagnostic testing for chromosomal abnormalities to all pregnant women. This enables pregnant women and their partners to make decisions on whether to opt for screening and the implications of a positive result.

TYPES OF CHROMOSOMAL ABNORMALITIES

There are two ways in which chromosome abnormalities occur:

Numerical Abnormalities

Numerical abnormalities occur due to the addition or deletion of an entire single chromosome. When there is addition of a complete chromosome to a pair resulting in three copies, this is termed *trisomy*. When there is complete loss of a chromosome leading to only one chromosome instead of a pair, this is known as *monosomy*. A minority of the numerical abnormalities may support fetal development to term. This is often due to the fact that the additional chromosomes, such as the Y chromosome, 13, 18 and 21 chromosomes have relatively few genes or because there is a natural mechanism to adjust gene dosage as seen in the X chromosome. The common numerical abnormalities are shown in Table 1.1.[1]

Structural Changes

This occurs due to the deletions (when part of a chromosome is deleted or missing), duplications (when extra genetic material is added) and translocations (when part of one chromosome is transferred to another).

Most of these errors occur within either the ovum or the sperm resulting in the genetic abnormality being present in

TABLE 1.1 Numerical Chromosome Abnormalities

Chromosomal Abnormality	Genetic Syndrome	Incidence Per 10,000 Births
Trisomy 21	Down	15
Trisomy 18	Edward	3
Trisomy 13	Patau	2
Monosomy X	Turner	2 (female)
XXY	Klinefelter	10 (male)

every cell in the body. However, some errors occur after fertilization and do not affect the chromosomes in every cell in the body, leading to a condition known as *mosaicism*. Although most chromosomal abnormalities occur 'de novo', some can be inherited.

SCREENING

Screening tests for chromosomal abnormalities are most often carried out during the first or second trimester. First trimester screening, where available, is preferable because it leads to earlier diagnosis with the option of earlier termination of pregnancy or, more often, earlier reassurance for the parents.

First Trimester

First trimester screening for chromosomal abnormalities is currently carried out between 11^{+0} and 13^{+6} weeks' gestation, equivalent to a crown rump length (CRL) of 45–84mm. Various methods are used which can also be combined to improve the sensitivity of the screening. These tests include nuchal translucency (NT), serum beta-hCG, serum pregnancy associated plasma protein A (PAPP-A) and maternal age (Box 1.1).

In the last decade, there has been a shift from second trimester screening and diagnosis of chromosomal abnormalities to first trimester. There is also emerging evidence that screening at 11–13 weeks of gestation is useful not only for the assessment of chromosomal abnormalities, but also for the prediction of other serious and treatable complications of pregnancy, including preterm birth, pre-eclampsia, gestational diabetes mellitus, stillbirth, fetal growth restriction and macrosomia.[2]

BOX 1.1 First Trimester Screening

Carried out

- Between 11^{+0} to 13^{+6} weeks' gestation.
- Or with crown-rump length (CRL) of 45–84mm.

Using

- Maternal age
- Nuchal translucency
- Maternal serum beta-hCG level
- Maternal serum PAPP-A level
- Additional ultrasound markers

Nuchal Translucency

Nuchal translucency (NT) is a measurement of the fluid in the neck region on first trimester ultrasound (Fig. 1.1). It was described by Nicolaides and co-workers in 1992 as being a sensitive marker for the chromosomal anomalies.[3] Nuchal translucency is increased in fetuses with chromosomal abnormalities. However, it is also increased with congenital heart defects (CHD), some genetic syndromes and other structural abnormalities such as exomphalos and congenital diaphragmatic hernia. Nuchal translucency varies with gestational age and begins to be reabsorbed after 13 weeks' gestation. The position of the fetus in the uterus, with regard to imaging, and measurement also changes at about 13 weeks' gestation, which limits the utility of this screening method beyond 14 weeks.

It is imperative that accurate measurements of the NT are obtained. The ultrasound should be performed by an appropriately trained individual. The criteria for accurate measurement of NT are shown in Box 1.2.[4]

Maternal Age

Advanced maternal age increases the likelihood of having a pregnancy affected by a chromosomal abnormality.[5] The risk of trisomies 13, 18 and 21 all increase with advancing maternal age. However, the risk of Turner syndrome is not altered with maternal age. The risk of a chromosomal anomaly is also related to gestational age. This is due to spontaneous miscarriage of aneuploidic fetuses leading to a decrease in probability with increasing gestational age of the remaining ongoing pregnancies. Table 1.2 shows the risk of trisomies according to maternal age and gestational age.[4]

In 1970, age of around 5% of the pregnant population in the United Kingdom was over 35. However, this figure has been rising steadily and is now over 20%.[4] The detection rate (DR) of trisomy 21 in a woman over 35, using maternal age only, is 30% for a false positive rate (FPR) of approximately 5%. By combining maternal age and NT, the DR increases to 75–80%. Adding additional parameters including biochemical markers further increases the sensitivity.

Biochemical Markers

The current screening programmes in the United Kingdom use both beta-hCG, a sub-unit of the glycoprotein human chorionic gonadotrophin, and PAPP-A, both produced by the placenta. These are combined with the NT and maternal

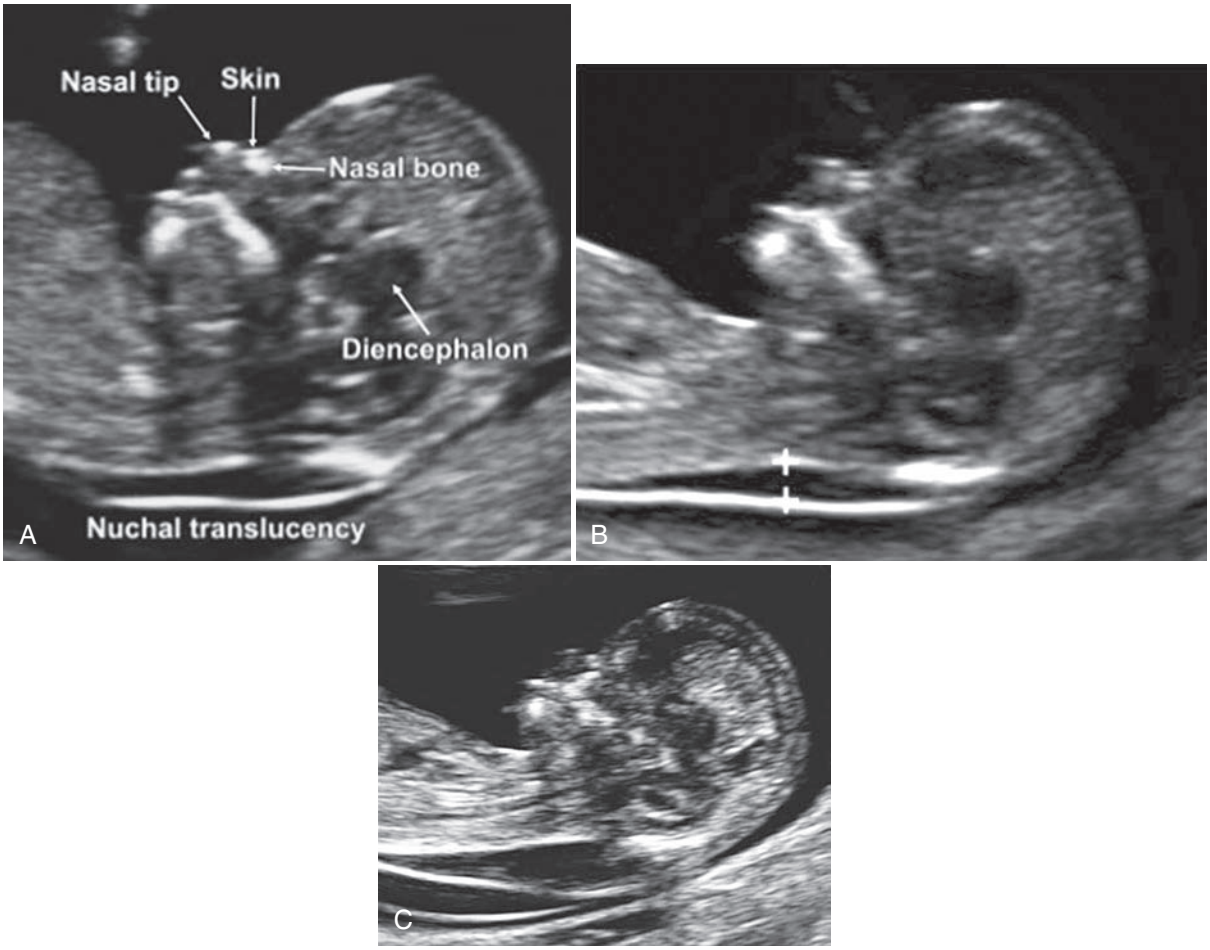


FIGURE 1.1 Midsagittal view of the face (**A**), Normal nuchal translucency (**B**), Increased nuchal translucency (**C**). *(Adapted from "www.fetalmedicine.com").*

BOX 1.2 Criteria for Accurate Measurement of Nuchal Translucency

- The crown-rump length should be 45–85mm.
- Mid-sagittal view of head and upper thorax, occupying the whole screen, should be obtained.
- The head should be in neutral position in line with the spine. Hyperextension falsely increases nuchal translucency measurement and flexion falsely decreases nuchal translucency measurement.
- The fetal neck skin should be differentiated from the amnion, shown by fetal movements.
- The widest part of nuchal translucency should be measured
- The callipers for measurement should be placed on the inner borders of the white lines (skin and skull).
- The nuchal translucency measurement should be repeated and the maximum reading that meets the above criteria should be used.

age in first trimester screening to calculate the risk of fetal chromosomal abnormality.

Beta-hCG is increased in fetuses with trisomy 21 from the end of the first trimester and throughout the second trimester, making it a useful serum marker in both the first and second trimesters. It is decreased in the other trisomies, that is trisomy 13 and 18, as shown in Table 1.3.[6] Maternal factors such as ethnicity, weight, smoking status and method of conception can alter the biochemical markers. These changes must be taken into account and the marker values are adjusted statistically using the multiples of the median (MoM).

In the first trimester, PAPP-A is reduced in the majority of fetuses with aneuploidy. The difference in PAPP-A levels between aneuploidic and normal pregnancies decreases with gestational age, so it is a useful biochemical marker only before 14 weeks.[7] The PAPP-A MoM values in different trisomies are shown in Table 1.3.

It has been suggested that measuring maternal serum PAPP-A at 9 weeks, then performing the NT scan and beta-hCG levels at 12 weeks' gestation could increase the sensitivity of screening for Down syndrome to 95%.[4] However,

TABLE 1.2 Maternal Age and the Risk of Having a Fetus with Trisomies

Maternal Age (Years)	Gestation (Weeks)	Risk of Trisomy 21	Risk of Trisomy 18	Risk of Trisomy 13
20	12	1 in 1000	1 in 2500	1 in 8000
20	39/term	1 in 1500	1 in 18000	1 in 42000
35	12	1 in 250	1 in 600	1 in 1800
35	39/term	1 in 350	1 in 4000	1 in 10000

TABLE 1.3 Serum Beta-hCG and PAPP-A Levels at 11–13 Weeks in Pregnancies Complicated with Trisomies

Beta-hCG	Median MoM	PAPP-A	Median MoM
Normal karyotype	1.0	Normal karyotype	1.0
Trisomy 21	2.0	Trisomy 21	0.5
Trisomy 18	0.2	Trisomy 18	0.2
Trisomy 13	0.5	Trisomy 13	0.3

this would require the woman to visit the screening centre on more than one occasion and have two separate blood tests. This might lead to decreased compliance resulting in reduced detection of chromosomal abnormalities.[4]

Additional First Trimester Ultrasound Markers for Chromosomal Abnormalities

Other first trimester ultrasound markers, which have been reported in association with chromosomal abnormalities include the absence of the nasal bone (Fig. 1.2), reversed a-wave in the ductus venosus [Fig. 1.3(a)] and tricuspid regurgitation [Fig. 1.3(b)]. These features can all be observed by trained sonographers at the NT scan. When these additional ultrasound markers are combined with maternal age, NT and serum biochemistry, the DR can be increased from 93% to 96%, while the FPR is decreased from 5% to 2.5%.[5,8] Individual risk-orientated two-stage screening for trisomy 21 can potentially identify, in the first trimester of pregnancy, more than 90% of affected fetuses for a FPR of 2–3% (Fig. 1.4).[9]

Trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome) are the second and third most common trisomies after trisomy 21. Both trisomies 18 and 13 are lethal and the majority of affected fetuses will die during the course of pregnancy or within the first few days of life. Just as with Down syndrome, the risk for trisomies 18 and 13 increases with the maternal age and decreases as the pregnancy advances (Fig. 1.5) – the rate of fetal death between the 12th and 40th week is around 80%. Fetuses affected by trisomies 18 and 13 are more likely to have the ultrasound markers described above, including increased NT, absent nasal bone, reversed a-wave in the ductus venosus and tricuspid regurgitation (Fig. 1.5). In trisomy 13, the fetal heart rate (FHR) is substantially increased and is above the normal range in 85% of cases. In both trisomies 18 and 13, both free β-hCG and PAPP-A are reduced to around one-third of the normal (Fig. 1.5).

A wide range of structural abnormalities have been detected in the first trimester in fetuses with chromosomal abnormalities. These include cardiac defects such as atrioventricular septal defect in trisomy 21, exomphalos in trisomies 18 and 13, holoprosencephaly in trisomy 13 and megacystis in trisomies 18 and 13 (Fig. 1.6).

Special Circumstances

Women with HIV

Beta-hCG levels in women who are HIV positive and are on treatment have been shown to be lower than women without HIV and those with HIV not receiving treatment. In contrast, PAPP-A levels and NT are not affected by HIV status.[10] This research contradicts a previous study suggesting that PAPP-A levels are also altered.[11] Further research is clearly needed but this information should prompt discussion and research into current guidelines when screening women who are HIV positive and receiving antiretroviral treatment, as screening could either underestimate the risk of trisomy 21 or over estimate that of trisomies 13 and 18.[10]

Second Trimester Screening

There are three main tests used in screening for chromosomal abnormalities in the second trimester, namely detailed ultrasound, the triple test and the quadruple test (Box 1.3). The biochemical markers used in the triple test are beta-hCG, alpha fetoprotein (AFP) and free estriol. The quadruple test adds in inhibin A.

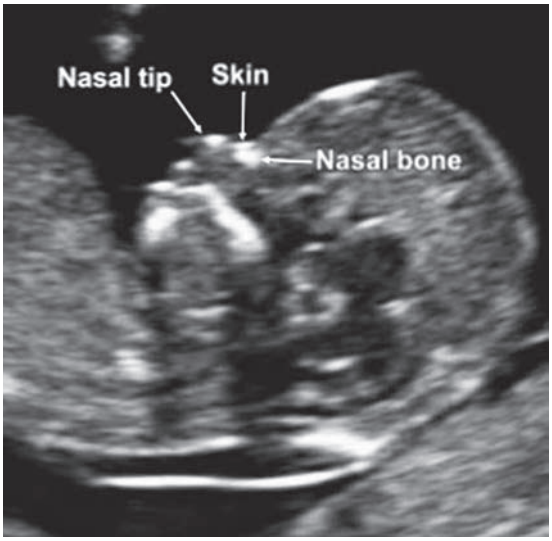
Biochemical Markers

Beta-hCG

In normal pregnancy, free beta-hCG peaks at 15 weeks' gestation, following which there is a rapid decline until

A

- 11^{+0}-13^{+6} weeks / CRL 45–84 mm
- Magnification: head and upper thorax occupy the whole screen
- A mid sagittal section
- The transducer should be parallel to the direction of the nose
- Three distinct lines should be seen:
  - The top line represents the skin
  - The bottom one, which is thicker and more echogenic than the overlying skin, represents the nasal bone
  - A third line in front of the bone and at a higher level than the skin represents the tip of the nose



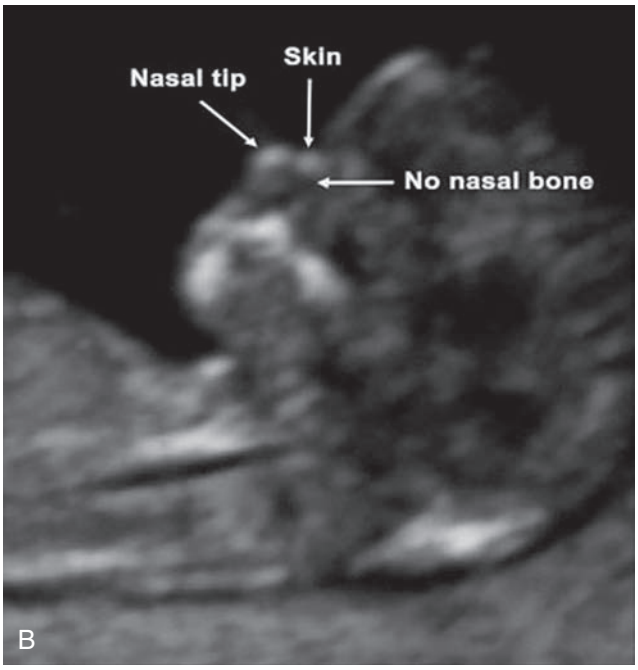


FIGURE 1.2 Nasal bone is present (**A**). Nasal bone is absent (**B**). *(Adapted from "www.fetalmedicine.com").*

17 weeks, then a further gradual fall between 17 and 22 weeks' gestation. In trisomy 21 pregnancies, beta-hCG is increased in both trimesters and for this reason is a useful screening tool.[5]

Alpha Fetoprotein

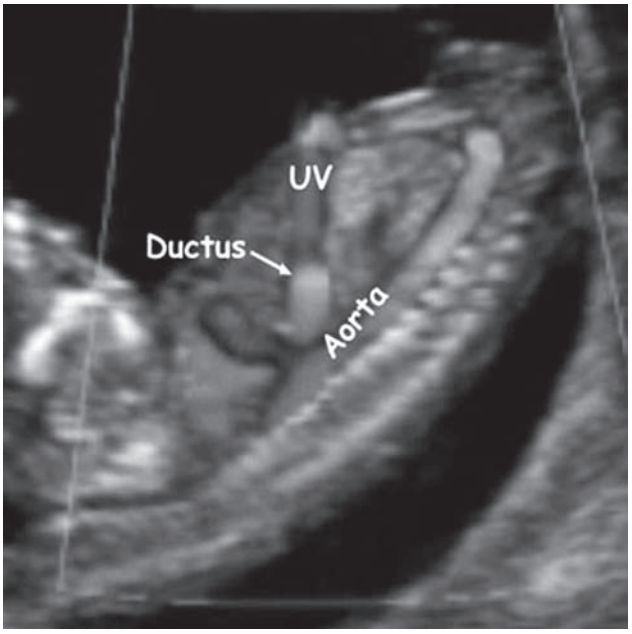
Alpha fetoprotein (AFP) is produced by the liver and gastrointestinal tract of the fetus and excreted in the urine into the amniotic fluid. It was first recognized and used as a marker for open spina bifida fetuses as maternal serum concentrations were found to be higher in these cases. It was also noticed that serum AFP levels are reduced by around 25% in cases of trisomy 21.

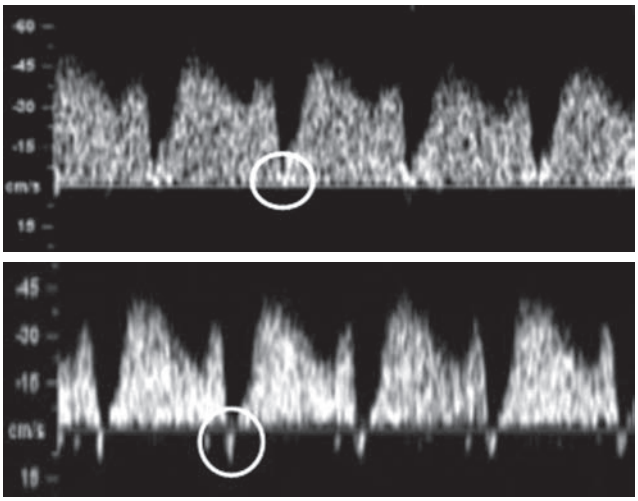
Free Estriol

Free estriol (uE3) is a product of the breakdown in the placenta of dehydroepiandrosterone sulphate, which is produced by the fetal adrenal glands. The concentration is decreased by approximately 25% in pregnancies complicated by trisomy 21.

Inhibin A

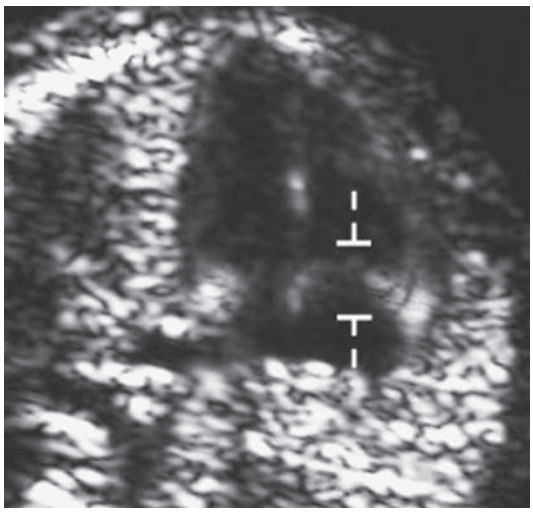
In non-pregnant women, inhibin A is produced by the corpus luteum. The levels of inhibin A are markedly elevated in pregnancy, as it is produced by the placenta to inhibit the release of FSH. First trimester inhibin A levels are similar in aneuploidy and unaffected pregnancies. However, the

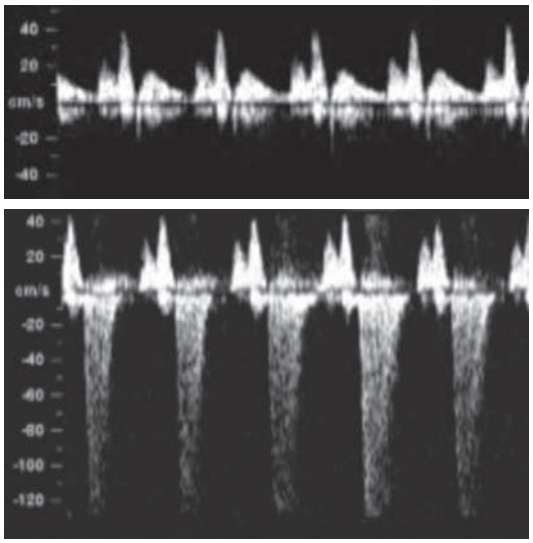




A

- Sample gate: 0.5 mm, Insonation angle: <30°
- Low frequency (50–70 Hz) to see whole waveform
- Sweep speed high (2–3 cm/s) to spread waveforms





B

Sample volume: 3.0 mm
Insonation angle <30°
Interrogate whole valve

FIGURE 1.3 Color Doppler of ductus venosus showing positive and reversed a-wave (**A**). Doppler assessment of tricuspid flow showing normal tricuspid flow and tricuspid regurgitation (**B**). *(Adapted from "www.fetalmedicine.com").*

inhibin A level is elevated in trisomy 21 to around 1.77 MoM in the second trimester. It is not used in calculating the risk for trisomy 18.

Comprehensive Ultrasound

Comprehensive ultrasound, sometimes referred to as a detailed anomaly scan, is carried out between 20 and 22 weeks of gestation. It is not the first choice to screen for chromosome abnormalities but can be used to screen for Trisomy 21 and other chromosome abnormalities in a woman who first presents at this stage. There are many markers that can potentially be seen on the second trimester ultrasound that suggest a possible chromosomal abnormality. These include but are not limited to changes in head

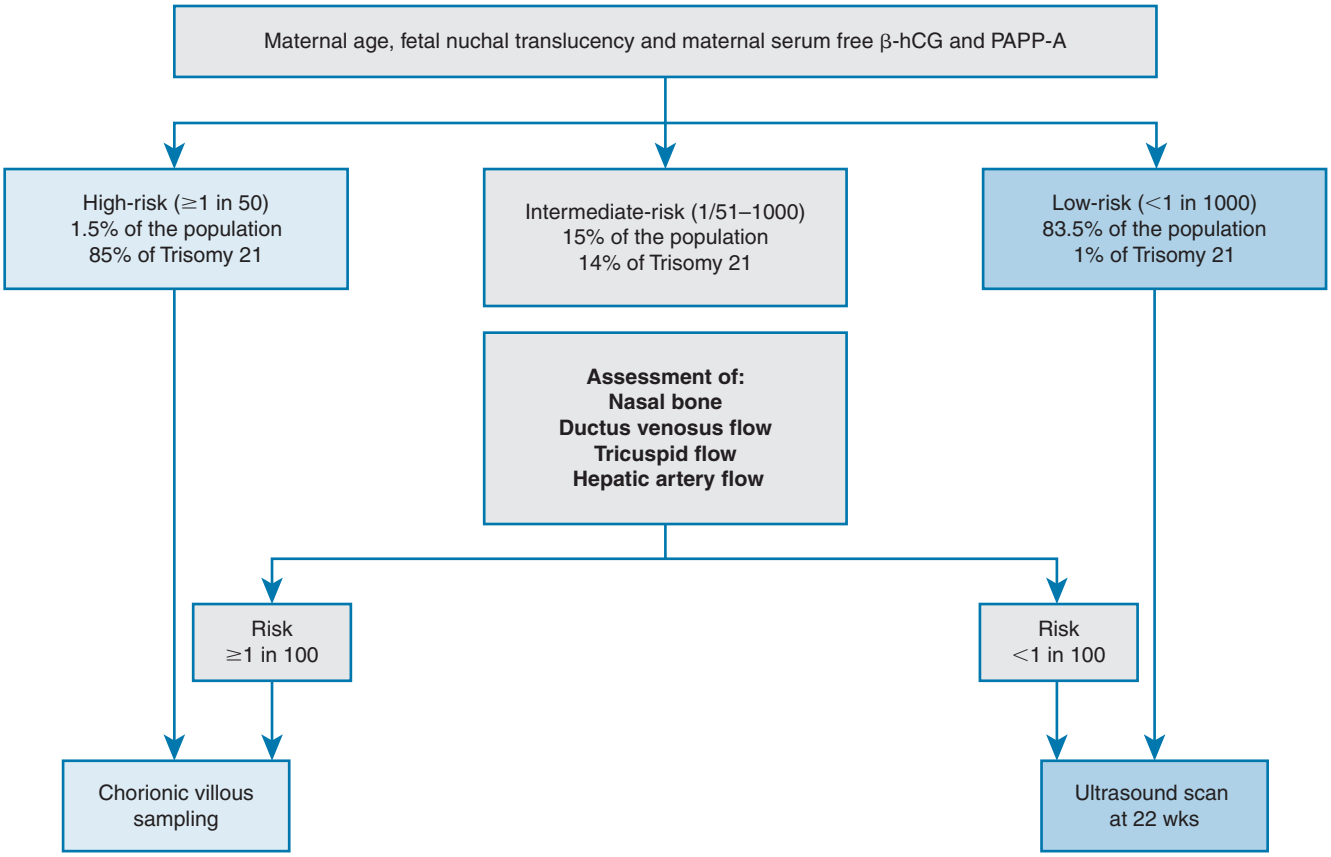
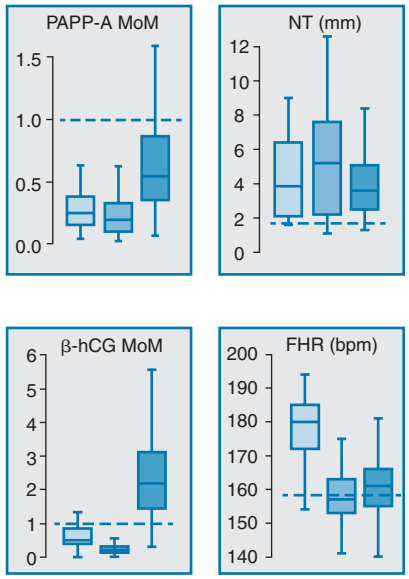


FIGURE 1.4 Individual risk-orientated two-stage screening for trisomy 21. *(Adapted from Reference 9)*

Age (yr)	Risk at 12 weeks T21	T18	T13
20	1100	2500	7800
25	1000	2200	7000
30	650	1500	4600
31	550	1300	4000
32	450	1100	3400
33	400	900	2800
34	300	700	2300
35	250	600	1800
36	200	450	1400
37	150	350	1100
38	120	270	860
39	90	210	650
40	70	160	500
41	50	120	370
42	40	90	280



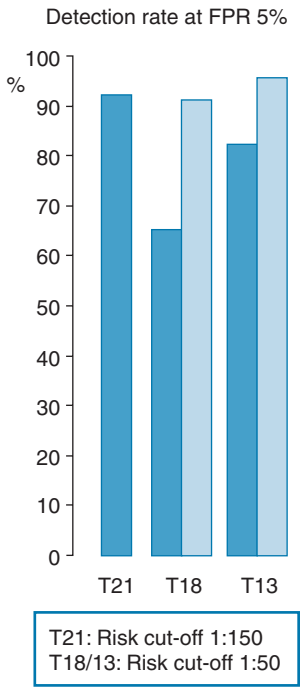


FIGURE 1.5 The risk of trisomy 21 (T21), 18 (T18) and 13 (T13) according to maternal age, nuchal translucency (NT), fetal heart rate (FHR), beta-hCG and pregnancy associated plasma protein A (PAPP-A). The detection rate (DR) and false positive rate (FPR) of 5% for each of these three aneuploidies using the combination of these markers are shown. *(Adapted from Snijders RJ, Sundberg K, Holzgreve W, Henry G, Nicolaides K. Maternal age- and gestation-specific risk for trisomy 21.* Ultrasound Obstet Gynecol *1999;13:167–170.)*

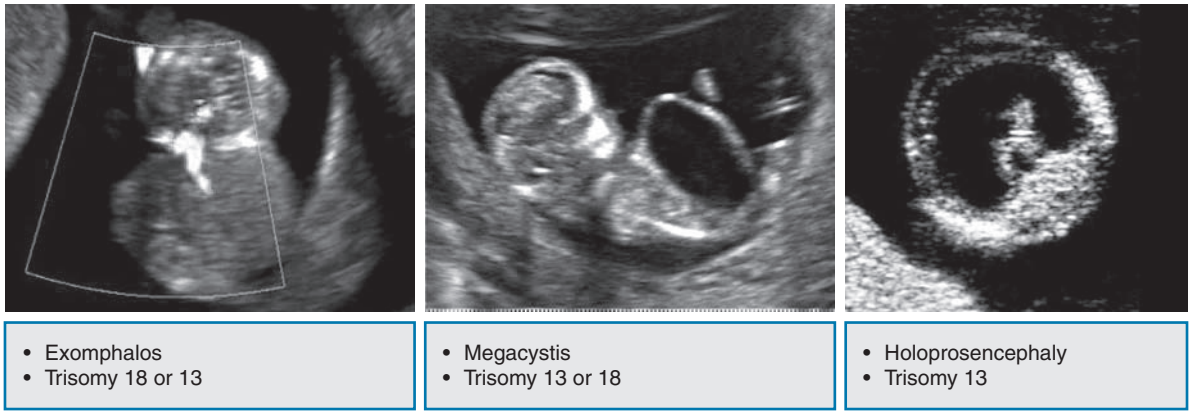


FIGURE 1.6 A wide range of structural abnormalities have been detected in the first trimester in fetuses with chromosomal abnormalities, e.g., exomphalos in trisomy 18 and 13, holoprosencephaly in trisomy 13 and megacystis in trisomy 18 and 13. *(Source: Reference 13)*

BOX 1.3 Second Trimester Screening

Carried out
- Between 15 and 21 weeks gestation.

Using
- Detailed ultrasound scan
- Maternal serum beta-hCG level
- Maternal serum AFP level
- Maternal serum uE3 level
- Maternal serum inhibin A level

shape, increased nuchal fold thickness, echogenic bowel and foci in the heart, short femur or humerus, absence of or hypoplastic nasal bone, cleft lip, dilated renal pelvis and cord abnormalities. These are sometimes referred to as 'soft markers'. However, the presence of one of these markers does not necessarily indicate a chromosomal anomaly, merely indicates an increased risk. The presence of one or more of these markers at the anomaly scan should prompt referral to a specialist with an interest in fetal medicine.

Nuchal fold thickness in isolation should not be used to alter the risk of aneuploidy, especially Trisomy 21, but is a useful marker when combined with other features observed on ultrasound.[12] The soft markers that increase the likelihood of trisomy 21 are thickened nuchal fold, absent or hypoplastic nasal bone, borderline ventriculomegaly, echogenic bowel, intracardiac echogenic foci, aberrant right subclavian artery (ARSA), mild hydronephrosis and a short femur or humerus (Fig. 1.7).[13] In most cases, if one of these markers appears in isolation there is only a small effect on modifying the pre-test odds for trisomy 21 (Fig. 1.8). However, with ventriculomegaly, nuchal fold thickness and ARSA, there is a 3–4-fold increase in the risk of trisomy 21. If a hypoplastic or absent nasal bone is detected, the risk of trisomy 21 increases 6–7-fold (Fig.1.9).[13]

Triple Test

The triple test includes a combination of the serum markers AFP, uE3 and beta-hCG. The triple test is used to screen for Trisomy 21 and is also useful for screening for trisomy 18. It has become less popular as the accuracy of first trimester screening has improved. The DR of the triple test is approximately 69% for a FPR of 5%.[14]

Quadruple Test

The quadruple test is the most commonly used method for second trimester screening. Its DR is between 81% and 85.8% for FPRs of 7–8.3%, respectively.[15,16]

DIAGNOSTIC TESTING

Diagnostic testing will confirm or exclude a suspected diagnosis of chromosomal abnormality. Adequate counselling about the procedure and its associated risks is essential. The options available to parents after a positive diagnosis of a chromosomal abnormality must also be discussed in advance. Most of the diagnostic tests are invasive and carry a risk of miscarriage. In the first trimester, the only diagnostic test available until recently is chorionic villus sampling (CVS). Diagnostic testing in the second trimester is usually performed using amniocentesis.

Chorionic Villus Sampling

Chorionic villus sampling is usually performed between 11 and 14 weeks' gestation, with cells obtained from the chorion (placenta) for karyotyping. There are two approaches: transabdominal and transcervical (Figs 1.10 and 1.11). Ultrasound imaging is performed to establish the site of the placenta and the shape of the uterus. The risks associated with CVS include fetal loss, post-procedural cramping and spotting, chorioamnionitis, rupture of membranes and isoimmunization of rhesus negative women. An aseptic technique, expert

Second trimester markers for Trisomy 21

- Ventriculomegaly
- Absent or hypoplastic nasal bone
- Increased nuchal fold thickness
- Intracardiac echogenic focus
- Aberrant right subclavian artery
- Hyperechogenic bowel
- Mild hydronephrosis
- Shortening of femur or humerus.

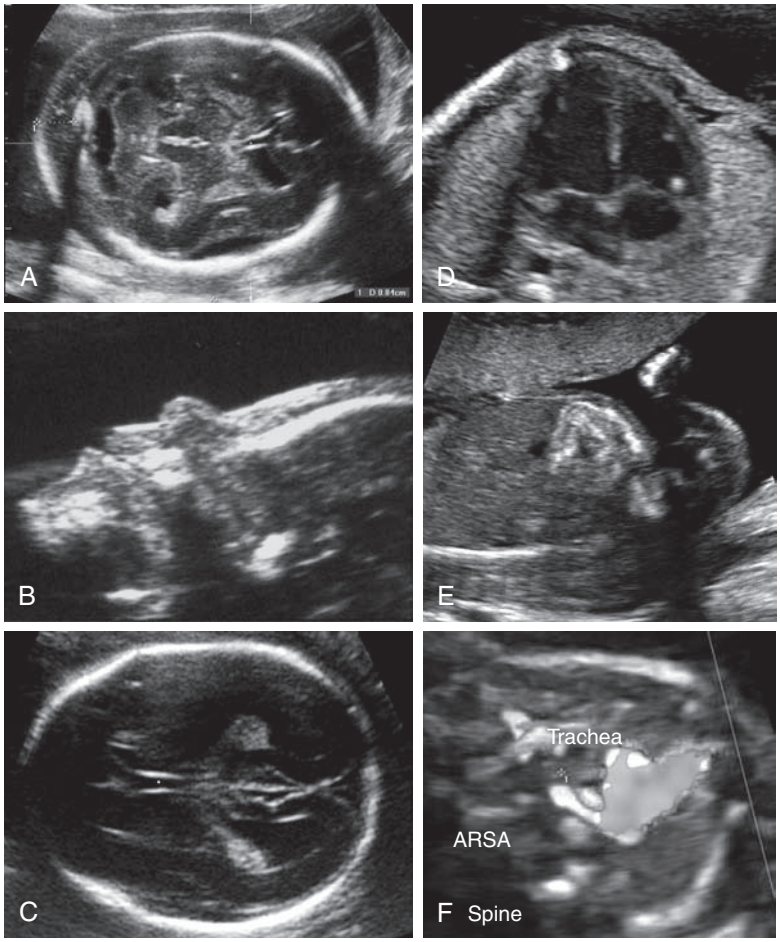


FIGURE 1.7 Second trimester soft markers seen in fetuses with trisomy 21, including thickened nuchal fold (**A**), absent nasal bone (**B**), borderline ventriculomegaly (**C**), echogenic focus in the heart (**D**), echogenic bowel (**E**) and aberrant subclavian artery (**F**).

Calculation of Risk for Trisomy 21

Background risk **X** LRs of each marker

Individual risk = a priori risk x LR1 x LR2 x LR3…..

	Normal	Tr 21	LR+	LR-	LRc
Mild hydronephrosis	2.6%	17.1%	6.8	0.85	1.0
Echogenic foci	4.4%	30.3%	6.4	0.75	1.0
Short femur	5.2%	42.0%	7.9	0.62	1.5
Echogenic bowel	0.6%	17.3%	21.2	0.87	3.0
Nuchal fold >6 mm	0.6%	41.1%	53.1	0.67	10.0
Major defect	0.7%	21.4%	33.0	0.79	5.0

Nicolaides Ultrasound Obstet Gynecol 2003, Nyberg et al 2001, Benacerraf et al 2002

FIGURE 1.8 Calculation of the risk for trisomy 21.[22–24] LR - likelihood ratio; Tri 21 - trisomy 21.

Marker	DR	FPR	LR + ve	LR – ve	Isolated marker
Cardiac echogenic focus	24.4	3.9	5.9	0.80	0.9
Ventriculomegaly	7.5	0.3	25.8	0.94	3.6
Increased nuchal fold	26.2	1.2	19.2	0.80	3.1
Echogenic bowel	16.7	1.1	11.4	0.90	1.7
Mild hydronephrosis	13.7	1.4	7.8	0.92	1.1
Short humerus	30.3	4.6	4.8	0.74	0.8
Short femur	27.7	6.4	3.7	0.80	0.6
ARSA	30.7	1.5	21.5	0.71	3.9
Absent or hypoplastic NB	59.8	2.8	23.3	0.46	6.6
No markers LR 0.13 = 7.7 fold reduction					

FIGURE 1.9 Meta-analysis of second trimester markers for trisomy 21, including 47 studies from 1995 to 2012.[12] LR - likelihood ratio; DR - detection rate; FPR - false positive rate; ARSA - aberrant right subclavian artery; NB - nasal bone. *(Adapted from reference 13)*

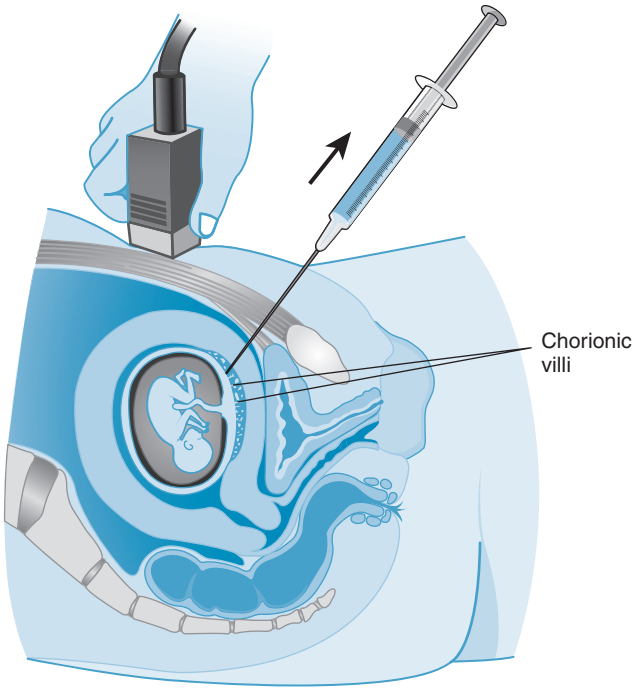


FIGURE 1.10 Technique for transabdominal chorionic villus sampling (CVS). A needle is guided from the patient's abdomen into the placenta under ultrasound guidance. Retrieved from http://www.uptodate.com/contents/image?imageKey=PI%2F54932&topicKey=DRUG_GEN%2F9549&source=see_link.

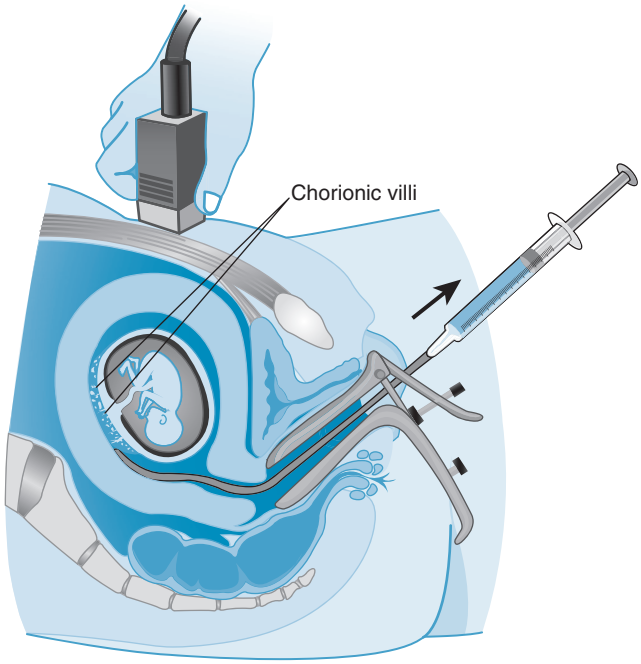


FIGURE 1.11 Technique for transcervical chorionic villus sampling (CVS). A very thin forceps is passed through the vagina into the placenta under ultrasound guidance. Retrieved from http://www.uptodate.com/contents/image?imageKey=PI%2F66814&topicKey=PI%2F6732&source=see_link.

ultrasound skills and prophylactic anti-D immunoglobulin given at time of procedure can help to reduce these risks. Transabdominal CVS is performed if the placenta is in the upper two-thirds of the uterus or if the patient has contraindications to transcervical CVS. The advantages include minimal risk of infection and less risk of vaginal bleeding. The disadvantages include the discomfort to the patient, the fact that less tissue is obtained for culture, difficulties arise if the placenta is posterior and it is technically more difficult than transcervical CVS.[17] The fetal loss rate for transabdominal CVS is 1.9%.[18] The fetal loss rate for transcervical CVS has been reported to be as high as 5.2% in the literature.[19]

Amniocentesis

Amniocentesis is performed after 16 weeks' gestation and involves obtaining fetal skin cells from the amniotic fluid for culture in order to karyotype the fetus. Determining placental location is important to ensure that the placenta is not punctured by the amniocentesis needle. Ultrasound imaging must be also used to ensure that there are no uterine vessels in the intended path of the needle. Maternal risks of this procedure include Rhesus isoimmunization. The woman's Rhesus status should be ascertained before the procedure and anti-D immunoglobulin administered if Rhesus negative. There is also a small risk of maternal infection, which is thought to be less than 1 in 1000. The fetal risks include miscarriage, an amniotic fluid leak and trauma to the fetus such as puncture of the skin by the amniocentesis needle, which is extremely rare. In a large 11 year national registry study in Denmark, the fetal loss rate for amniocentesis was lower than that of CVS at 1.4%.[18] However, most fetal medicine experts would quote a risk of miscarriage of approximately 1% for either CVS or amniocentesis.

Non-invasive Prenatal Testing

Most of the current research into non-invasive prenatal testing for chromosomal abnormalities is focused on the detection of cell-free DNA (cfDNA) in the maternal serum. Maternal serum is drawn at the first trimester screening session. Compared to unaffected pregnancies, in trisomy 21 pregnancies there is increased cfDNA originating from chromosome 21. It is thought that this increase is due to the fact that three copies of chromosome 21 are present compared with the two copies in a euploid pregnancy. Testing can be carried out by both sequencing the DNA and comparing it to the human genome, which is costly and time consuming. Alternatively, it can be performed by analysis of selected regions, loci, of selected chromosomes to determine whether they are maternal or fetal, and determining the fraction of the fetal trisomy chromosomes.

Current research suggests DRs of 100% for trisomy 21 and 98% for trisomy 18, both for a FPR of $<1\%$.[20] There are some limitations to the use of cfDNA. The fetal fraction in maternal plasma of cfDNA increases with serum PAPP-A and beta-hCG and decreases with increasing maternal weight.[21] So, for example, the amount of cfDNA obtained in an obese woman may be insufficient for testing. However, currently the main limiting factor to the widespread introduction of non-invasive prenatal testing is its cost. Please see chapter 3 for details.

Multiple Pregnancy

Women with a multiple pregnancy should be offered screening at a specialist centre or by an obstetrician with experience of and specialist interest in multiple pregnancy. Education and counselling are extremely important in multiple pregnancies due to the different screening techniques available, different tests and risks, and also the selection of options available if a chromosomal abnormality is diagnosed.

This section will focus on screening for trisomy 21 in multiple pregnancies, which has the greatest evidence base. Before screening women with multiple pregnancies for Down syndrome, it is essential to inform them of the greater likelihood of trisomy 21, and the higher FPR of screening tests, in twin and triplet pregnancies.[22] Women should be advised of the greater likelihood of being offered invasive testing, the increased likelihood of complications arising from invasive testing, and the physical risks and psychological implications in the short and long term relating to selective fetal reduction. It is essential that education about the screening pathway for both negative and positive screening test results is provided. It is also important to highlight the potential decisions that need to be made along this pathway.[22]

Twin Pregnancies

In twin pregnancies, screening in the first trimester (11^{+0} weeks to 13^{+6} weeks) is strongly advised. This is due to the greater accuracy of the first trimester screening tests for aneuploidy in both monchorionic and dichorionic pregnancies, compared to second trimester testing. The risk should be calculated per pregnancy in monochorionic twins and for each fetus in dichorionic twins. The triple or quadruple test should be offered to those women who present later in pregnancy when it is too late to perform first trimester screening.[22]

Triplet Pregnancies

Women with triplet pregnancies should be offered first trimester screening for trisomy 21 using NT and maternal age. There is little evidence to suggest that second trimester screening is accurate.[14] As is the case in twin pregnancies, the risk of trisomy 21 should be calculated per pregnancy for monchorionic triplets and for each fetus in di- or tri-chorionic triplets.

In those women that have a high risk for trisomy 21, referral to a tertiary level fetal medicine centre is advised.[22] Box 1.4 summarizes the screening guidelines for trisomy 21 in multiple pregnancies.[22]

INDIAN EXPERIENCE OF CHROMOSOMAL ABNORMALITIES

The methods of fetal tissue sampling and prenatal diagnosis have been well established in dedicated centres for genetic studies in metropolitan towns in India. Kotwaliwale and Ketkar reported that triploidy was a frequent cause of early

BOX 1.4 Trisomy 21 Screening in Multiple Pregnancy

- All women with multiple pregnancies should be referred to a health care professional with experience of caring for women with twin and triplet pregnancies.
- Women with multiple pregnancies should be aware of the greater likelihood of Down syndrome, the screening options and the likelihood of being offered invasive testing.

Health Care Professionals Who Screen for Down Syndrome in Twin Pregnancies Should:

- Use the combined screening test (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) for trisomy 21 in the first trimester.
- Calculate the risk of trisomy 21 per pregnancy in monochorionic twin pregnancies.
- Calculate the risk of trisomy 21 for each baby in dichorionic twin pregnancies.
- Where first trimester screening for trisomy 21 cannot be offered to a woman with a twin pregnancy consider second trimester serum screening.

In Triplet Pregnancies:

- Use nuchal translucency and maternal age to screen for trisomy 21(at approximately 11^{+0} to 13^{+6} weeks).
- The risk of Down syndrome should be calculated per pregnancy in monochorionic pregnancies.
- The risk of Down syndrome should be calculated per fetus in dichorionic and trichorionic pregnancies.
- Serum screening for Down syndrome should not be used.

pregnancy wastage.[25] Gogate, 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%.[26] There was no case of limb reduction defect following CVS in this study. He further quoted that in a multi-centric study on amniocentesis for various indications (chromosomal studies, NTD screening, biochemical studies, metabolic diseases, microbiological immunological investigations to detect congenital infections, Rhesus allo-immunization 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 labour, infection, feto- maternal transfusion, fetal trauma and amniotic band syndrome. Gogate reported on a series of over 1000 cordocentesis with a success rate of 93% and pregnancy loss rate of 2.85%.[26] However cordocentesis entails a long learning curve and should be performed by experienced operators. Dhillon-Pai reported on the value of early pregnancy screening, triple markers and ultrasonography, and concluded that the screening test including four markers (Triple test + AFP-L3) has a sensitivity of 81.5% with the false positive rate of 4.1% in women aged 35 years and a sensitivity of 83.3% and false positive rate of 2% in women aged 40 years.[27] Genetic causes account for up to 50% of abnormalities spontaneous first trimester abortions and about 20% of spontaneous second trimester abortions. Aneuploidy and polyploidy have been implicated.

Important Points

- Every pregnant woman is at risk of carrying a fetus with a chromosomal abnormality. Screening for chromosomal abnormalities should be an integral part of prenatal care.
- The most frequent chromosomal abnormalities are trisomy 21, trisomy 18, trisomy 13, 45X (Turner syndrome) and sex chromosome abnormalities.
- First trimester screening is currently carried out between 11^{+0} to 13^{+6} weeks' gestation using the combination of NT, serum beta-hCG, PAPP-A and maternal age. The DR is around 90% for a 5% FPR.
- The DR can be increased and the FPR reduced further by using additional ultrasound markers, such as ductus venosus velocimetry and tricuspid blood flow.
- Second trimester screening includes the triple and quadruple tests, and anomaly ultrasound scan for structural abnormalities and/or soft markers. The DR is lower in the second compared to the first trimester.
- Pregnancies at high risk of chromosomal abnormalities are offered prenatal diagnosis, which includes CVS at 11–14 weeks, which could be performed via the transabdominal or transcervical route, or amniocentesis beyond 15 weeks' gestation. The risk of miscarriage following these invasive procedures is around 1%.
- In multiple pregnancies, screening is more complex as the options and the management are different from singletons, hence they should be referred to a fetal medicine centre with the appropriate expertise.
- The risk of chromosomal abnormalities is higher in multiple pregnancies. The most accurate screening test in this group is still the combined test. However, its accuracy is less than in singleton pregnancies, so multiple pregnancies are more likely to be offered invasive diagnostic testing.
- Recently, non-invasive prenatal testing (NIPT) has become available, which is accurate and very promising, but still expensive.
- With NIPT, the reported DRs for trisomy 21 and trisomy 18 are 100% and 98%, respectively, both for a FPR of <1%. However, the fetal fraction in maternal plasma of cell-free DNA depends on maternal and pregnancy characteristics, which must be taken into account.

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Chapter 2

Fetal Dysmorphology

Nirmala Chandrasekharan and Amarnath Bhide

Chapter Outline

INTRODUCTION

Structural abnormalities contribute to more than half of the perinatal mortalities worldwide. Ever since the ultrasound scans as been introduced, its use has revolutionized the field of obstetrics. The current practice is a policy to offer universal ultrasound screening to all pregnant women between 18 and 20^{+6} weeks (UK FASP).[1] The anomaly scan not only helps to identify the anomalies and gives the options of further investigations, but also helps the parents in making the decision to continue with the pregnancy or not. It gives the option of therapy in some conditions and aids to plan the neonatal management. It is also of emotional benefit to the parents by allowing them to come to terms with the birth of an abnormal baby or bonding with a normal one. The lower limit of the gestational age (18^{+0} weeks) was selected because of the limitations that arise in examining the fetal anatomy thoroughly prior to that point and the upper limit of 20^{+6} was selected so that once the abnormality is detected, it allows sufficient time for referral to the higher centres for subsequent assessment and if confirmed, a termination of pregnancy could be offered before the legal limit (24 weeks in the UK).

This chapter outlines the common structural abnormalities in the fetus and their management.

CENTRAL NERVOUS SYSTEM ABNORMALITIES

Neural Tube Defects

Neural tube defects are the collective terminology for defects that occur due to failure of the neural tube to close during the first 30 days of fetal development. The neural tube defects are anencephaly, encephalocele and spina bifida depending on the level of the defect. The incidence is about 3–5/1000 pregnancies. The incidence has declined after the introduction of preconceptual folic acid and the improved screening techniques. The aetiology is multifactorial including genetic factors and environmental factors, such as use of certain anticonvulsants, maternal diabetes, obesity (possibly due to the hyperinsulinaemia) and maternal folic acid deficiency. The biggest problem is the recurrence risk. This ranges from 3% to 8% for the subsequent child. Women with a previous history should be advised to take high dose folic acid (5 mg) prior to the subsequent pregnancy.[2] Neural tube defects by far are the anomalies that have a very high antenatal detection rates.

Anencephaly

Anencephaly is the absence of cranial vault. This occurs due to the failure of closure of the cranial end of the neural tube. This abnormality is incompatible with life. Anencephaly can be reliably diagnosed at the routine 12–14 week ultrasound scan, provided the sonographic features for this condition are specifically searched for. In the first trimester, the pathognomic feature is acrania, i.e., the absence of cranial bones, the brain being either entirely normal or at varying degrees of distortion and disruption. By second trimester, polyhydramnios would be a very apparent sign. In this condition, the cerebral hemispheres are present and are exposed to the amniotic fluid. In the absence of the cranial vault, the exposed cerebral tissue undergoes progressive degeneration to anencephaly. Once diagnosed, a termination should be offered.

Spina Bifida

Spina bifida (literally 'split spine') refers to the group of neural tube defect where there is failure of closure of the spine along some or the entire length of the vertebral column. The term *spina bifida occulta* is used when there is no tissue protruding through this defect. As the defect is completely epithelialized, patients are often asymptomatic. This is a milder form of the condition which might not be detected on prenatal ultrasound. The term *spina bifida aperta* is used to refer to all other forms of the defects where the neural tissue is protruding. The most severe form is the meningomyelocele where both the meninges and the neural tissue are present in the defect. Both meningocele and meningomyelocele are frequently associated with malformations of the fourth ventricle, medulla and hydrocephalus. Classical intracranial signs of spina bifida include the 'lemon sign' and the 'banana sign'.[3] Lemon sign refers to the shape of the skull in transverse plane caused by the concavity of the parietal bones (Fig. 2.1) and the banana sign refers to the shape of the cerebellum (Fig. 2.2), which is distorted as part of the Chiari type II malformation. The other intracranial signs are ventriculomegaly and small cerebellum. A thorough examination of the spine in the sagittal, coronal and axial planes would help identify the nature and the extent of the lesion. Recently, three-dimensional ultrasound has been of great help as it helps visualizing the entire spine in various planes. Depending on the level of the spina bifida defect, features vary and include abnormalities or paralysis of the lower extremities, urinary and faecal

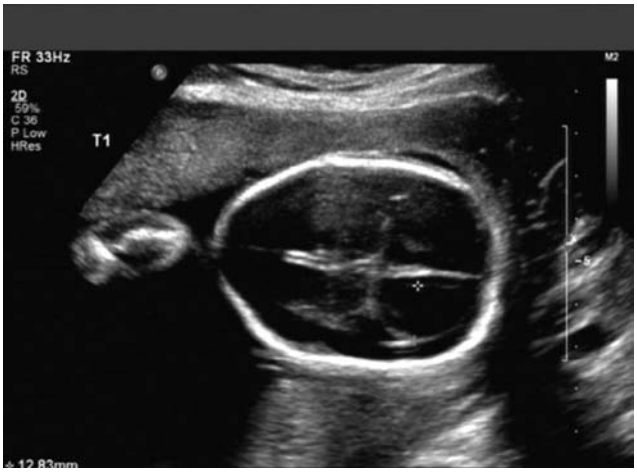

FIGURE 2.1 Classical 'lemon'-shaped head in a fetus with spina bifida. Also note enlargement of the posterior horn of the lateral ventricle.

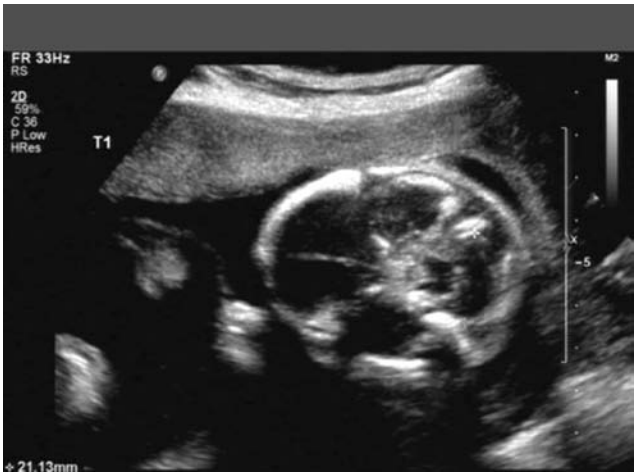

FIGURE 2.2 Banana-shaped cerebellum (see the asterixes) in a fetus with spina bifida.

incontinence, or just anaesthesia of the skin. Once diagnosed, parents should be counselled regarding these and the possible need for immediate postnatal surgery. A prospective randomized study has also shown that fetal surgery prior to 26 weeks may preserve neurological function, reverse the hindbrain herniation of the Chiari type II malformation and obviate the need for postnatal placement of a ventriculo-peritoneal shunt, but it also has a significant risk of preterm birth and maternal morbidity.[4]

Ventriculomegaly

Ventriculomegaly is defined as a lateral ventricle diameter of 10 mm or more. It is seen in approximately 1% of all pregnancies at the anomaly scan (Fig. 2.3). Ventriculomegaly could be isolated or associated with other pathologies in the brain like chromosomal and genetic abnormalities, intrauterine haemorrhage, congenital infections or other structural malformations like neural tube defects and agenesis of the corpus callosum. Prognosis will depend upon the aetiology and presence of other malformations. In general, isolated mild ventriculomegaly has good prognosis. Once diagnosed, karyotyping and TORCH screening should be offered. Fetal MRI has been proved to be of benefit in identifying associated lesions in an otherwise apparently isolated ventriculomegaly.[5] Treatment will depend again on the aetiology and the termination should be offered for severe ventriculomegaly due to the associated neurodevelopmental delay.[6]

Holoprosencephaly

This is a spectrum of abnormalities that result from incomplete cleavage of the forebrain. Depending on the degree of cleavage, it is classified into alobar (single ventricular cavity with thalamic fusion), semi-lobar (partial segmentation of the ventricles and cerebral hemispheres with incomplete thalamic fusion) and the lobar (normal separation of the cerebral hemispheres and thalami, but absence of cavum septum pellucidum). The alobar and semi-lobar types usually present with microcephaly and mental retardation and are lethal. The lobar type is less lethal, but associated with mental retardation, spastic quadriparesis, athetoid movements, endocrine disorders, epilepsy and other serious conditions. Aetiology is either genetic (either inherited or chromosomal abnormalities like trisomy 18) or non-genetic like diabetes, infections, exposure to drugs, etc.

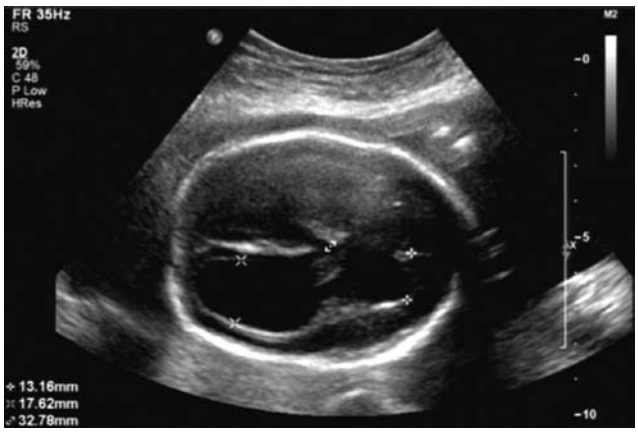

FIGURE 2.3 Severe ventriculomegaly seen on prenatal scan.

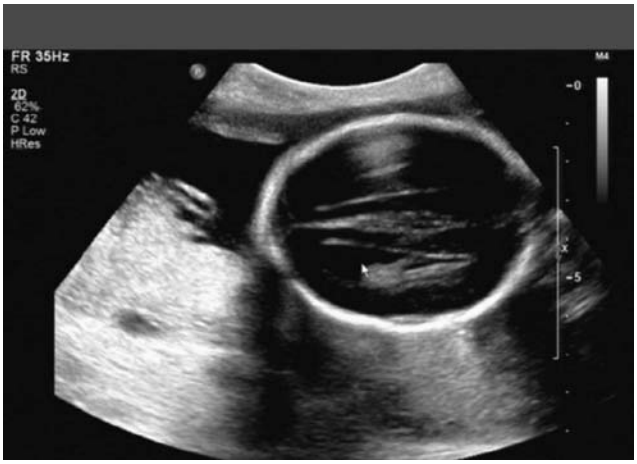

FIGURE 2.4 Ultrasound scan of a fetus with agenesis of the corpus callosum (ACC). Note the typical 'tear-drop' shape of the lateral ventricles.

Agenesis of Corpus Callosum

Agenesis of corpus callosum (ACC) (Fig. 2.4) occurs in about 5 per 10,000 births.[7] This is a defect where there is complete or partial agenesis of the bundle of fibres that connect the two cerebral hemispheres. The disorder is due to either maldevelopment of secondary to a destructive lesion, but more commonly due to chromosomal abnormalities, usually trisomy 18 or 13. As corpus callosum develops only after 12 weeks, this is a second trimester diagnosis. It could be isolated or complex (coexisting with other abnormalities). Prognosis depends on the cause, with nearly good prognosis in the isolated ones. Affected individuals show cognitive disturbances, epilepsy, social and behavioural disturbances, etc. Recently, fetal MRI has proven of great value in diagnosing ACC due to the multiplanar capability and high soft-tissue contrast that are possible with MRI.

ABNORMALITIES OF THE NECK

Cystic Hygroma

Cystic hygroma (Fig. 2.5) is a congenital abnormality of the lymphatic system where the jugular lymph sacs fail to join the lymphatic system. The posterior triangle of the neck is

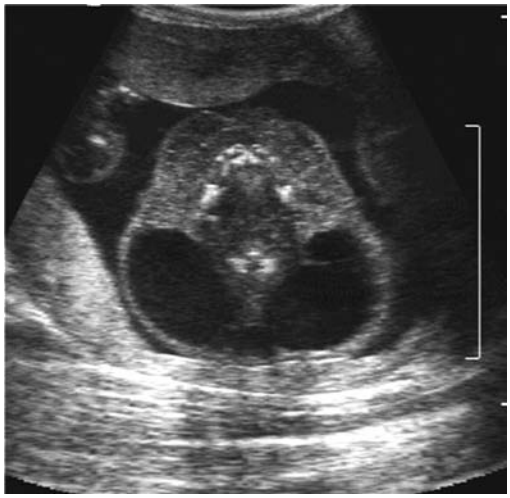

FIGURE 2.5 Image of the fetal neck in transverse section. Note the presence of bilateral cystic hygromas.

most commonly affected. It has an incidence of 1 in 6000 to 1 in 60,000. About 70% of it is associated with chromosomal abnormalities like Down and Turner syndrome. There is also an association with non-chromosomal abnormalities like Noonan and multiple pterygium syndromes. Hence, once diagnosed, a karyotyping and fetal echocardiography should always be offered.[8] Termination of pregnancy should always be offered especially if hydrops is present or if the fetus is aneuploid due to poor prognosis. There is a higher incidence of polyhydramnios due to impaired fetal swallowing and preterm labour as a result of that. In very large tumours, a fetal EXIT (Ex-utero intrapartum treatment) may be needed.

Cardiac Abnormalities

Cardiac abnormalities are present in 5–10 per 1000 live births and 30 per 1000 still births.[9] The aetiology is multifactorial including maternal diabetes mellitus or collagen vascular diseases, exposure to drugs (e.g., lithium), infections during pregnancy (e.g., rubella), chromosomal abnormalities (trisomies, Turner, etc.). The routine four-chamber view would identify only 70% of the abnormalities and adding the tracheal and the three-vessel view would detect another 10% of abnormalities. Prenatal diagnosis of cardiac abnormalities remains poor. Prenatal diagnosis was made successfully in less than one out of four fetuses with serious cardiac abnormalities in the UK.[9] Fetal echocardiography should be offered to all the high-risk groups mentioned above and also to women with previous history of fetus with cardiac abnormalities, increased nuchal in the first trimester (more than 99th centile or >3.5 mm with a normal karyotype), presence of other structural abnormalities, etc.

Ventricular Septal Defect

Ventricular septal defect (VSD) is the most common defect representing 30% of all the congenital cardiac defects.[10] It is either isolated or part of a major complex cardiac problem. There are various types of VSDs like perimembranous, inlet, trabecular or outlet defects depending on the location, with perimembranous being the most common. VSD normally has a good prognosis and more than 90% close spontaneously after birth. Very larger defects associated with massive shunts can cause congestive cardiac failure at birth. Surgery is safe and more than 90% survive surgery with normal life expectancy.

Atrio-ventricular Septal Defects

In this abnormality, there is a faulty development of the endocardial cushions which represents the primordia of the atrioventricular septum and atrioventricular valves (Fig. 2.6). These could be complete or incomplete defects. In a large majority of cases, the defect is associated with chromosomal abnormalities (60% of which is T21). It is associated with other cardiac abnormalities, mainly tetralogy of Fallot. Once diagnosed, karyotyping is essential and termination is an option in large defects and in association with aneuploidies. Surgical correction is normally associated with good outcome.

Atrial Septal Defect

Atrial septal defect (ASD) is of two types – Primum and secundum. The secundum defects are the most common and could be related to other cardiac lesions and also could be part of syndromes (e.g., Holt Oram). In-utero diagnosis could be very difficult unless the defect is very large due to the physiological presence of the foramen ovale. The prognosis is usually very good.

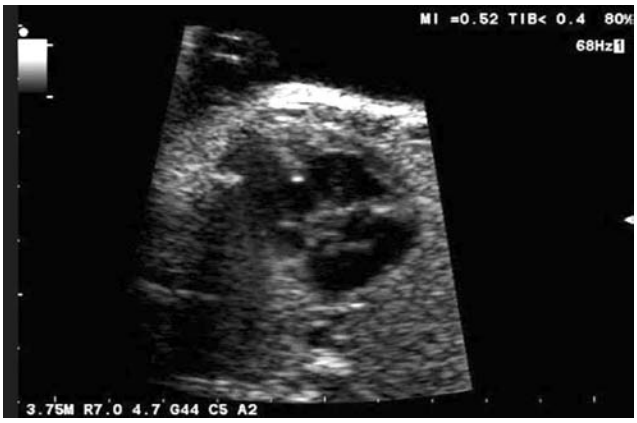

FIGURE 2.6 Atrioventricular septal defect.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) is a spectrum of disorders, which is characterized by a very small left ventricle with mitral and/or mitral atresia or hypoplasia (Fig. 2.7).[11] The entire systemic circulation is by the right ventricle through the pulmonary artery. The diagnosis is normally easy with the ultrasound as there is an obvious discrepancy between the two ventricles. It is normally well-tolerated in-utero due to the physiological connections due to the foramen ovale and the ductus arteriosus. It is associated with aneuploidies, cardiac and extra cardiac abnormalities and few genetic syndromes (e.g., Holt Oram). Hence karyotyping should be offered and termination should be considered. Treatment would involve either a primary cardiac transplantation or a three-stage Norwood repair.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is found in 1 per 3000 births.[10] It comprises VSD, right ventricular outflow tract obstruction, right ventricular hypertrophy and aortic overriding of the interventricular septum. The right ventricular hypertrophy is a neonatal finding and not a prenatal finding. It can sometimes be associated with other cardiac abnormalities and chromosomal abnormalities like Di George syndrome (Deletion of 22q11). Hence karyotyping should be offered. Termination is also an option especially if hydrops ensues or is associated with other abnormalities and chromosomal problems. Surgical correction postnatally offers a more than 95% survival rate.

Double Outlet Right Ventricle

Double outlet right ventricle (DORV) is defined as a form of ventriculo-arterial connection in which both great arteries arise completely or predominantly from the morphologic right ventricle. It is not a single malformation, but just refers to the position of the great vessels found in association with VSD, TOF, TGA and univentricular heart, hence prenatal detection could be a challenge. The incidence is 1 per 10,000 live births.[10] It is associated commonly with other extra cardiac and chromosomal abnormalities. Prognosis depends on the severity and the presence of other conotruncal abnormalities. Congestive cardiac failure is more common in the postnatal period. Surgical correction has a mortality of 10%.

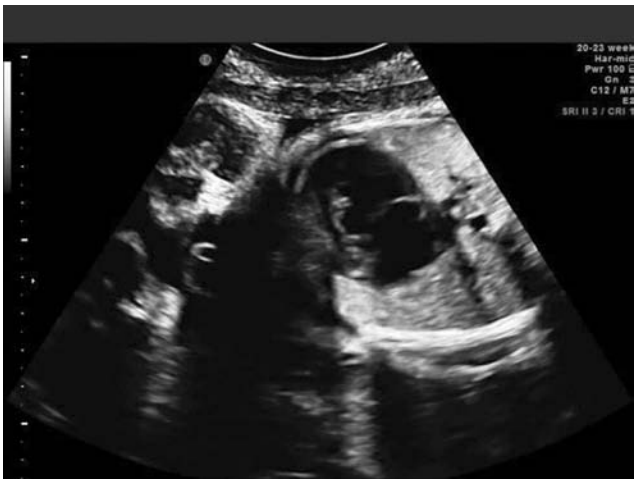

FIGURE 2.7 Hypoplastic left heart syndrome (HLHS). Note inability to visualise the left ventricle.

Ebstein's Anomaly

In Ebstein's anomaly, the septal leaflet of the tricuspid valve is displaced towards the apex of the right ventricle of the heart, resulting in a considerably enlarged right atrium at the expense of the right ventricle. Associated abnormalities include ASD, VSD, pulmonary atresia and supra ventricular tachycardia. It is commonly associated with trisomies 13 and 21, Turner and Marfan syndromes, and is also thought to be associated with maternal lithium intake. Ebstein's anomaly severe enough to be detected antenatally carries a very poor prognosis.

Coarctation of Aorta

Coarctation is a localized narrowing of the juxtaductal arch, most commonly between the left subclavian artery and the ductus. It occurs in 4 per 10,000 live births and is more common in boys than girls.[10] In 90% of the cases, other cardiac abnormalities are present like aortic stenosis and regurgitation, ASD, TGA and double outlet right ventricle. The most common chromosomal abnormality found with this condition is Turner syndrome. The antenatal detection rate is very low and in most cases, it can only be suspected. Karyotyping should be offered if detected antenatally. Prostaglandin treatment is essential in the immediate postnatal period and surgical correction offers a good prognosis with an incidence of 15% restenosis.

Transposition of Great Arteries

Transposition of great arteries (TGA) is an abnormality where the aorta arises entirely or in large part from the right ventricle and the pulmonary artery from the left ventricle. The incidence is about 1 in 3000 births.[10] About 50% of the lesions have other cardiac abnormalities in association like VSD (most common), pulmonary stenosis, etc. Complete TGA is very difficult to diagnose antenatally as the appearances are normal. Once diagnosed, karyotyping should be offered including for 22q11 deletion. Termination of pregnancy (TOP) could be offered if diagnosed early or is associated with chromosomal or other cardiac abnormalities.

Surgery is indicated for all cases and carries good 5-year survival rate.

Cardiomyopathies

These are very rare diseases in fetuses with poor outcome. The incidence is around 2–7% of all congenital heart defects,[12] but probably during the fetal life the prevalence is higher, around 6–11%. The high intrauterine loss, occurring in one-third of affected fetuses, likely accounts for these differences. The two types are dilated and hypertrophic cardiomyopathies. Fetal echocardiography is the main diagnostic tool. They can be isolated or associated with other cardiac abnormalities. Genetic, structural, infective and metabolic causes are associated with dilated cardiomyopathies and it carries poor prognosis. Maternal diabetes is associated with hypertrophic cardiomyopathies and is normally associated with better prognosis. Detailed evaluations of fetal and maternal condition provide prognostic information for prenatal counselling and may lead to improved outcome of at least some affected pregnancies.

Fetal Arrhythmias

Rhythm abnormalities are present in 2% of fetuses and most commonly are due to isolated atrial or ventricular premature contractions.[13,14] These are normally benign and disappear spontaneously. The other dysrhythmias include tachyarrhythmia and bradyarrythmias. The most common tachyarrythmias are the supraventricular tachycardias (SVTs). The rest are atrial flutters and atrial fibrillations. About 10% of SVTs are associated with an accessory pathway (e.g., Wolff–Parkinson–White syndrome).[12] Forty to fifty per cent of the fetuses with SVT will develop hydrops. The fetuses that are more prone to develop hydrops are the more persistent SVTs, early (<32 weeks) onset SVTs and those associated with structural abnormalities. Atrial flutters are associated with structural abnormalities more commonly than SVTs like Ebstein's anomaly and pulmonary stenosis. Fetal therapy will depend on the type of arrhythmias and the gestation. If after 32 weeks, fetuses could be delivered and treated ex-utero. If earlier, anti-arrhythmic drugs could be used. These are propranolol, verapamil, digoxin, flecainide, adenosine, etc., in isolation or in combination. Fetuses with normal rhythm after treatment but persistent hydrops still carry a very poor prognosis.

Although the most common cause for bradyarrythmias is sinus bradycardia, fetal bradycardias are caused by fetal heart blocks, long QT syndromes. Fifty per cent of the complete AV blocks are caused by structural abnormalities and the rest are due to the presence of maternal autoantibodies like anti-Ro or anti-La. Maternal treatments with dexamethasone, beta-sympathomimetic, plasmapheresis, etc., have been attempted with varying degrees of success.

Cardiac Tumours

The tumours of the heart are rhabdomyoma and intrapericardial teratomas. Rhabdomyoma is the most common primary cardiac tumour with a prevalence of 1 per 1000 of those referred for echocardiography.[15] In 50% of the cases, the tumours are associated with tuberous sclerosis. Cardiac complications include arrhythmias, obstruction of the ventricular outflow tracts and secondary cardiogenic shock. Prognosis will depend upon the number, size and location of the tumours and the association with tuberous sclerosis (TS). In general, multiple tumours are associated with TS. Tuberous sclerosis and the associated neurodevelopmental complications dominate the clinical picture, and should form an important aspect of the prenatal counselling of parents. If isolated, they regress spontaneously and are very benign.

Intrapericardial teratomas are more common on the right side and could lead to pericardial effusions, cardiac tamponade and hydrops.

THORACIC ABNORMALITIES

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) has an incidence of 1 in 3000 to 1 in 5000 births. It results when there is failure of the pleuroperitoneal canal to partition at 9–10 weeks gestation. In the presence of the defect in the diaphragm, there is a herniation of the abdominal viscera into the thorax at about 10–12 weeks. It is usually a sporadic abnormality, but about 50% could be associated with chromosomal abnormalities like trisomies 13 and 18 and Pallister–Killian syndrome) and genetic syndromes (Marfans, Fryns and De Langes syndromes) and other defects like spina bifida and cardiac abnormalities. The sonographic diagnosis of CDH is based on mediastinal shift and presence of stomach or bowel loops in the chest. The combination of abnormalities includes pulmonary hypoplasia, lung dysmaturity and pulmonary hypertension. Polyhydramnios is present in about 75% of cases due to impaired fetal swallowing. Antenatal prediction of the severity of pulmonary hypoplasia is vital in planning treatment and in counselling patients. The poor prognostic factors are the presence of liver herniation and poor lung–head ratio (lung area divided by the head circumference). Once diagnosed, a karyotyping should be offered and an echocardiography should be performed. Fetal MRI could give information about the lung volumes. Fetal therapy in the form of endoscopic tracheal occlusion has been carried out with the idea of improving the dry lung weight, airway branching and improve pulmonary vascular growth.[16] Postnatal primary closure gives good prognosis.

Congenital Cystic Adenoid Malformation of the Lungs

Congenital cystic adenoid malformation of the lungs (CCAM) is a developmental abnormality of the lungs that is due to the overgrowth of the terminal respiratory bronchioles. It can involve a single lobe or the whole lung or both the lungs. They are more commonly left sided. The lesions could be microcystic (<5 mm) or macrocystic. They are classified into five types (0–4) depending on the size of the cysts and the cellular characteristics. Ultrasound can demonstrate a hyperechogenic lung tumour, which is cystic, solid or mixed. Studies have investigated the role of *HOXB5* gene and protein expression, as well as other growth factors such as mesenchymal platelet-derived growth factor-BB. The main problems are the compromised lung growth, pulmonary hypoplasia, mediastinal shift and compression of the inferior vena cava leading to hydrops. Hydrops carries worst prognosis. Polyhydramnios is frequent. Once diagnosed, patients should be offered an Echo and a fetal MRI, if available. MRI can help in getting better views, differentiate from a CDH and also measure the volume of the lungs. Large intrathoracic cysts with mediastinal compression and hydrops could be treated by insertion of thoraco-amniotic shunts. Majority of lesions regress after birth. Very few will need surgery for correction and surgery carries a very good prognosis.

Bronchopulmonary Sequestration

Bronchopulmonary sequestration (BPS) is a portion of the non-functioning primitive lung tissue that has no connection with the airways. The blood supply for this abnormal lung tissue is from a systemic artery, which is the thoracic aorta in 85% of cases rather than the pulmonary vessel. The incidence is about 1 in 1000. It could be intra-lobar (no separate pleural covering from the lung) or extra-lobar (with separate pleural covering). These lesions can be intra or extra-thoracic. BPS is a sporadic abnormality but could be rarely associated with other congenital malformations (mostly diaphragmatic hernia and cardiac lesions). Prenatal ultrasound can identify a brightly echogenic homogeneous mass in the lower lobes of the lungs or below the diaphragm. Colour Doppler can identify the vascular supply of the sequestrated lobe. The sequestrated lobe can act as an A-V fistula and cause high output cardiac failure and hydrops. In addition, intrathoracic lesions can cause mediastinal shift and pulmonary hypoplasia. Once diagnosed, fetal echo should be considered and an MRI can help differentiate from CCAM and other lung lesions. Majority regress spontaneously and fetal therapy in the form of thoraco-amniotic shunt is reserved for the more severe ones with hydrops. Postnatal resection of the sequestrated lobe carries good prognosis.

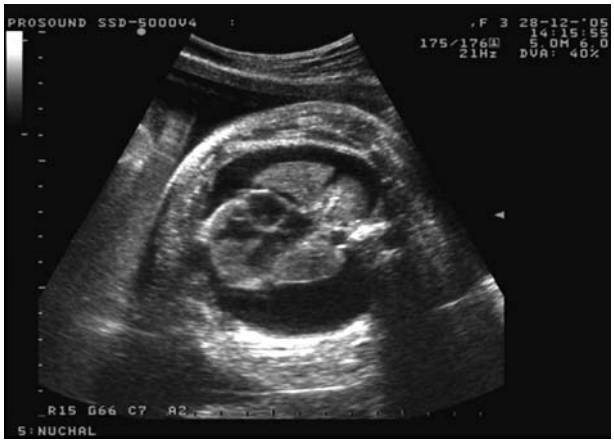

FIGURE 2.8 Ultrasound appearance of bilateral hydrothorax.

Hydrothorax (Fig. 2.8)

Pleural effusions in the fetus can be primary (leakage of chyle into the pleural space) or secondary (associated with hydrops). Primary hydrothorax is a diagnosis of exclusion. Hence, once diagnosed, the work up should be similar to that of hydrops, although unilateral isolated hydrothorax on ultrasound is more likely to be primary rather than secondary. Primary effusions can regress spontaneously, remain stable or progress to hydrops. Large effusions can cause mediastinal shift, cardiac tamponade and pulmonary hypoplasia. Oesophageal compression can lead to polyhydramnios. In the biggest review conducted to date, involving 124 patients, fetuses that have poorer outcomes are the ones with hydrops and the ones that need to be delivered early. Majority of the effusions can be managed conservatively by surveillance, while fetal thoracocentesis and thoraco-amniotic shunting is indicated in large effusions causing pulmonary hypoplasia.[17]

ABDOMINAL ABNORMALITIES

Gastroschisis

Gastroschisis refers to full thickness abdominal wall defect with evisceration of the intestines, believed to result from an ischaemic insult to the developing anterior abdominal wall. It is found in about 1 in 4000 births.[18] Studies worldwide have indicated that young women (under 20 years of age) are most commonly possibly affected due to lifestyle factors like smoking, recreational drug use, increase in frequency of genitourinary infections, low BMI, all consistent with the ischemic disruption theory. Gastroschisis is not normally associated with aneuploidies, but other associated anomalies can be found in a small percentage of babies like intestinal stenosis or atresia's, Meckels diverticulum, etc. Prenatal diagnosis is based on the demonstration of a normally situated umbilicus and the herniated intestine, which

would be free floating in the amniotic fluid. The complications of the condition include intrauterine growth restriction (30%), oligohydramnios, preterm labour and sudden fetal death. Also, chemical peritonitis can cause distension and thickening of the bowel wall. IUGR, increasing bowel distension and oligohydramnios indicate a poor prognosis. Once diagnosed, echocardiography should be offered and serial growth scans are a must. Postoperative survival in the postnatal period is about 90%. Mortality is usually a consequence of short gut syndrome.

Exomphalos

Exomphalos results from the failure of normal embryonic regression of the mid-gut from the umbilical stalk to the celomic cavity. A membrane (consisting of three layers, peritoneum, amnion and the Wharton's jelly in-between) covers the herniated viscera and the umbilical cord is attached to the membrane. The herniated contents could be the mesentery, stomach, small and large bowel although the liver can also be included in varying degrees. The incidence of this abnormality is 1 in 4000 and is more common in women in their extremes of age.[18] About 40% are associated with aneuploidies, most common being trisomies 13, 15, 18 and Beckwith–Wiedemann syndrome. Other abnormalities co-exist in more than 50% of cases, cardiac abnormalities being the predominant ones. Hence, once diagnosed, detailed ultrasound examination should be directed towards defining the extent of the lesion and searching for other anomalies, including Beckwith–Wiedemann syndrome (BWS). Deregulation of imprinted growth regulatory genes within the 11p15 region is the major cause of BWS. Echocardiography should be performed and karyotyping should be offered. Diagnosis of Beckwith–Wiedemann syndrome requires specific testing. Termination is an option, if associated with other anomalies and if aneuploidy is detected. Prognosis after primary closure depends on the presence of other malformations and aneuploidies.

ABNORMALITIES OF THE URINARY TRACT

Congenital abnormalities of the urinary tract constitute one-third of all the abnormalities that are detected with prenatal ultrasound.

Hydronephrosis

Varying degrees of pelvi-calyceal dilatation is seen in 1–2% of babies.[19] Although some amount of hydronephrosis is common, urinary tract obstruction and vesico-ureteric reflux (non-obstructive) can be the causative factor. This can prevent normal development of the renal tract. The other major problem with obstructive uropathy is the oligo/anhydramnios and pulmonary hypoplasia. Prognosis depends on the severity of the hydronephrosis and the level of obstruction. The severity as determined by the size of the renal pelvis, if more than 15 mm, has a very high association with congenital anomalies of the renal tract. If isolated hydronephrosis, the risk of aneuploidy is not high, hence karyotyping should be reserved for only cases with other abnormalities. Hence detailed ultrasound should look for other renal tract abnormalities and the level of obstruction (which might not always be possible). One study proved that oligohydramnios and megacystis were predictive of an obstructive aetiology. Parents should be counselled regarding the postnatal follow up and possible need for surgery.

Obstructive Uropathy

Fetal lower urinary tract obstruction (Fig. 2.9) complicates 2 per 10,000 pregnancies. In male fetuses, posterior urethral valves (a thin membranous tissue that obstructs the proximal urethra) constitute more than 90% of the cases, the other common cause being urethral atresia. In female fetuses, the pathology might be more complex, like cloacal plate anomalies, including megacystis microcolon syndrome (dysfunctional smooth muscle in bladder and distal bowel). The morbidity is due to cystic renal dysplasia and abnormal renal (glomerular and tubular) function. Progressive renal dysfunction may lead to severe oligohydramnios, predisposing the fetus to pulmonary hypoplasia and positional limb abnormalities. Oligohydramnios is an important prognostic factor on ultrasound. Fetal MRI has proved to be of great benefit. Termination is an option if associated with severe oligohydramnios early in pregnancy. In patients who opt out of termination, fetal therapy in the form of vesico-amniotic shunting could be considered. Metaanalysis has proven that this improves the fetal outcome significantly,

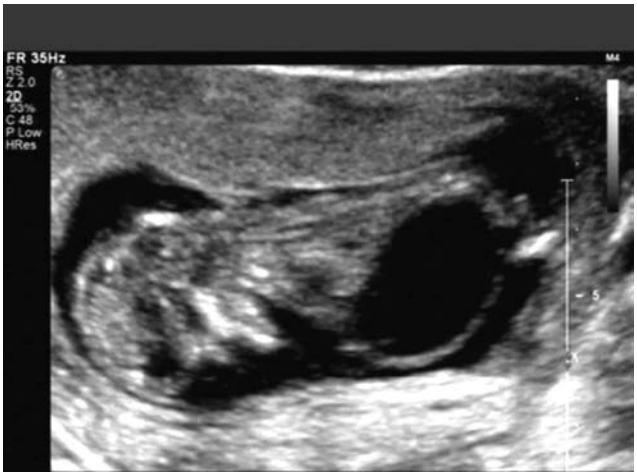

FIGURE 2.9 First trimester scan showing megacystis due to bladder outlet obstruction.

but only in babies who belonged to the already 'poor prognosis' group.[20]

Multicystic Dysplastic Kidneys

Multicystic dysplastic kidney (MCDK) disease is a condition where the collecting tubules of the kidneys are replaced by cysts of varying sizes that determine the size of the kidney. The incidence is about 1 in 4000 births for unilateral and 1 in 10,000 for bilateral disease.[21] Bilateral disease is incompatible with life with anhydramnios and pulmonary hypoplasia, whereas the outcome with unilateral kidney disease is usually normal. The condition is not inherited and is not normally associated with aneuploidies, but can be rarely associated with trisomy 13, Meckel–Gruber syndrome, etc. In majority of the situations, the kidneys normally regress and it is thought that the adult unilateral renal agenesis is possibly a regressed MCDK. A metaanalysis has shown that about one-third of the cases of unilateral MCDK is associated with abnormalities in the contralateral kidneys, most common being vesico-ureteric reflux. Termination is an option for bilateral disease. As the abnormal kidneys contain aberrant tissues like cartilage, etc., there is a small chance of malignancies (e.g., Wilms tumour). Hence some urologists advocate elective nephrectomy after the age of 2, if involution does not occur to prevent tumours and hypertension.

Autosomal Recessive (Infantile) Polycystic Kidney Disease

Infantile PCKD is currently called *autosomal recessive PCKD*. It has an incidence of 1 in 40,000 live births.[21] The condition is associated with cystic dilatation of renal collecting ducts associated with hepatic abnormalities of varying degrees, including biliary dysgenesis and periportal fibrosis. The gene (*PKDHD1*) is localized to the short arm of chromosome 6. Prenatal diagnosis is possible with CVS. The disease is characterized by non-obstructive, bilateral, symmetrical dilatation and elongation of 10–90% of the renal collecting ducts, focally accounting for a wide variability of renal dysfunction. Fetuses with severe renal impairment present with severe oligohydramnios and pulmonary hypoplasia. In babies who survive the neonatal period, prognosis can be affected by the periportal fibrosis. Recurrence risk is small, but genetic counselling is essential.

Adult PCKD

Adult PCKD, otherwise called as autosomal dominant PCKD, is a very common cause of end stage renal failure and has an incidence of 1 in 1000 live births.[21] It is characterized by progressive cystic dilatation of the renal tubules with extra-renal manifestations involving the gastrointestinal tract, cardiovascular system, brain, etc. The disease has two loci chromosomes 16 and 4. Even though the disease can be identified in the prenatal period, it might not present itself until adulthood. Hence in patients with a positive family history, a normal scan does not rule out adult PCKD. The recurrence risk of severe early onset adult PCKD is about 25%.

SKELETAL ABNORMALITIES

There are more than 200 skeletal dysplasias and are found in 1 in 4000 births.[22] Antenatal management will depend upon the identification of the dysplasia and assessment of the lethality of the condition.

Lethal Skeletal Dysplasias

The lethal types of skeletal dysplasias are the ones that have an earlier onset, have severe phenotypic abnormalities and can be diagnosed early. The diagnosis is important as it allows counselling regarding termination and regarding future pregnancies. The most common lethal dysplasias are osteochondrodysplasias (including thanatophoric dysplasia and achondrogenesis) and osteogenesis imperfecta type II. The other less common forms are chondroectodermal dysplasia, campomelic dysplasia.[23] Antenatally, the diagnosis is made by assessment of the long bones, examination of the fetal movements, evaluation of the hands and feet, evaluation of the fetal head and thorax. The prediction of lethality is by assessing the thorax as this determines the severity of pulmonary hypoplasia. The parameters used are thoracic circumference below the 5th percentile, an abnormal thoracic, abdominal circumference and a markedly narrowed sagittal anteroposterior diameter of the thorax to diagnose lethality. Polyhydramnios is common and may be related to a combination of factors, including oesophageal compression (by the small chest), micrognathia, associated gastrointestinal abnormalities and hypotonia.[24]

Once suspected, three-dimensional ultrasound and MRI could be complimentary to the diagnosis. Diagnosis is confirmed by karyotyping. Once diagnosed, termination is an option. In patients who decide to continue with the pregnancy, counselling should be offered with geneticists and neonatologists. If termination is considered, detailed postmortem examination including radiological examination should be considered. As genetic abnormalities are identified in majority of the cases, preimplantation genetic diagnosis is an option for the parents.

Thanatophoric Dysplasias

This is the most common lethal skeletal dysplasia with a prevalence of 1 in 10,000. There are two types – type 1 and 2, both autosomal dominant. Type 2 is associated with the characteristic 'clover leaf' skull due to the premature

craniosynostosis. The bone mineralization is normal and is normally associated with macrocranium and brain abnormalities. Polyhydramnios is very common.

Achondrogenesis

The second most common type of lethal skeletal dysplasia which consists of two types – type 1 (autosomal recessive) which is characterized by poor mineralization of skull and vertebra and fractures and type 2 (autosomal dominant) in which there is hypomineralization of the vertebrae, but not skull. There can be severe thoracic abnormalities.

Osteogenesis Imperfecta Type 2

This is a severe form of skeletal dysplasia with generalized demineralization and multiple fractures and majority die in-utero due to severe fractures and pulmonary hypoplasia. The recurrence risk is 6%.

Non-lethal Skeletal Dysplasias

The most common form of non-lethal skeletal dysplasia is achondroplasia followed by the other types of osteogenesis imperfecta.

Achondroplasia

This is the most common form of dwarfism. This autosomal dominant disease has a prevalence of 0.5–1.5 in 10,000.[22] The primary defect found in patients with achondroplasia is abnormal endochondral ossification. The trunk is normal with rhizomelic shortening of the limbs. The clinical features are secondary to the new mutations in the Fibroblast Growth Factor Receptor-3 (FGR-3) genes. More than 99% of the people with achondroplasia carry a point mutation of the gene, which make prenatal diagnosis easy. Advance paternal age is an important associated factor. Most prenatal cases are diagnosed in the third trimester due to shortened long bones. Once suspected, FGR-3 testing can be done in the fetal DNA in maternal blood. Karyotyping can also be considered. Adequate parental counselling is essential. Life expectancy and intelligence are normal. The homozygous state is a lethal condition, which is associated with a narrow thorax and a small foramen magnum. Death results from spinal compression. If both parents are achondroplastic, there is a 1 in 4 chance for the fetus to have a homozygous achondroplasia.

Sacro-coccygeal Teratoma

Sacro-coccygeal teratoma (SCT) is the most common neoplasm in the fetus with an incidence of 1 in 40,000 births. There is a 3:1 female: male ratio. Most tumours are sporadic. Diagnosis is suspected when a complex mass is detected at the base of the spine. It is believed to arise from the totipotent cells of the Hensens node or as a 'twinning accident' due to incomplete separation of the twins during embryogenesis. There are four types based on the amount of presacral extension. The tumour could be entirely solid, cystic or mixed. The tumours can be extremely vascular and can lead to high output cardiac failure in the fetus. Polyhydramnios can occur due to transudation from the tumour or due to fetal polyuria secondary to the high output state. Once diagnosed, fetal echocardiography should be offered. Fetal MRI could be useful. Fetal therapy is possible in the form of LASER treatment in high output states with polyhydramnios and cardiac failure. Most tumours are benign with malignant changes seen more with solid tumours and male fetuses. Elective section is the mode of delivery with care to avoid trauma to the tumour. Poor prognosis in half of the babies is mainly due to hydrops and preterm delivery (both spontaneous due to polyhydramnios and iatrogenic). Prognosis after postnatal resection depends on the type of the tumour with poor prognosis in tumours with large presacral extensions.

MISCELLANEOUS

Oligohydramnios

This refers to the amniotic fluid volume that is less than expected for gestational age. The aetiology is multifactorial. In the second trimester, it is mainly due to preterm premature rupture of membranes (PPROM), fetal urinary tract abnormalities and intrauterine growth restriction (IUGR). In the third trimester, it is mainly due to IUGR of PPROM. The criteria used for diagnosis are the deepest vertical pool less than or equal to 1 cm or an amniotic fluid index (sum of the vertical measurements of fluid in all four quadrants) of less than 5 cm. Once diagnosed, a detailed anatomical survey of the fetus should be done including Doppler assessment, which might not be easy in the absence of the acoustic window. History and examination should be helpful in diagnosing PPROM. Severe and early onset oligohydramnios can result in postural abnormalities in the fetus and pulmonary hypoplasia. Counselling and prognosis will depend upon the aetiology of the condition.

Polyhydramnios

Polyhydramnios is defined as the accumulation of excess of amniotic fluid. It is assessed quantitatively by using either the deepest vertical pool of more than 8 cm or an AFI of more than 25 cm. The reasons of polyhydramnios are either due to impaired fetal swallowing or fetal polyuria or increased placental secretion. The conditions that impede fetal swallowing are craniospinal defects (anencephaly) gastrointestinal disorders [oesophageal atresia, TOF, duodenal atresia (Fig. 2.10) etc.], pulmonary disorders (CDH, CCAM) skeletal dysplasias, etc. The conditions that cause

polyuria in fetuses are maternal diabetes, hyperdynamic fetal circulation due to fetal anaemia, sacrococcygeal teratomas, pulmonary sequestration and twin-to-twin transfusion syndrome. Placental chorioangiomas are another cause of hyperdynamic circulation in fetuses. Although 80% are idiopathic, the ultrasound examinations should be directed to identify the cause. Screening for maternal diabetes should be undertaken. Karyotyping can be considered depending on the underlying cause. Treatment again will depend on the underlying pathology and amnioreduction can be considered if it is a tense polyhydramnios. Several large observational studies have proved the association of idiopathic polyhydramnios and 2–5 fold increase in stillbirth. Hence early induction of labour could be considered.

Non-immune Hydrops

Hydrops fetalis is the terminology used to describe abnormal fluid collections in 2 or more spaces—ascites, pleural effusion, pericardial effusion and skin oedema. Due to the widespread use of anti-D prophylaxis, currently more than 90% of the hydrops are due to non-immune aetiology.[25] Non-immune hydrops occurs due to a variety of maternal and fetal reasons like:

- Aneuploidies (monosomy X, trisomies 18, 13, 21)
- Genetic syndromes (e.g., arthrogryposis, myotonic dystrophy)
- Metabolic-storage disorders
- Cardiovascular diseases of the fetus
- Fetal anaemia (alpha thalassemia, red cell enzyme deficiencies, etc.)
- Thoracic disorders (CCAM, CDH, pulmonary sequestration, primary hydrothorax, etc.)
- Infections (parvovirus, TORCH, listeria)

In the evaluation of hydrops, a thorough search should be made for the aetiology including a detailed ultrasound (including the middle cerebral artery dopplers) and an echocardiogram. Karyotyping is mandatory. A detailed history of the patient's ethnic background and personal and family history to look for heritable disorders associated with hydrops, such as alpha-thalassemia, metabolic disorders and genetic syndromes should be obtained. TORCH, Kleihauer test and antibody screening of the mother should be done. Regardless of the aetiology, the mortality due to hydrops is very high. The absence of aneuploidies and any major structural abnormalities offer a good prognosis. Termination could be considered in the presence of aneuploidies or any other major genetic or structural abnormalities.[26]

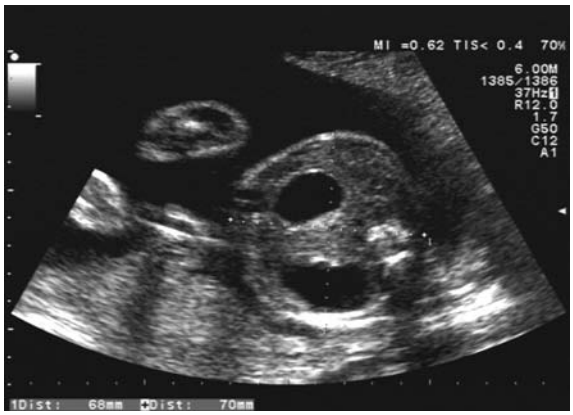

FIGURE 2.10 Ultrasound features of duodenal atresia. Note the classical 'double-bubble' appearance.

ENVIRONMENTAL FETAL RISKS

Diagnostic Radiation in Pregnancy

The use of diagnostic radiation in pregnancy is associated with huge degree of anxiety in the pregnant mother and the obstetricians. In general, the imaging modalities that cause anxiety are the ones involving ionizing radiations unlike the ultrasound and magnetic resonance imaging, which are safe. Fetal health effects of ionizing radiation depend on the radiation dose absorbed and gestational age at the time of exposure. The effects of ionizing radiation are cumulative. Multiple diagnostic procedures involving radiation may place the fetus at risk for negative health effects. The risks of ionizing effects are mainly teratogenic effects, carcinogenesis and genetic effects of the mutations.

Human studies from the atomic bomb survivors have sown that the main teratogenic effects are microcephaly, growth restriction and mental retardation. The radiation-induced brain damage happens mainly during the 8–15 weeks of pregnancy and it appears to be a linear function of the dose of radiation exposure. It has been suggested that a threshold for this adverse effect may exist in the range of 20–40 rads. Although a single barium enema or a CT of the abdomen and pelvis could result in such a dose, even multiple diagnostic X-ray procedures rarely result in ionizing radiation exposure to this degree. On the other hand, the only risk that is statistically proven is that of a small increase in childhood malignancies in fetuses exposed to the ionizing radiations but such risks are not likely to exceed 1 in 1000 children per rad. The other most important sources of ionizing radiation are the nuclear medicine scans that are performed during pregnancy. Radioactive iodine readily crosses the placenta. It can be taken up by fetal thyroid, especially if used after 10–12 weeks of gestation and lead to adverse effects. Radioactive isotopes of iodine used for treatment of hyperthyroidism should not be used during pregnancy, and such therapy should be delayed until after delivery. Ventilation-perfusion scans, that are commonly used in pregnancy for diagnosis of pulmonary embolism is another source of radiation. But, the amount of radiation to which the fetus is exposed is

extremely small (approximately 50 mrad). Nevertheless, the British Thoracic Society recommends that it is better to perform a CT as the risk of carcinogenesis is low and CT can pick up other aetiologies.

In the absence of high dosage radiation delivered directly to the abdomen or pelvis, diagnostic radiography during pregnancy is not seen to be associated with significant adverse events in practice.[27] The theoretical risks of fetal effects should be balanced against potential benefits for the use of diagnostic X-ray procedures in pregnancy.[28] During pregnancy, alternative imaging techniques, not associated with ionizing radiation (e.g., ultrasonography, MRI), should be considered instead of X-rays when appropriate.

Alcohol and Recreational Drug Use

Despite being clearly established as a teratogen since the nineteenth century, alcohol is used by approximately 15% of pregnant women. It causes both maternal and fetal problems. The fetal effects are well-established – miscarriage, teratogenic effects (fetal alcohol syndrome, FAS), mental retardation and learning difficulties. Any alcohol consumption in the first trimester may increase the risk of spontaneous abortion by as much as 4-fold as noted by one retrospective study.

The fetus is exposed to alcohol longer than the mother, due to the deficiency of the enzyme alcohol dehydrogenase in the fetus, hence the damage is profound. Several terms are used to describe the spectrum of fetal effects of prenatal alcohol exposure. FAS is mainly diagnosed by using a combination of facial abnormalities (microcephaly, small palpebral fissures, a flat nasal bridge, a smooth or indistinct philtrum, a thinned upper lip and flattening of the midface), growth retardation, intellectual impairment and difficulties in learning, memory, problem-solving and attention as well as experiencing additional problems with mental health and social interactions. The absence of facial features and the presence of other cognitive abnormalities constitute the fetal alcohol spectrum disorders (FASD), which is 10 times more prevalent than the FAS. Hence the current recommendation is to avoid any drinking at all or restrict to one or two units a week.[29]

Substance Misuse

Many of the effects of drug use in pregnancy are not, in fact, related to drug misuse, but instead to poverty and poor access to health care. The various recreational drugs that are commonly used are cocaine, opiates, cannabis, heroine, amphetamines and benzodiazepines. In majority of the cases, it will be a case of multiple drug misuse. Drug misuse is generally associated with low-birth weight, teratogenic effects, preterm labour and poor perinatal outcome.

Cocaine

Cocaine is a potent vasoconstrictor. It causes vasoconstriction of the uterine and placental bed and leads to abnormal placentation and fetal hypoxia, spontaneous miscarriage, abruption and sudden fetal death. Studies adjusted for alcohol and smoking show that there is a strong association with IUGR, microcephaly and neurodevelopmental delays.[30]

Benzodiazepines

Benzodiazepines, most commonly used for anxiety and insomnia, are another commonly misused drug. The main concern is the teratogenic effect of the drug in causing dysmorphic features like alcohol and facial clefts. Even though a meta-analysis showed no association, large case control studies have shown a strong association with facial clefts. Hence, until further research is obtained in this subject, patients need a detailed ultrasound in the second trimester.

Opiates Including Heroine

Generally used for analgesia, these are misused by 2% of the population. A meta-analysis of six studies show the increased incidence of antepartum haemorrhage in opiate abuse, but these studies have been confounded by tobacco and alcohol misuse as well. Opiate use is associated with a significant decrease in mean birth weight.

Medications in Pregnancy

Prescription drug use is so common in pregnancy. The UK General Practice registry has estimated that 1 in every 160 pregnant woman is exposed to a class X drug (there is positive evidence of human fetal risk based on adverse reaction data and the risks involved in use clearly outweigh potential benefits). The baseline prevalence of congenital defects is 2–3% of which at least 1% is due to medication use.

Anti-epileptic Drugs (AEDs)

These are the most studied groups of drugs in pregnancy. To date, no AEDs are safe in pregnancy and polytherapy is associated with more teratogenesis than monotherapy. The risks of congenital malformations are higher with valproate (7.2%) compared to carbamazepine (2.3%) and lamotrigene (3%).[31] The most common abnormalities identified included cardiovascular malformations (in particular ventricular septal defects), musculoskeletal defects, of ear/neck/face defects, cleft lip and spina bifida. The occurrence of these defects was significantly increased in both with mono and polytherapy. Valproate exposure is associated with neural tube and skeletal defects, carbamazepine use with neural tube and congenital heart defects, and phenytoin use with congenital heart defects, digital abnormalities and orofacial

clefts. Studies have also proved valproate exposure causes low mean IQ and long-term cognitive problems. As folate therapy is clearly found to reduce neural tube defects in general population and few anti-epileptic medications work by folate antagonism, it is prudent to advise women to take high dose of folic acid and have a detailed anatomy scan in the mid trimester.[32]

Antidepressants

Up to 4% of women use antidepressants in pregnancy. The common group of drugs are the SSRIs and the tricyclic antdepressants. NICE guidelines 2007 recommend that fluoxetine is the drug of choice in pregnancy as it is associated with less cardiovascular malformations in the fetus. But a large multicentre cohort study has concluded that both fluoxetine and paroxetine are associated with cardiovascular malformations, in fact, fluoxetine more than paroxetine.[33] So the safety is not well-established.[34] The association of SSRIs and exomphalos is established in few studies but not confirmed in larger studies.

Lithium, a mood stabilizer has long been known to cause Ebstein's anomaly in the fetus. A prospective control study that looked into lithium use in 148 pregnant women indicated that lithium was not a major human teratogen and that the risk for Ebstein's anomaly is 0.5%, or 1/2000 babies whose mothers took lithium during pregnancy.[35] Hence women on lithium should have a detailed ultrasound and possibly offered an echocardiogram to rule out the abnormality.

Progesterone

Earlier studies that looked into the effects of progesterone, found an association between progesterone and masculinization of the female fetuses due to the incidental affinity for the androgen receptors. There have also been older reports about the increased incidence of hypospadias in male fetuses. Larger studies have proven that both progesterone and 17-hydroxyprogesterone have not been shown to increase the prevalence of fetal malformation. The newer progesterones, which are found in the combined oral contraceptive pills, are very low-dose synthetic progesterones that are found to be safe.

Steroids

The anti-inflammatory and the immunosuppressive property of the corticosteroids have been utilized in a wide variety of clinical conditions like asthma, autoimmune diseases, cancer, various dermatological conditions, etc. The association of corticosteroids and non-syndromic oro-facial cleft has been suspected and studied. There is epidemiological evidence to favour this, but they are confounded by recall bias. A Cochrane review has concluded that the available evidence is limited and more studies are needed. A Danish population-based study has proved the safety of oral, inhaled and topical steroids in pregnancy.

Antimicrobials

Antimicrobials are the most commonly used drugs in pregnancy. Despite this, the safety of many drugs remains unclear. The commonly used antibiotics like the penicillin, erythromycin and clindamycin are found to be safe in pregnancy and there have been no reports of teratogenicity in humans. The first and the second generation cephalosporins are found to be safe in pregnancy but the newer third generation cephalosporins are not studied in pregnancy and the safety is not established. On the other hand, sulphonamides and nitrofurantoin have been reported to cause multiple birth defects in animal studies.[36] Sulphonamides, by their folate antagonistic action, are believed to induce teratogenicity in the first trimester and by the bilirubin displacing property, can cause kernicterus in the third trimester. Tetracyclins, although not found to be associated with birth defects, are found to be causing discolouration of the deciduous teeth in the newborn. Aminoglycosides like streptomycin are associated with a theoretical risk of 8th nerve damage but the studies that examine the effect in the first trimester are very limited. Hence, the use of antibiotics to the pregnant population should be with caution and one should use only the appropriate antibiotics for a limited duration.[37]

Metronidazole

Among the studies that looked into the effect of metronidazole in the first trimester, only very few reported birth defects. These abnormalities were of no particular pattern and were non-consistent. Hence with the limited evidence, there is probably no increased risk with the use of metronidazole in pregnancy.

Antihypertensives

The choice of an antihypertensive in pregnancy is very limited. Safety of the commonly used drugs like methyldopa, calcium channel blockers, labetalol and hydralazine are well established in pregnancy.

ACE Inhibitors and the Angiotensin Receptor Blockers

These drugs are contraindicated in pregnancy. While their use in the first trimester is associated with cardiac and nervous system malformations in the available studies, their use in the second and third trimester are associated with reduced renal perfusion and a condition similar to the Potters sequence (i.e., bilateral renal agenesis).[38]

Diuretics

Diuretics have long been avoided in pregnancy and were believed to cause volume contraction and limit fetal

growth. They are also reported to cause neonatal thrombocytopenia and jaundice. But the outcome data from all the RCTs have showed that this might be overrated. Spironolactone should be avoided in particular due to the anti-androgenic effects.

Beta-Blockers

Although this group of drugs are not associated with teratogenicity, the adverse effect on fetal growth is established in small studies. This particularly has been proven for atenolol. Studies comparing atenolol with other agents have proven that it causes significant IUGR. Labetalol, a non-selective beta-blocker, has an established safety profile in pregnancy.[39]

Antimalarials

There is very limited evidence of safety of the antimalarials in pregnancy as pregnant women are excluded from all the trials. A Cochrane review in 2009 concluded that data on uncomplicated malaria in pregnancy were scant and, while some combinations appeared effective, data on safety were lacking. The commonly used medications like chloroquine, hydroxyl chloroquine, artemisinin and its derivatives are proven to be safe in pregnancy. There are no teratogenic effects that have been demonstrated with the antimalarial use. But halofantrine, doxycycline and primaquine are generally avoided in pregnancy. Halofantrine is found to be embryotoxic in animals and doxycycline as the potential to affect the bone growth and cause teeth discolouration. Primaquine causes haemolysis in G6PD-deficient patients and as the status of fetus is not known, it is best avoided.[40]

In general, the risks to the mother and the baby due to untreated malaria outweigh those of treatment and treatment should not be withheld.

Antituberculosis Agents

As with malaria, untreated TB causes more harm to the mother and her fetus than what the medications can. The British Thoracic Society recommends that all the first line anti-TB drugs (i.e., isoniazide, rifampicin, ethambutol and pyrazinamide are safe for use in pregnancy. Streptomycin is avoided due to the risk of ototoxicity. Ethionamide is also generally avoided due to the risk of growth retardation, central nervous system and skeletal abnormalities in animal studies which has also been demonstrated in humans.

Anticancer Drugs

In general, chemotherapy is avoided in pregnancy due to the fetal cytotoxic effects. The two common drugs that might be used in pregnancy as disease modifiers in autoimmune diseases are methotrexate and azathioprine.[41]

Methotrexate

Methotrexate, both in standard and low doses is associated with significant teratogenicity. Methotrexate works by folate antagonism and that is responsible for part of the birth defects like the neural tube and the central nervous system abnormalities. It is also found to cause skeletal abnormalities like limb defects. Even the third trimester exposure is shown to cause severe developmental delays. In the event of the patient choosing to continue the pregnancy after methotrexate treatment/exposure, proper counselling should be undertaken and high-dose folic acid should be prescribed.

Azathioprine

Azathioprine is widely used currently in post-transplant recipients, inflammatory bowel diseases (IBD), SLE, etc. In more than 40 pregnancies exposed to azathioprine, very few anomalies were reported and those were non-consistent, possibly due to the confounding effects of the disease itself rather than the drug. A meta-analysis on the use of azathioprine in IBD has shown that the drug caused no more congenital abnormalities than the background risk.

Aspirin

The effect of low-dose aspirin in pregnancy has been studied extensively. The use of low-dose aspirin is generally safe, and is not associated with an increased incidence of fetal abnormalities. Furthermore, no increase in bleeding complications, fetal oligo-uria or constriction of the ductus arteriosus has been associated with low-dose aspirin. Long-term exposure to higher doses of aspirin (>300 mg/day) in pregnancy may be associated with hemorrhagic disease of the newborn and premature closure of the ductus arteriosus resulting in abnormal pulmonary vasculature and persistent pulmonary hypertension in the newborn. Therefore, long-term use of Aspirin and other non-steroidal agents should be avoided.

INDIAN EXPERIENCE OF FETAL DYSMORPHOLOGY

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

Liquor Amnii and Its Significance in Monitoring Fetal Health

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

Hydramnios

Incidence of polyhydramnios has been previously estimated using pregnancy range between 0.4% and 1.5% with ultrasonography, it is now possible to estimate amniotic fluid volume objectively. Amniotic fluid index (AFI) provides a common standard for evaluation of amniotic fluid volume and its role in assessing fetal health prognosis. Table 2.1 lists factors associated with polyhydramnios.

Bansal et al. reported an incidence of hydramnios in diabetic pregnant women to be about 28%.[42] The incidence of polyhydramnios in diabetic subjects following strict diabetic control is now reducing. Routine practice of blood determination during antenatal care, identifying all rhesus negative women and the widespread acceptance of the use of anti-D prophylaxis has reduced the incidence of hydrops fetalis. Presence of hydrops fetalis in the absence of red cell antibodies has been designated as non-immune hydrops (NIH). With increasing use of ovulation-induction drugs and wider use of assisted reproductive technology (ART) in the treatment of infertility, there has been a rise of multiple births. This has led complications associated with multiple pregnancy and hydramnios. Placental abnormalities like chorioangiomas occurred in 1–5% of patients. Large chorioangiomas >5.0 cm in diameter are associated with complications like hydramnios. Colour Doppler reveals predominant vessels at that site.[43]

TABLE 2.1 Etiology of Polyhydramnios

Etiology	Incidence (%)
Idiopathic	34.0
Gestational diabetes mellitus	24.6
Congenital fetal anomalies	20.0
Red cell Allo-immunization	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 Ed) New Delhi: FOGSI publication, Jaypee Publishers, 2001: Chap. 65; 380.

Important Points

- Structural abnormalities contribute to more than half of the perinatal mortalities worldwide.
- The current practice is a policy to offer universal ultrasound screening to all pregnant women between 18 and 20^{+6} weeks.
- Spina bifida is one of the most difficult defects to diagnose by prenatal ultrasound. Cranial signs of spina bifida include the lemon and banana signs, obliteration of cysterna magna and ventriculomegaly.
- Prenatal surgery for spina bifida remains a controversial intervention and can be associated with considerable morbidity to the mother.
- Atrial width of 10 mm or more in the lateral ventricles constitutes the diagnosis of ventriculomegaly. Prognosis depends on the cause, and presence of other malformations.
- The most common chromosomal abnormality associated with cystic hygroma is Turner syndrome (45X).
- The sonographic diagnosis of CDH is based on mediastinal shift and presence of stomach or bowel loops in the chest.
- Prenatal diagnosis was made successfully in less than one out of four fetuses with serious cardiac abnormalities in the UK.
- Addition of three-vessel view to the four-chamber view leads to improvement in prenatal diagnosis of congenital heart disease.
- Atrioventricular septal defect is associated with a chromosomal abnormality in over 50% of fetuses.
- Cono-truncal cardiac defects are associated with deletion of 22q11 (Di George syndrome).
- Gastroschisis has no sac, and associated chromosomal abnormalities are uncommon. Caesarean section should be performed for obstetric indications only, since there is no evidence of influence of delivery mode on the outcome of foetuses with gastroschisis.
- Exomphalos has a sac covering its contents. There is a high likelihood of associated chromosomal abnormalities.
- Mild renal pelvic dilatation is a relatively common finding and resolves spontaneously in a large majority.
- Obstructive uropathy in a male fetus is most likely to be due to posterior urethral valves. In a female fetus, cloacal type of abnormalities should be suspected.
- Shortening of long bones is far more likely to be due to physiological variation or placental insufficiency than skeletal dysplasia.
- There are several varieties of skeletal dyplasias. Clinically they are classed as lethal and non-lethal varieties. It is very uncommon for achondroplasia to present with significant skeletal shortening before 24 weeks.
- The most common cause of polyhydramnios is unexplained. Diabetes is the most common maternal cause. Fetal congenital abnormalities are the most common fetal cause.
- Due to the widespread use of anti-D prophylaxis, currently a large majority of cases of hydrops are due to non-immune aetiology.
- Anti-epileptics are the most studied drugs in pregnancy. Almost all are associated with fetal structural abnormalities. Polytherapy increases the risk of teratogenicity.

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Chapter 3

Impact of Advances in Genetics on Prenatal Diagnosis

Tessa Homfray

Chapter Outline

INTRODUCTION

Abnormalities of the developing fetus may be suspected following routine pregnancy screening or because of a family history of a previous genetic disorder within the family.

Prenatal diagnosis is performed to guide management of the pregnancy, delivery, and neonatal period. It gives parents the opportunity to understand the possible problems associated with specific abnormalities and potentially the chance of interrupting the pregnancy depending on the abortion laws of the state and country in which they reside.

METHODS OF PRENATAL DIAGNOSIS

Non-invasive Procedures

- Ultrasound
- Fetal MRI
- Free fetal DNA

Ultrasound remains the major screening tool for prenatal diagnosis; it requires expertise by the user. Ultrasound technology continues to improve with increased resolution allowing earlier diagnosis along with 3D ultrasound and colour Doppler.

Invasive Procedures

- Amniocentesis
- Chorionic villus sampling (CVS)
- Fetal blood sampling
- Fetal biopsy
- Fetal surgery

CONFIRMATORY TESTS FOR PRENATAL DIAGNOSIS

Chromosome Abnormalities[1]

- Karyotype by conventional chromosome analysis
- Fluorescent in situ hybridization (FISH)
- Multiplex ligation-dependent probe amplification (MLPA)
- Comparative genomic hybridization (CGH)

Single Gene Analysis

- Sanger sequencing
- Next generation sequencing (NGS)
- Other tests such as amplification refractory mutations mystem (ARMs)

A genetic diagnosis may be made by ultrasound during the first trimester, the advances in ultrasound technology increasingly allows earlier diagnosis. Screening by nuchal translucency for Down syndrome is now routine in many parts of the World but many other syndromes can be identified at 12 weeks without resorting to invasive testing.[2,3]

Examples of ultrasound abnormalities identifiable at 12 weeks:

- Exomphalos
- Short long bones (some lethal skeletal dysplasias)
- Anencephaly
- Major congenital heart disease

For a couple with a high risk for a genetic syndrome, for example, because of a previously affected baby or because of a family history of a disorder it may be possible to pick up abnormalities that would not be routinely identified at the 12-week scan such as polydactyly. Other abnormalities cannot be viewed early in pregnancy as they are not identifiable at an early gestation such as agenesis of the corpus callosum, hydrocephalus and many other brain abnormalities. If ultrasound can reliably identify a syndrome at 12–13 weeks then undertaking an invasive test which may cause a miscarriage and will not give an earlier diagnosis is unnecessary. Hence understanding the natural history of the disorder will allow a decision on which test is most appropriate. For example, a short limb dwarfing syndrome called *Ellis Van Creveld syndrome* presents with short long bones by 14 weeks, whereas achondroplasia will not present with short long bones before 24 weeks despite the final height of an adult being much less for achondroplasia than Ellis Van Creveld syndrome.

3D/4D ultrasound can identify dysmorphic features and fetal abnormalities, which is not possible with standard ultrasound; but it must only be used as a complimentary to standard ultrasound and by experts in 2D ultrasound.

Many chromosome translocations that when unbalanced result in such a large genetic imbalance that the pregnancy will miscarry rather than result in the birth of an abnormal baby. Hence undertaking an invasive test under these circumstances would be unnecessary. The patient may already have undergone a number of miscarriages and will not wish to possible inducing this following an unnecessary test.

Prenatal invasive testing of a fetus for a suspected abnormality can be performed:

- *From 11 weeks by chorionic villus sampling (CVS)*: Chorionic villi are part of the placental tissue.
- *From 16 weeks by amniocentesis*: Amniocytes are derived from the fetal urinary tract and fetal skin. Early amniocentesis has been attempted but studies in the 1990s suggested that there was an increase risk of miscarriage following early amniocentesis over CVS.[4-8]
- *From 18 weeks by fetal blood sampling.*
- *From 18 weeks by fetal biopsy*: Fetal biopsy will only be required for those conditions for which no DNA diagnosis is possible. For example, enzyme diagnosis is required for an enzyme that is only expressed in the liver or a skin disorder requiring a histological diagnosis. As genetic analysis becomes increasingly available, there will be less and less need for these tests.

Chorionic Villus Sampling

Chorionic villus sampling (CVS) material can be used for the majority of tests required for prenatal diagnosis. As with material from amniocentesis a rapid limited karyotype result can be available within two days using QFPCR (See below).

A rapid karytoype can also be performed on cells derived from the syncytiotrophoblast, these are non-dividing cells from the epithelial lining of the placenta, these can be analyzed where there is a concern over the karytoype identified by other techniques or for specific abnormalities such as analysis from a known translocation carrier.[9]

The placental and fetal tissues can have different karyotypes. The identification of chromosome mosaicism (the presence of different karyotypes in different cells) on CVS will require a second invasive test to be performed by amniocentesis to see if this is confined to the placenta or is present in the baby. In the absence of ultrasound abnormalities, 75% of cases of placental mosaicism are confined to the placenta.[10]

CVS has the advantage of a both earlier diagnosis and the presence of a greater amount of DNA than can be extracted from uncultured amniocytes. With the development of more sensitive techniques for DNA amplification, amniocytes can be increasingly used for tests that previously required chorionic villi for effective analysis.

For all single gene analysis, it is necessary to exclude a significant maternal tissue contribution of the sample and this should be routinely undertaken in all cases.

Amniocentesis

As many ultrasound abnormalities are not identified until the second trimester scan, amniocentesis is often the test of choice for chromosome or single gene analysis. It has a lower miscarriage rate associated with it than CVS as well as being technically easier test to perform. It can be performed from 16 weeks gestation. Earlier amniocentesis has a higher miscarriage rate than CVS and should not be performed before this time.[4,5] If a standard karyotype is to be performed on the amniocytes, this is more likely to succeed

in the second rather than the third trimester as there are many dead cells in the amniotic fluid in the latter part of the pregnancy, which will not divide in culture.

Fetal Blood Sampling

Fetal blood sampling (FBS) can be performed from 18 to 20 weeks and will be undertaken if fetal anaemia is suspected and a fetal blood transfusion is being considered. Chromosome testing can be performed more rapidly from a fetal blood sample and the length of the chromosomes seen on analysis from an FBS may be longer and therefore it may be easier to identify small abnormalities on a standard karyotype than it would be on either a placental sample or amniocytes.

CHROMOSOME ANALYSIS

Standard Karyotype (Fig. 3.1)

A standard karyotype will take approximately 2 weeks to be analysed in view of the need to culture the cells and the need for dividing cells for analysis.

The majority of abnormalities identified will be the major trisomies 13, 18, 21 and sex chromosome abnormalities. (Fig. 3.2) Although other trisomies are present at conception, the majority will spontaneously miscarry prior to prenatal diagnosis.

Karyotype Nomenclature

46XY normal male
46XX normal female
P short arm (petit)
Q long arm

The numbers after p and q describe the light and dark band with their distance from the centromere (Fig. 3.3).

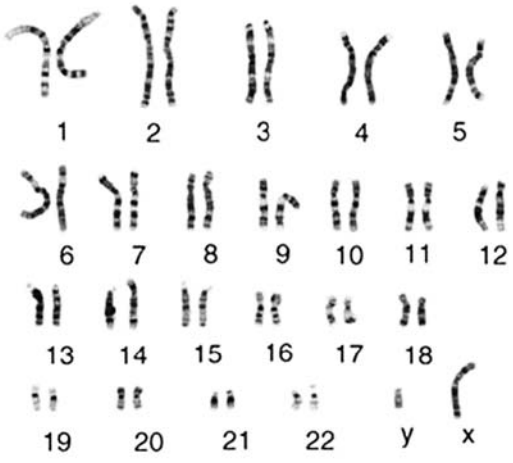


FIGURE 3.1 Standard karyotype 46XY (male).

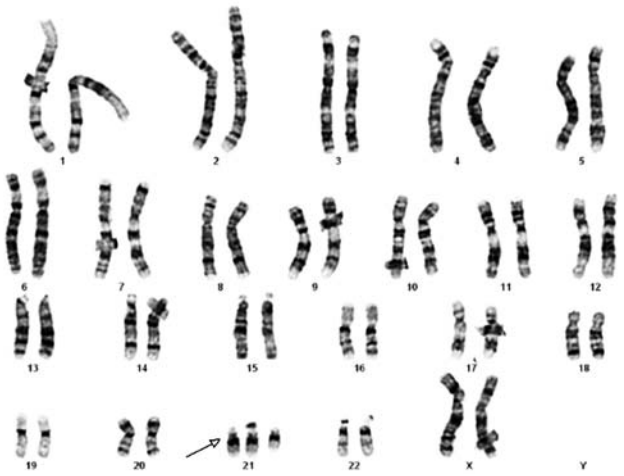


FIGURE 3.2 Trisomy 21 (Down's syndrome).

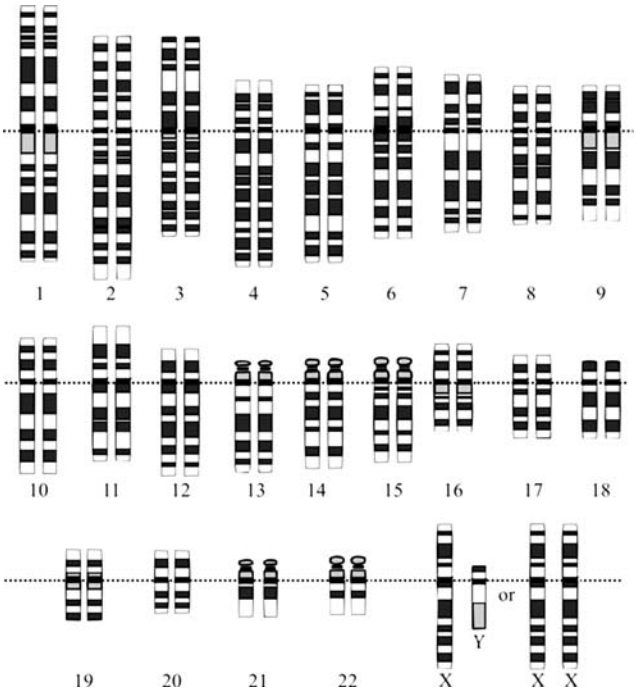


FIGURE 3.3 Ideogram of karyotype showing light and dark bands identifying different chromosomal regions, the nomenclature describes this.

Translocation

A translocation is where one part of one chromosome exchanges material with another chromosome. There are two types of translocations:

- Robertsonian translocation
- Balanced reciprocal translocation

Robersonian Translocation

A Robertsonian (Fig. 3.4) translocation is a translocation involving two acrocentric chromosomes. The short arms of

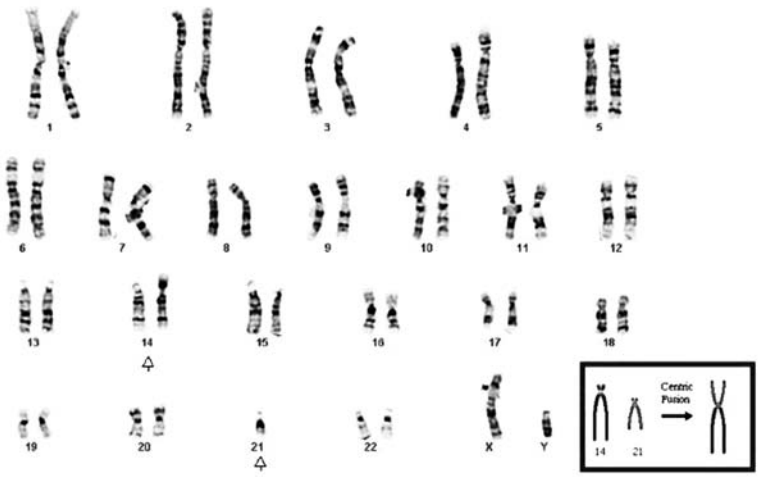


FIGURE 3.4 Robertsonian translocation 45XY t(14;21)(q11;q11). Fusion of 2 acrocentric chromosomes (13,14,15,21,22), the short arms contain multiple copies of ribosomal proteins and therefore are not essential for development.

these chromosomes contain only ribosomal DNA for which there are multiple copies and therefore losing one set of these short arms has no phenotypic effect.

The acrocentric chromosomes are 13, 14, 15, 21, 22.

The resultant balanced karyotype though shows only 45 chromosomes. The overall incidence of a Robertsonian translocation is 1:1000 with 75% being the 13:14 translocation.

Male carriers of a Robertsonian translocation have a higher incidence of infertility although this is inconsistent with many men having normal fertility. Female carriers are more likely to produce pregnancies with unbalanced karytoypes than are male carriers. Invasive testing by CVS or amniocentesis is recommended for all carriers of Robertsonian translocations.

Empirical risk of trisomy 13 at second trimester examination from a 13:14 translocation is 0.4%. This would be higher at 12 weeks.
Empirical risk of trisomy 21 from a female 14:21 is 15% and male 14:21 carrier is <0.5%.

Additional studies looking for evidence of *uniparental disomy* should be requested if the translocation involves chromosome 14 or 15 (which are imprinted chromosomes).

An imprinted chromosome is a chromosome that has a different pattern of gene expression if it has been inherited from the mother rather than the father. Example:

- Paternal uniparental disomy of chromosome 15 results in a baby with Angelman syndrome.
- Maternal uniparental disomy of chromosome 15 results in a baby with Prader–Willi syndrome

For a fetus to survive following conception with these lethal trisomies, one copy of the extra chromosome has to be lost during replication. This is called *trisomic rescue* and is well-recognized for a number of chromosomes including 15, 16 and 22.

Balanced Reciprocal Translocation (Fig. 3.5)

Balanced reciprocal translocation in which no missing genetic material can be identified. Apparently balanced chromosome translocations normally result in a normal phenotype.[11] In 6% of cases that have arisen de novo congenital abnormalities will be present secondary to either microdeletions or gene disruption at one of the breakpoints.[12,13]

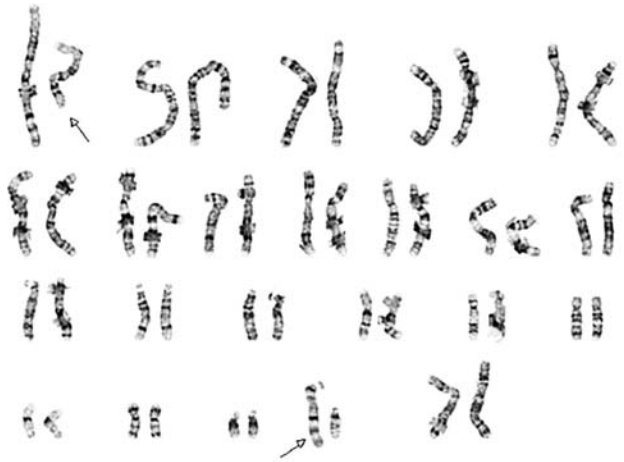


FIGURE 3.5 Balanced reciprocal translocation 46XX t(1;22)q25;q13. Exchange of chromosome material between two non-homologous chromosomes, as all the genetic material is preserved there is no adverse effects from this.

Six percent of babies with balanced de novo translocations will have developmental abnormalities.[14]

Surprisingly other deletions/duplications are more frequently identified in other areas of the genome not related to the de novo translocation[15] suggesting a more generalized problem occurring during meiosis.

Unbalanced karyotype resulting from a parent with a balanced translocation (Fig. 3.6)

A translocation can involve more than two chromosomes and in these cases the risk of fetal abnormality is much higher. Not only are the number of breakpoints increased to have potential deletions and gene disruptions but mitosis may be impaired and growth retardation is common in this group.

The larger the translocated segments, the less likely the unbalanced rearrangements will give rise to viable offspring.

Inversions

An inversion is where a chromosomal segment has undergone 180° rotation. If the inverted segmented occurs on the same side of the centromere, it is a *paracentric inversion* and if on opposite sides, it is a *pericentric inversion*.

The only possibility of a viable fetus resulting from abnormal recombinants from an inversion is where the inverted segment is large and the resulting recombinants result in small deletions and duplications.

Chromosome Deletions and Duplications

Unbalanced karyotypes other than numerical whole chromosome changes will result in either deletions or duplications of genetic material. The majority will arise de novo in the fetus but they may be secondary to a balanced chromosome translocation (Fig. 3.6) or more rarely an inversion in a parent. Identifying small deletions and duplications is skilled and molecular techniques are increasingly used to characterize these. The phenotypic effect of these abnormalities may be difficult to predict, this is especially the case for small duplications.

Following identification of a deletion or duplication, it is frequently necessary to confirm that the parents do not carry the same abnormality and are themselves asymptomatic and therefore it may not have a major effect on the baby's development. In these circumstances, it is important to confirm that the parent carrying the abnormality has not had medical or developmental problems. The parent may themselves have significant learning difficulties and may not be able to manage a child with problems.

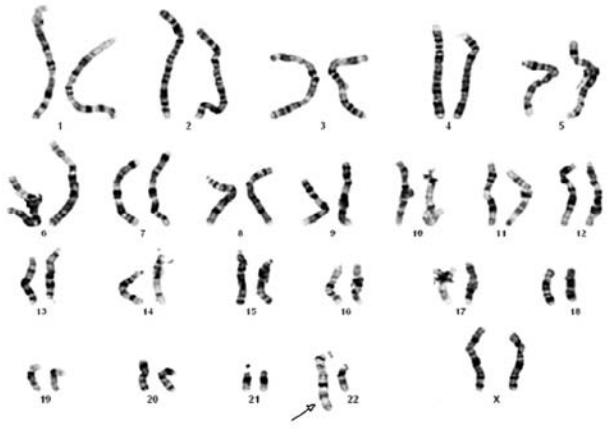


FIGURE 3.6 Unbalanced karyotype arising from balanced 1;22 translocation. Trisomy 1q25 and monosomy 22q13.

Marker Chromosomes

A small extra amount of chromosome material may exist as an extra chromosome and this is known as a *marker chromosome* (Fig. 3.7). The origin of the marker chromosome will dictate if it will have a phenotypic effect on the developing fetus. Many only contain euchromatin which will not contain active genes and will not be associated with problems although the future fertility of the baby potentially could be affected by this. Hence it is important that the origin of the marker chromosome is identified which will require more advanced techniques (see below).

Surprisingly large marker chromosomes can have no phenotype and hence it is essential to undertake parental karyotyping when one is identified.

Marker chromosomes may be entirely innocent depending on their chromosomal origin.

Marker chromosomes are often mitotically unstable and therefore will get lost during cell replication and frequently will be mosaic.[16,17]

Chromosome Mosaicism

Not all cells may contain the same number of chromosomes.[18] Hence, there will be an abnormal karyotype in some cells and a normal karyotype on other cells. This mosaicism may involve a whole extra chromosome or a marker chromosome.

As only a few trisomies are compatible with a prolonged gestation, trisomic rescue may take place where by one copy of a chromosome is lost during mitosis and the cells then with the normal chromosome numbers will proliferate more effectively than the abnormal cells. There may well be a remaining abnormal trisomic cell line that could have a phenotypic effect on the baby.[19]

Trisomic rescue allows survival of a fetus that would otherwise have miscarried.[20]

Chromosome mosaicism is frequently confined to the placenta and is known as *confined placental mosaicism*. Any CVS that identifies two cell lines will require a second invasive test to clarify the significance of the placental mosaicism to the baby.[21]

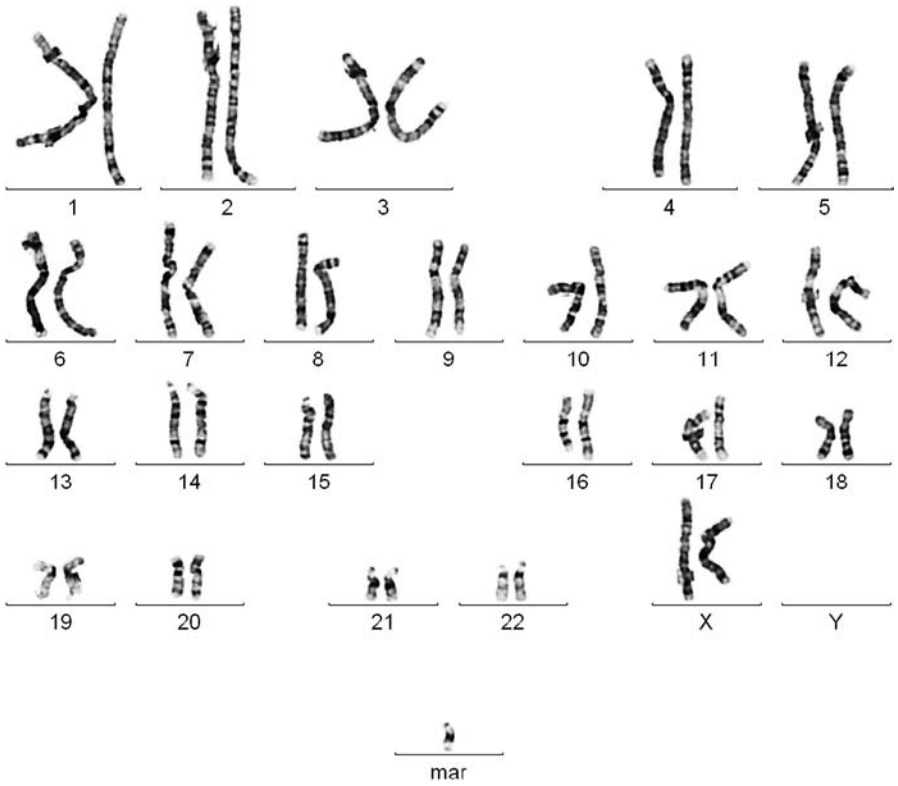


FIGURE 3.7 Marker chromosome.

A marker chromosome may also exist in a mosaic form, as the marker may not replicate well during mitosis as it has not natural pair.

Confined placental mosaicism (CPM) may cause restricted growth in the fetus later in gestation as the placental function may be affected by the extra chromosome.[22-24] This is most commonly seen with CPM for trisomy 16.[25,26]

Molecularly Based Karyotype Tests

A standard karyotype requires cell differentiation and therefore cannot be undertaken rapidly and it can only identify a 5–10 Mb deletion as anything smaller will appear balanced when examined under the light microscope. Even this size deletion may be missed especially on chorionic villi and amniocytes where it is more difficult for the chromosomes to elongate during the culture process. Laboratories routinely assess the quality of the chromosome preparations and may report that the quality of a sample is substandard. Other tests have been developed to identify smaller deletions and duplications.

Quantitative Fluorescent Polymerase Chain Reaction

Quantitative fluorescent polymerase chain reaction (QFPCR) (Fig. 3.8) has been developed so that the most common

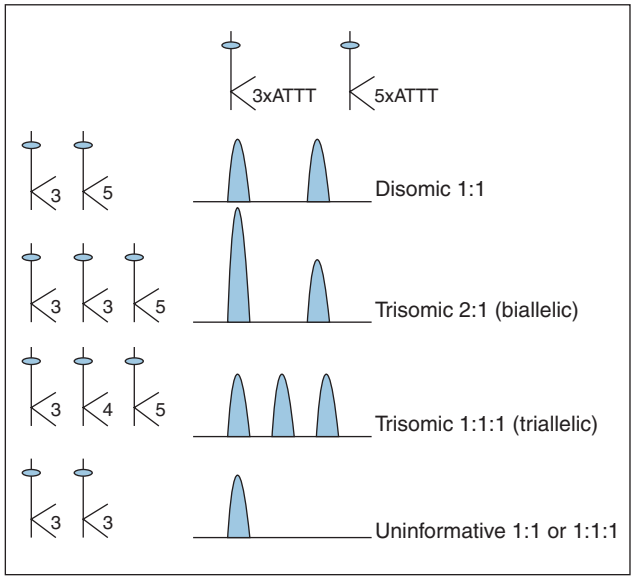


FIGURE 3.8 QFPCR for rapid analysis for the common trisomies. QFPCR analysis includes amplification, detection and analysis of chromosome-specific DNA sequences known as genetic markers or small tandem repeats (STRs). The above figure shows three alleles of 3, 4 and 5 ATTT repeats. Trisomies can be detected in the middle two examples. Many chromosome specific markers are used for each of the chromosome of interest.

abnormal karyotypes can be identified within 48 hours of the sample test.[27,28] This will identify the major trisomies, which are chromosomes 13 (Patau syndrome), 18 (Edward syndrome), 21 (Down syndrome) and the sex chromosomes and monosomy X (Turner syndrome). It will also identify a triploid (69 chromosomes) pregnancy. The QFPCR test for these chromosomes has been developed as these account for approximately 90% of the identifiable abnormalities on a standard karyotype.[29] Other chromosome trisomies could be incorporated into this test if the clinical utility was felt to be high enough. Some laboratories include markers on chromosomes 15 and 16. This may be particularly useful investigating the underlying cause of miscarriage. Miscarriages are frequently caused by fetal trisomies.

QFPCR is a quantitative test looking at the ratios of the DNA at different DNA markers on the chromosomes of interest (Fig. 3.8). A marker is a short run of DNA that is specific for the chromosome in question. A polymorphic marker is a marker that has multiple different variations at that locus. To identify that a fetus has a variation in the number of these markers, it is necessary to use only polymorphic markers. Hence there should be either two different peaks at each marker (one from each parent) or some peaks with twice the height of the other markers indicating that the parents carries the same marker sequence at that point. As it is a ratio, a marker is said to be uninformative if only one peak is present. The presence of three markers across the chromosome would suggest a trisomic fetus. If there are some markers that have two peaks with one twice the height of the other, this again would suggest trisomy at that locus.

If the origin of the extra set of chromosomes arose from non-disjunction at meiosis I, then the two copies of the extra chromosome will be different, this is the commonest origin of Down syndrome and is associated with an increased incidence with maternal age. If the abnormality arises from a meiosis II error, then the extra chromosome will be the same as one of the other copies, that is, there will be peaks that are twice the height rather than having three separate peaks. This is similar to the pattern that will occur if the additional chromosome occurred during mitosis in the placenta. This is important in differentiating true mosaicism from confined placental mosaicism (see below).

TECHNIQUES FOR IDENTIFICATION OF SMALLER CHROMOSOME ABNORMALITIES

Fluorescent In Situ Hybridisation (FISH) (Fig. 3.9)

A chromosome sample is denatured on a glass slide so that the DNA is single stranded and then mixed with a DNA probe. This is a sequence of DNA that is complimentary to the sequence of interest. A fluorescent probe may be already annealed to the probe DNA otherwise a further step will be required after the probe and the patient's sample have been mixed together. If a chromosome preparation shows only one signal, then there is a deletion of the second copy of the DNA sequence in question (Fig. 3.9), if there are more than two signals then a duplication is present. Duplications are difficult to identify using FISH. A control DNA probe sequence on the same chromosome is always used to make sure the analysis is successful in that specific sample.

FIGURE 3.9 FISH. Deletion of 22q11.2 (Di George Syndrome). Only one red 22q11 fluorescent marker is seen. Two green markers shows control site is not deleted.

This technique is excellent for identifying a specific abnormality, for example, a 22q11.2 deletion in a fetus with a cono-truncal cardiac defect.

FISH will only identify a known microdeletion syndrome and therefore can only be used to confirm a specific diagnosis suspected from clinical features. Table 3.1 lists common microdeletion syndromes.

Multiple Ligation Probe Amplification (MLPA) (Fig. 3.10)

This technique can identify many more abnormalities in one reaction than can be identified by FISH but it is still limited to the commonest deletions such as those at the telomeres (ends of the chromosomes) and the commonest microdeletion syndromes. Forty probes can be used per experiment.[30]

Prenatal Bacterial Artificial Chromosomes on Beads (BoBs)

This can provide dosage information on a number of predetermined chromosome regions. It can identify the common trisomies 13, 18, 21 X/Y and the nine commonest microdeletion syndromes.

A *bacterial artificial chromosome* (BAC) is a sequence of DNA that has been incorporated into a bacterium to allow a large amount of the sequence of interest to be manufactured,

TABLE 3.1 Common Microdeletion Syndromes

Microdeletion	Syndrome	Prenatal features	Additional features postnatally
22q11.2 2-3Mb	Di George	Conotruncal defects, absent thymus	Cleft palate, immunodeficiency, MR
7q11.23 1.5-1.8Mb deletion	Williams	Supravalvular aortic stenosis, pulmonary stenosis	MR Dysmorphic
15q11.2, 5.3Mb + deletion (pat)	Prader Willi[50]	None	Hyptonia, poor feeding, MR
15q11.2, 5.3 Mb + deletion (mat)	Angelman	None	MR, ataxic gait, happy disposition
17p13.3 350Kb+	Miller Dieker	Ventriculomegaly, MR, lissencephaly	Severe MR, wrinkled skin over the glabella
1q21.1, 200Kb	TAR	Absent radius	Thrombocytopaenia
4p16.3 2.5Mb+ deletion	Wolf Hirschhorn	CHD, IUGR, cleft lip/palate	Severe MR

MR - mental retardation.

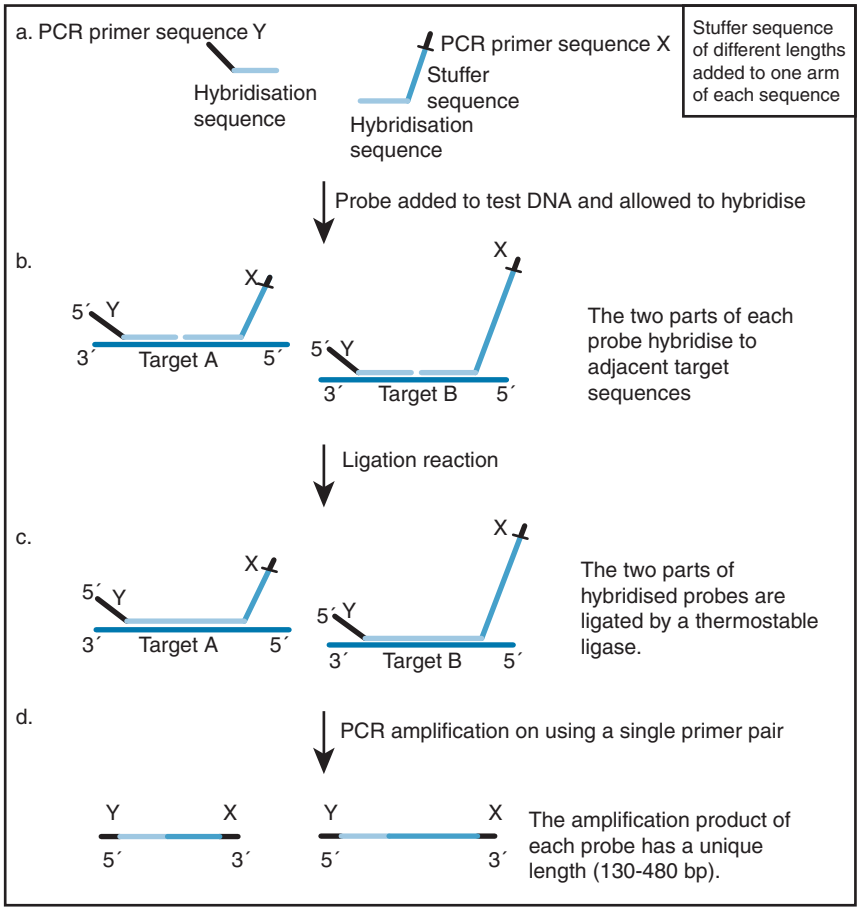


FIGURE 3.10 Multiple ligation probe amplification. Probes are ligated and amplified only if the target DNA is present in the sample. This technique can be used to find the relative copy number of the target DNA.

this can then be used to test for the presence of this sequence in a fetal sample.

Prenatal BoBs uses 85 microspheres or beads. BACs derived from each chromosome region of interest have been immobilized on each bead, which then has three fluorochromes attached for quantifying the reaction. The sample DNA is then added and analyzed using the PerkinEmer software. This technique can produce a rapid result and is more informative than QFPCR with high specificity >99% and sensitivity >98%.[31] This technique can also be used for identifying the chromosomal cause of recurrent miscarriage. Standard karyotypic investigation of products of conception (POC) is notoriously unsuccessful as the chromosomes fail to grow as they originate from dead tissue and maternal contamination is common and hence any 46XX result is always suspect. BoBs using two probes/chromosome arm and three for each acrocentric chromosome has been shown to be an accurate method of identifying trisomies.[32] Terminal deletions and duplications have a lower overall pick up rate and may not be suitable for this analysis. Eighty to ninety per cent of chromosomal defects in POC are due to numerical chromosomal abnormalities. Mosaic abnormalities may be detected but at a lower rate and maternal cell contamination remains the major cause of test failure.

Comparative Genomic Hybridization (CGH)

Comparative genomic hybridization (CGH) (Fig. 3.11) is a molecular technique that identifies DNA copy number changes.[33] It can be described as a molecular karyotype. A standard karyotype can identify abnormalities of 5–10 Mb depending on the location of the abnormality, the quality of the sample and the expertise of the cytogeneticist, CGH can identify abnormalities that are <100 kb in size. Hence it can identify abnormalities that are 15× smaller than those identified in the standard karyotype.[34-36]

Arrays utilize the complimentary nature of DNA. An array is a glass slide onto which thousands of short sequences of DNA (probes) are spotted. Arrays are available in various formats: 4×44K, 8×60K, 2×105K, 4×180K depending on the number of probes that are used to cover the genome and the number of samples that can be run concurrently. The patient DNA is labelled with one coloured fluorescent dye and the control sample with another coloured dye. The patient and control samples are then denatured to become single-stranded and then mixed together and applied to the slide.

Hybridization occurs, where the DNA anneals to the matching probes on the array.

The array is then scanned to measure the intensity of each dye. CGH is now the standard test of choice in many countries for the investigation of the developmentally delayed child without an obvious diagnosis. The advantage over a standard karyotype has been confirmed by many studies.[37,38] It identifies the underlying cause of mental retardation in an additional 10–15% of children previously without a diagnosis.

The disadvantage of the test is that it may identify variations in quantity of DNA that are of unknown significance. These are known as variants of unknown significance (VUSs) or copy number variants (CNVs). Comparison with the parental genome will show whether the copy number variation is present in a parent or has arisen de novo.

- De novo variations are more likely to be disease causing but this is not always the case and therefore the results need to be correlated with the ultrasound findings.

  If the fetus is identified on ultrasound with radial aplasia and a 200 kb deletion is identified on chromosome 1q21.1, one parent may carry this and have no limb abnormality. It has been found that in association with a rare point mutation on the other chromosome in a gene called RBM8A causes TAR syndrome (thrombocytopenia absent radius).
- There are many other examples of variants that are known to carry an increased risk of developmental disorders, but it is possible to be a normal carrier of the variant. An, as yet undiscovered, abnormality on the other chromosome or even in another part of the genome may be causing these effects.

Hence the results of CGH need to be very carefully analysed to check that the CNVs have not been over interpreted. The need to undertake parental analysis is more frequent than in a standard karyotypic analysis. Although it is requested following abnormalities on a standard karyotype, this is normal to ascertain the recurrence risk for future pregnancies. CGH abnormalities may be completely benign and hence parental analysis may alter the risk to the present pregnancy. As we understand more about CNVs the numbers that are potentially falsely thought of as significant is decreasing.[39] CGH has been evaluated in the prenatal setting in a number of studies and the identification of extra-likely pathogenic abnormalities that would not have been identified on a standard karyotype is of the order of 6% when ultrasound abnormalities are present. This is following a normal standard karyotype analysis.

CGH identifies the cause of fetal abnormalities in 6% more cases than does a standard karyotype.[40,41]

Introduction of prenatal CGH as an alternative to a standard karyotype is being introduced in a number of centres in the World at the present time. Many centres are limiting what they report to known syndromic disorders and large deletions and duplications. This is controversial as there may be information that is withheld, which in the future may be interpreted as significant. Information may also be available about a future condition such as a cancer predisposition that is not related to the prenatal findings.

Assessment by a clinical geneticist may ensure that the test is used most appropriately requested. Certain ultrasound

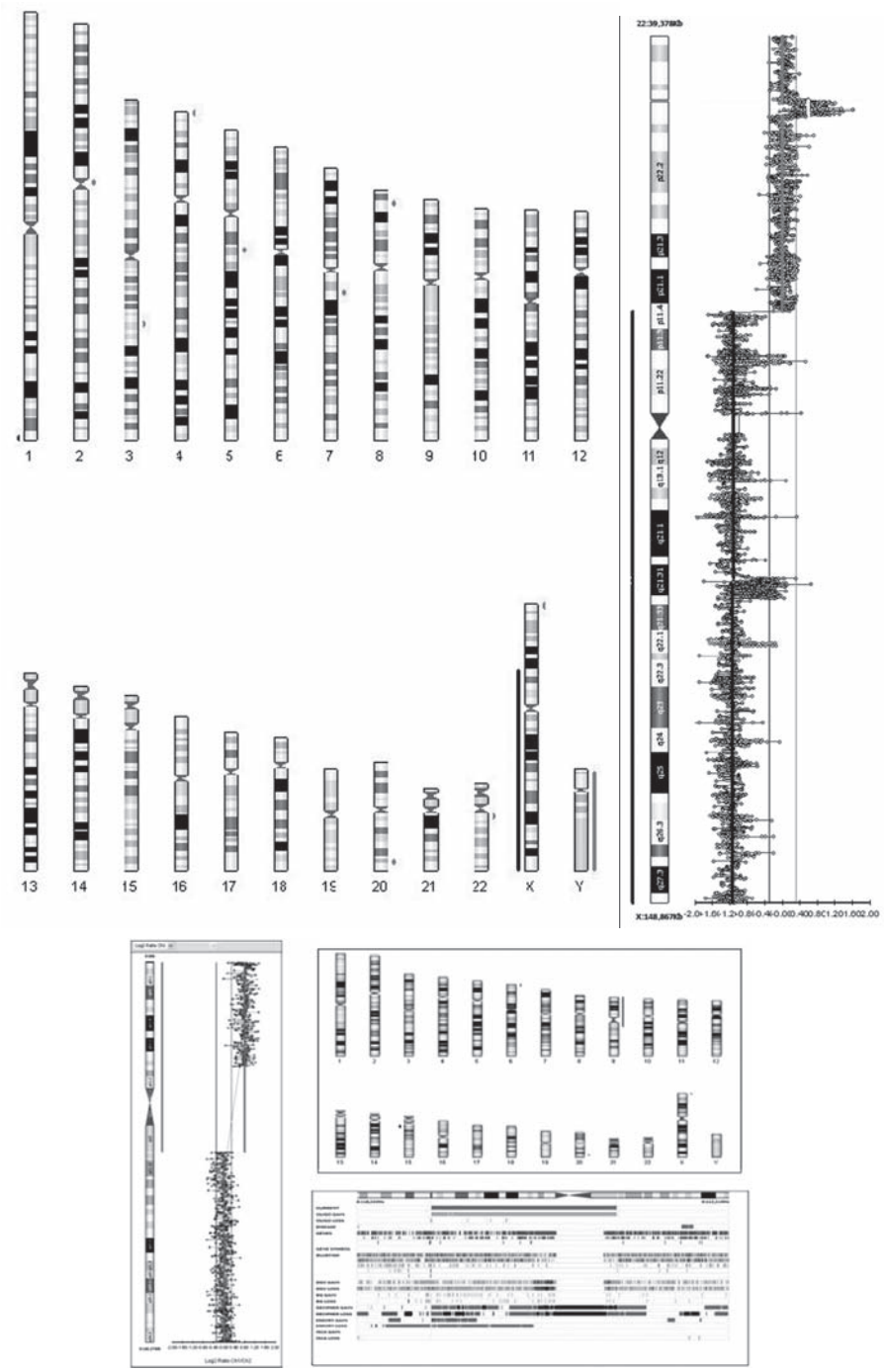


FIGURE 3.11 Comparative genomic hybridisation (CGH) test. DNA (hybridised with red dye) and 'normal' DNA (hybridised with green dye) compete for binding with probes. The ratio of green to blue dye, i.e., expected to be 1:1 in the absence of imbalance in test DNA. 20,000 to 60,000 probes may be used in each array platform. The site of imbalance can be mapped to a region on the chromosome using computer software.

abnormalities may be suggestive of single gene disorders such as bent short long bones in thanatophoric dysplasia and osetogenesis imperfecta.

CGH will not identify point mutations or the majority of small intragenic deletions which are the cause of the majority of single gene disorders.

As free fetal DNA technology becomes more widely available and the major trisomies are excluded before detailed ultrasound examination then the technology will become the test of choice over standard karyotyping. In present time, the cost of CGH analysis remains above that of a standard karyotype as the reagents used for analysis are more expensive.

CGH analysis can be automated and therefore larger volume work is possible. It does not depend on culturing the cells and therefore the failure rate observed with failed culture will not occur. Certain DNA samples appear to be more difficult to analyse than others so there will still remain a failure rate for the test. As the cost continues to fall and offering CGH as the first line test after QFPCR may eventually be more cost effective.

CGH will not identify a balanced translocation and it will not identify a triploid fetus, the former should not cause an effect in the fetus in the absence of an associated deletion and the latter will be identified on the QFPCR.

Free Fetal DNA (Fig. 3.12)

Lo and co-workers first reported the possibility of using cell-free DNA derived from the fetus circulating in the maternal plasma in 1997.[42] They identified the presence of Y chromosome material and since that time research has concentrated on identifying new technologies to amplify fetal DNA in the maternal circulation for prenatal diagnosis for the identification of the major trisomies and single gene disorders.

Circulating fetal DNA consists of short fragments, 80% are less than 200 bp. The fetal DNA consists of approximately 3–6% of the circulating free DNA in the maternal circulation. It can be first detected at Day 18 after embryo transfer in IVF fetuses and it increases in amount during the pregnancy. It is cleared from the maternal circulation within about an hour of delivery.[43] The source of this DNA is placental in origin. Fetal sexing has been routinely used in some countries to identify foetuses at risk from X-linked or sex-limited disorders now for some years with >99% accuracy.[44]

Free fetal DNA (ffDNA) accurately identifies the sex at 9 weeks gestation, hence only male fetuses would need invasive tests to identify babies at risk from X-linked recessive diseases.

Since free fetal DNA was first identified in the maternal circulation, the development of newer technologies has now made it possible to have commercial tests available for the identification of the major trisomies. Following

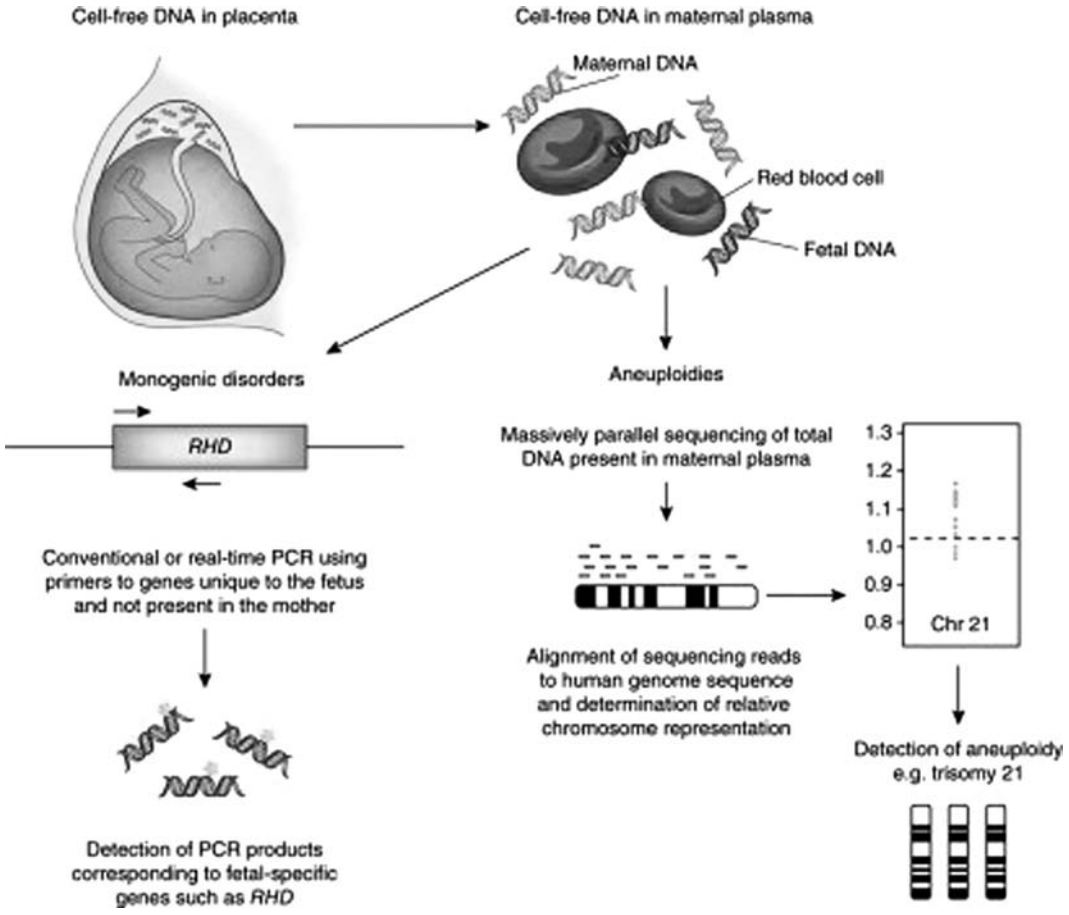


FIGURE 3.12 Free fetal DNA identification of Trisomy 21. (Reprint Diana Bianchi. *Nature Medicine* 2012;18:1041–1051)

clinical validation, the test is now available from different companies using different techniques for commercial application.

The sensitivity is highest for trisomy 21 and appears to be approaching 100%, the specificity is lower than the sensitivity and therefore it is recommended that identification of trisomy 21 on ffDNA still requires confirmation by invasive prenatal diagnosis. Hence it remains as a screening test at the present time. The sensitivity and specificity are lower for trisomies 18 and 13.

It is anticipated that ffDNA technology will expand to identify other chromosome abnormalities in the future. (ffDNA for single gene disorders see below)

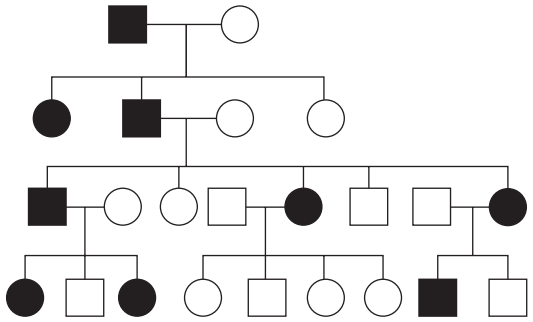


FIGURE 3.14 Autosomal dominant pedigree. (By kind Permission NHS National Genetics and Development Education Centre)

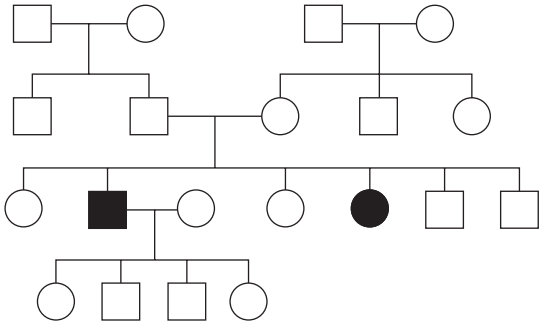


FIGURE 3.15 Autosomal recessive pedigree. (By kind Permission NHS National Genetics and Development Education Centre)

SINGLE GENE DISORDERS

Inheritance Patterns

Pedigree Drawing Symbols (Fig. 3.13)

- *Autosomal dominant* (Fig. 3.14)

  One parent affected, 50% risk to offspring, may be very variable severity of the disease even within a family. Examples include, neurofibromatosis type 1, Marfan syndrome and Huntington's chorea.
- *De novo mutation*

  New dominant mutations are common especially where the disease is very severe and the fetus/baby will not have a prolonged survival. Severe osteogenesis imperfect and thanatophoric dysplasia are lethal disorders normally secondary to de novo new dominant mutations.
- *Autosomal recessive (*Fig. 3.15)

  Both parents will be carriers and in the majority of diseases will be asymptomatic. The baby will only be affected when he/she inherits two abnormal copies of the gene and hence there is a 1:4 chance of any baby being affected. Examples include thalassemia, cystic fibrosis and sickle cell anaemia.
- *X-linked recessive* (Fig. 3.16)

  As women have 2X chromosomes, a mutation in a gene on one of these is unlikely to cause an abnormality but boys with only one copy of the gene may have a very serious disease associated with this. Examples include

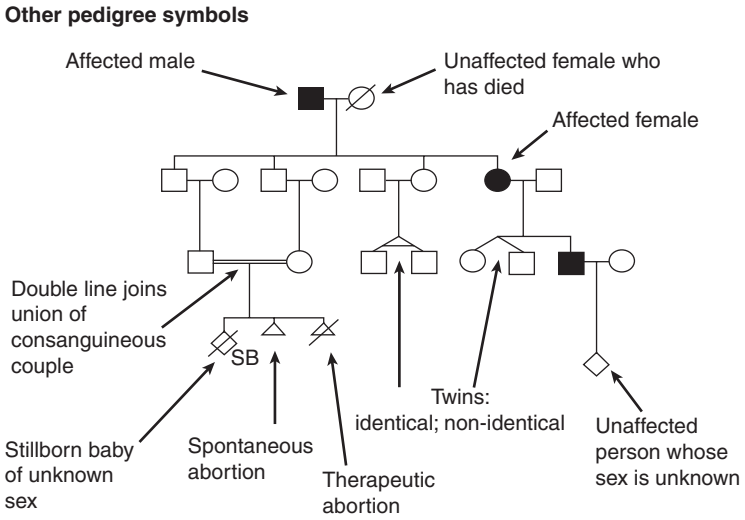


FIGURE 3.13 Standard symbols are used in drawing a pedigree diagram. (By kind Permission NHS National Genetics and Development Education Centre)

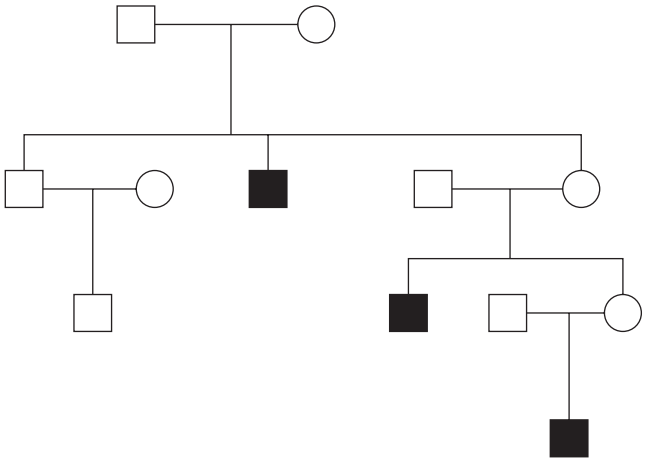


FIGURE 3.16 X-linked recessive pedigree. (By kind Permission NHS National Genetics and Development Education Centre)

Duchenne muscular dystrophy, fragile X syndrome and X-linked hydrocephalus.

- *X-linked dominant*

  A few diseases may be so severe in affected boys that the pregnancy miscarries prior to disease recognition and therefore only affected girls are born with the disease. Examples include Aicardi syndrome (severe mental retardation with agenesis of the corpus callosum), Rett syndrome (severe mental retardation with progressive microcephaly, developmental regression and abnormal hand movements) and Incontinentiapigmenti with a crusting skin abnormality at birth which improves but there may be visual problems and mental retardation and abnormal hair growth.

- *Imprinting disorders*

  Certain genes are only active if they are inherited from a male or a female parent.[45] Hence if a disease mutation is inherited from a parent where the gene should not be active then there will be no phenotype, but if inherited from the parent where it should be then the baby will exhibit the disease.[46-48] For example, a baby with a mutation in CDKNC1 will have Beckwith–Weidemann syndrome if the mother carries the mutation and may present antenatally with an exomphalos, but if the father is a carrier there will be no phenotype. If a mother carries a mutation in UEB31, which she has inherited from her father she will be normal but if she passes this on to her child, the child will have Angelman syndrome.

Molecular Techniques for Identifying Mutations in Single Gene Disorders

The presence of a single gene disorder may be identified by screening during pregnancy or there may be a known genetic disorder within the family. In either case it is necessary to be certain that the mutation causing the disorder within the family is known prior to undertaking invasive diagnosis.

A gene is divided into exons and introns, the coding regions are the exons and these need to be sequenced along with sequencing either side of the exon/intron boundaries (Fig. 3.17).

Sanger Sequencing (Fig. 3.18)

Sanger sequencing remains as the gold standard for gene sequencing. It requires that double-stranded DNA is denatured, normal nucleotides and altered nucleotides labelled with a fluorescent dye and a polymerase are then added and run on a sequencer. The problem with this technique is that only a small amount of DNA can be analysed in any one reaction, which makes the technique slow and expensive.

For mutation identification, Sanger sequencing requires amplification by PCR of genomic fragments of approximately 200 bp each and then these are analysed for a mutation against the known sequence. If a mutation is identified, it needs to be verified that it is disease causing and not part of normal variation.

Certain DNA sequences are much more difficult to analyse than others. It is also relatively slow and only a small part of a gene can be targeted in anyone reaction. It is though excellent for sequencing accurately for a known mutation.

Amplification Refractory Mutations System (ARMS) Test

Oligonucleotides, which are complimentary to a given DNA sequence except for a mismatch at their 3'OH residue, will not function as primers in the PCR under appropriate conditions. Therefore for each mutation that is examined there will be two reactions. One with the normal and one with the abnormal sequence, the normal sequence will only amplify the normal and the abnormal will only amplify the abnormal. This is a rapid method for looking for common mutations as seen in cystic fibrosis or thalassemia. It is only suitable for single base changes or small deletions.

Next Generation Sequencing (NGS)

Many single gene disorders present clinically with very similar clinical features and there is an even greater limitation of phenotypes antenatally. Interpretation of the abnormalities is

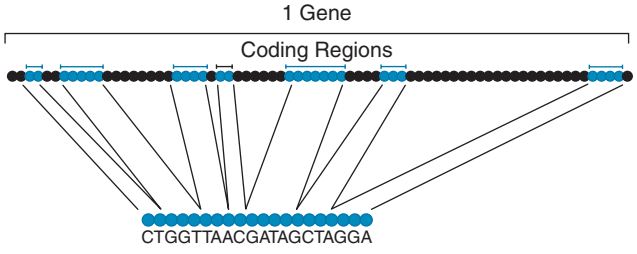


FIGURE 3.17 Coding regions of the gene.

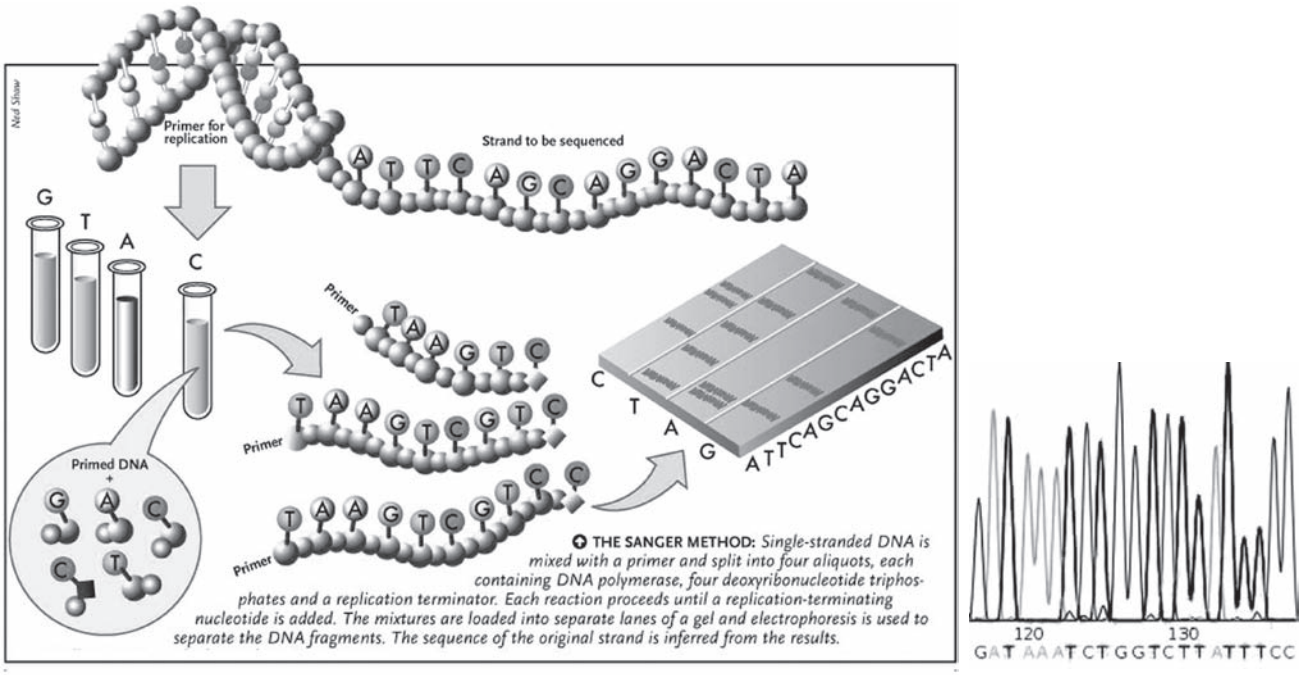


FIGURE 3.18 Sanger sequencing *(Image Courtesy www.nedshaw.com).*

therefore limited and parental decisions frequently have to be made on limited information. Sequencing of genes using conventional Sanger sequencing is slow and expensive, and therefore if there are a number of genes that can cause the phenotype analysis is unsuitable using this technology in the field of prenatal diagnosis that needs to be rapid. Next generation sequencing can analyse whole genomes. Most testing analyses only the exomes (the coding regions of the genome). Total exome sequencing is used for identification of new genes. This though creates an enormous amount of data, which is very difficult to interpret, and is not suitable for prenatal diagnosis at the present time.[49] The technique involves fragmentation of the whole genome. The areas of interest are then pulled down on to a slide, which consist of DNA probes. The rest of the unwanted DNA is washed off the sample. The sample DNA is then amplified and then read by a number of different platforms [Fig. 3.19 (a)]

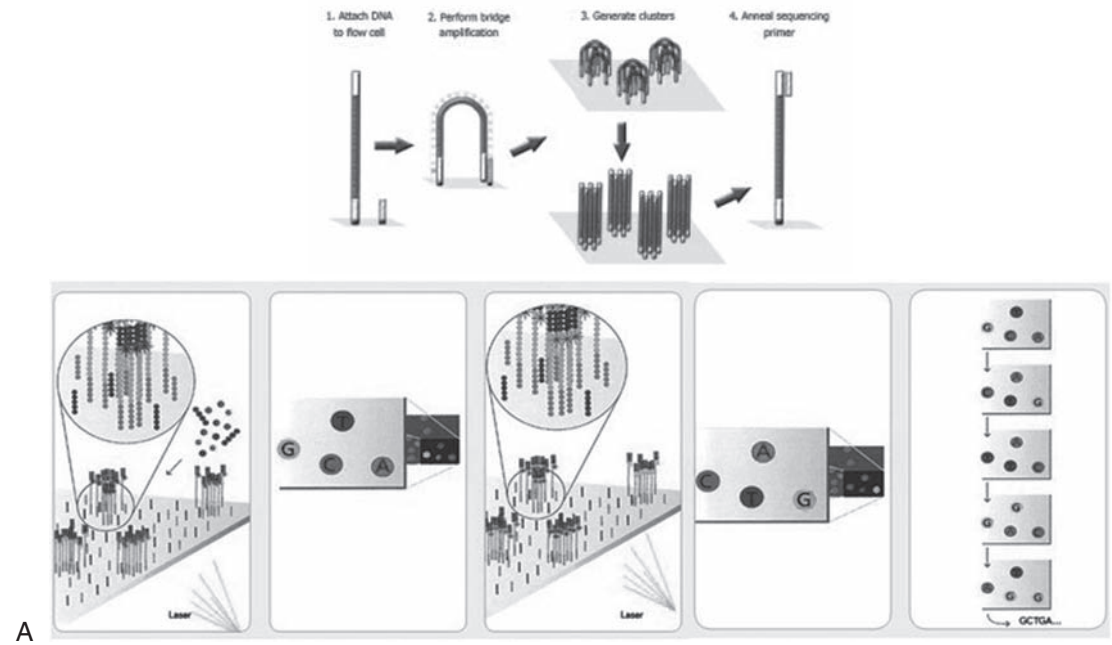
The accuracy of the test will depend on how many copies of each region of interest are captured and is known as the depth of the read [Fig. 3.19 (b–d)].

Having sequenced multiple genes the data needs to be analysed, large number of variants are identified and then it is necessary to identify which variant if any is likely to be pathological [Fig. 3.19(e)].[49]

Many diseases are caused by more than one gene and therefore even in the postnatal setting multiple genes are most effectively examined concurrently and hence more and more panels of genes are being developed. Gene panels using this technology can allow rapid cost-effective analysis for the commoner fetal abnormalities identified by ultrasound that are not caused by chromosome imbalance. For example, the persistence of or a very high nuchal translucency (Fig. 3.20) may be caused by a gene mutation within the MAP-K Rasopathy or more commonly known as the *Noonan pathway* (Fig. 3.21). Sanger sequencing is too slow to analyze such a large number of genes to be effective for a prenatal diagnosis. The amount of DNA required for this technique remains above that for standard analysis at the present time.

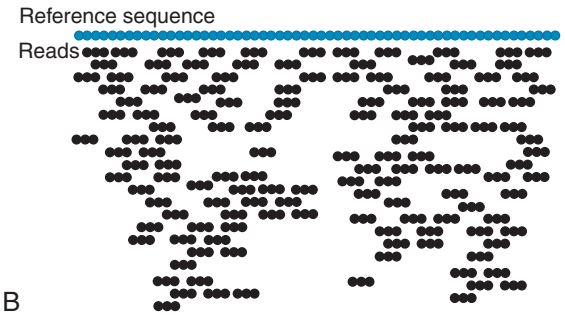
Next generation sequencing allows large amounts of DNA to be sequenced at the same time. The difficulty of NGS is the amount of data that is generated. Whole genome sequencing can be performed or exome sequencing (1% of total DNA) or targeted sequencing of the genes of interest. NGS has proved to be a powerful tool to identify mutations in genetic diseases without a previously identified gene. If there is a distinctive phenotype then comparing affected children for mutations within the same gene is a very powerful way of identifying the underlying genetic cause of the phenotype. In the prenatal setting, this would not be possible at present as phenotyping on ultrasound is rarely distinctive.

The possibility of undertaking mutational analysis of gene panels for diseases with a phenotype that can be caused by multiple different genes such as Noonan syndrome would be extremely useful. A number of these panels have now been established for postnatal confirmation of a suspected diagnosis and the use of these is starting to be



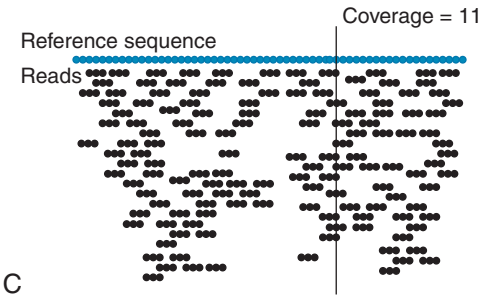
A

FIGURE 3.19a Next generation sequencing using Illumina HiSeq. Each sequence of the test DNA can be mapped to a specific region of a chromosome.



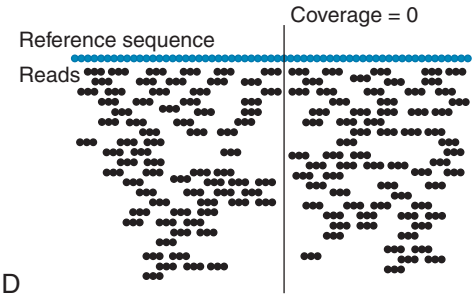
B

FIGURE 3.19b Reads of each sequence of DNA.



C

FIGURE 3.19c 11 Reads of target sequence.



D

FIGURE 3.19d 0 Reads of target sequence.

realised antenatally. Mutations identified on NGS continue to be validated on Sanger sequencing at the present time.

Free Fetal DNA (ffDNA) and Single Gene Analysis

A number of fetal genetic mutations have been identified from maternal blood as have been the common trisomies. A new mutation can be identified if there are only a very limited number that cause the disease such as in achondroplasia with FGFR3 and Apert syndrome with FGFR1. Paternal mutations can also be identified but it remains more challenging to identify a maternal mutation in a fetus in autosomal recessive and X-linked diseases although techniques are being developed for these.

Indications for Invasive Prenatal Diagnosis

- **Known mutation within a family with positive family history**: Single Gene disorders can be detected easily on chorionic villi if the disease mutation is known prior to the onset of the pregnancy. It is always essential for a sample undergoing analysis to have maternal contamination studies undertaken in case the mother rather than

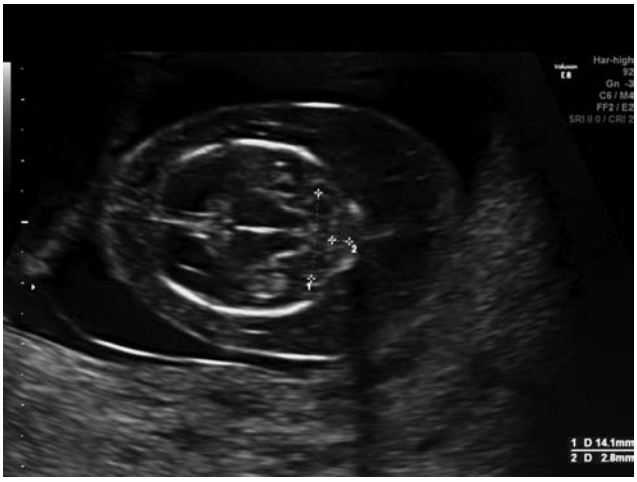


FIGURE 3.20 Fetal hydrops secondary to mutation in a noonan gene.

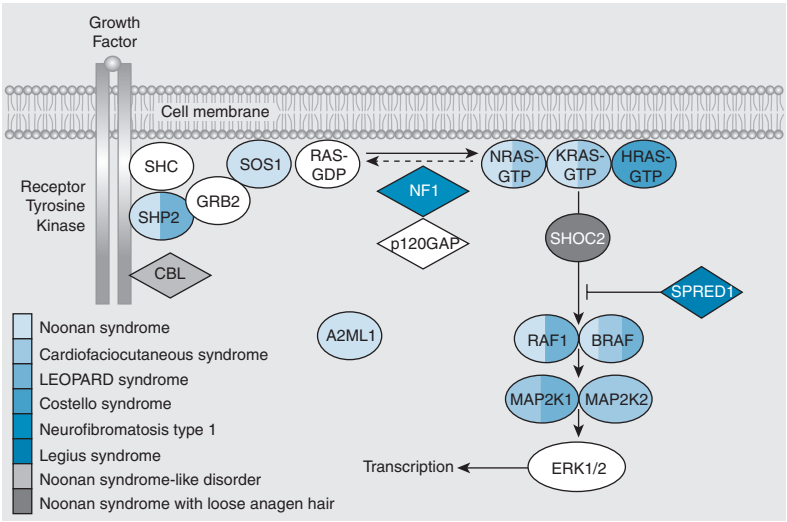


FIGURE 3.21 Noonan syndrome and related syndrome genes.

the fetus has been biopsied and the result will then be an indication of her genotype not that of the fetus.

- **No family history**: Genetic disorder suggested by maternal screening or ultrasound abnormality of the fetus.

Maternal Screening

Routine screening of the mother either pre-pregnancy or at the first pregnancy visit is routine in many countries. The commonest genetic diseases to be screened are the haemoglobinopathies, cystic fibrosis and Tay–Sacs disease. These may be targeted towards women of specific racial origins where the incidence of the disease is the highest.

Abnormalities of the β globin gene may be suspected by the presence of microcytosis on a full blood count in the absence of anaemia and is confirmed by abnormal haemoglobin electrophoresis.

Beta thalassemia is caused by multiple different mutations within the β globin gene and precise mutational analysis is required for prenatal DNA diagnosis.

Alpha thalassemia can only be suspected by a microcytic picture on a full blood count and then confirmed on DNA analysis. Haemoglobin electrophoresis is not looking at the α globin protein.

There are many different mutations identified in the genes for the above diseases but as the genes are so well-characterized, it is possible to identify the mutation in most carriers. Patients from different racial origins often have a different mutation profile.

Mutation Identification

Prior to invasive prenatal testing being undertaken, it is essential to test the partner's carrier status as all these diseases

for which screening is offered during the first trimester are autosomal recessive diseases and the baby will only be at risk if the partner is also a carrier.

For the thalassemias, it is necessary to know the mutation prior to the invasive testing as the CVS is analysing DNA, not fetal blood. Fetal blood cannot be analysed until 20 weeks. The presence of fetal haemoglobin may make the diagnosis difficult for beta thalassemia on fetal blood.

Single Mutation Causing the Disease

There are certain genetic disorders for which there is only one mutation within the gene that causes the disease. In these diseases mutation testing can be undertaken in any patient without a complicated mutation detecting progress.

- Sickle cell disease is the commonest disease caused by a single mutation.
- Triplet repeat diseases such as myotonic dystrophy, fragile X syndrome and Huntington disease can become increasingly severe as they pass down the generations. The risk of expansion of the triplet repeat may depend on the sex of the transmitting parent.

Only a woman can pass on an expanded fragile X allele, a male will only pass on the pre-mutation whatever the size of his expansion.

Myotonic dystrophy may present antenatally with ultrasound identification of talipes followed by progressive arthrogryposis. The affected parent normally the mother may be unaware of her diagnosis or may have such mild symptoms that she would not have considered the diagnosis a significant handicap. Congenital myotonic dystrophy may be lethal in the newborn period or associated with severe mental handicap. Maternal myotonic dystrophy should be considered in any baby with progressive arthrogryposis.

Diseases caused by triplet repeat expansions may increase in severity as they are transmitted through the generations. This is called *anticipation.*

Small Number of Mutations Cause the Majority of Disease

Diseases such as thalassemia, both alpha and beta, the majority of cases are caused by a small number of mutations. These may be dependent on the geographical origin of a family, hence this information is invaluable to the laboratory performing the analysis. Mutation analysis can be performed relatively rapidly potentially in time for a prenatal diagnosis following screening by a FBC and haemoglobin electrophoresis at the beginning of pregnancy.

Some phenotypes are associated with very specific gene mutations and a diagnosis following identification of scan abnormalities can be confirmed very easily. For example, the G–A transition or G–C transversion at nucleotide 1138 resulting in the substitution of arginine for glycine at position 380 of the mature protein in the FGFR3 gene in achondroplasia. Other mutations that occur in the gene cause a different clinical presentation.

Diseases Caused by Multiple Mutations in Multiple Genes

Therefore analysis may be time consuming and if it takes a prolonged length of time to identify the mutation it may not be available for prenatal diagnosis unless the specific mutation within a family has been identified prior to the pregnancy. As strategies for screening large and multiple genes improves particular using NGS (see above), this is now possible following the identification of ultrasound abnormalities.

For example, a single cardiac rhabdomyoma (Fig. 3.22) is associated with tuberous sclerosis in 50% of cases. Tuberous sclerosis is associated with epilepsy and mental retardation which may be severe in 60% of cases. Identifying the mutation in either TS1 or TS2 confirms the diagnosis.

There are a number of abnormalities identified on ultrasound that are so severe that identification of the underlying cause is only of significance for the recurrence risk in further pregnancies. The underlying cause will change the prognosis little for the present pregnancy. For example, the identification of holoprosencephaly (failure of division of the cerebral hemispheres) is most commonly caused by trisomy 13, but it could be secondary to a mutation in Sonic Hedgehog (SHH) or other single gene mutations. The former is likely to have a very low recurrence risk as long as it is not secondary to an inherited Robertsonian translocation.

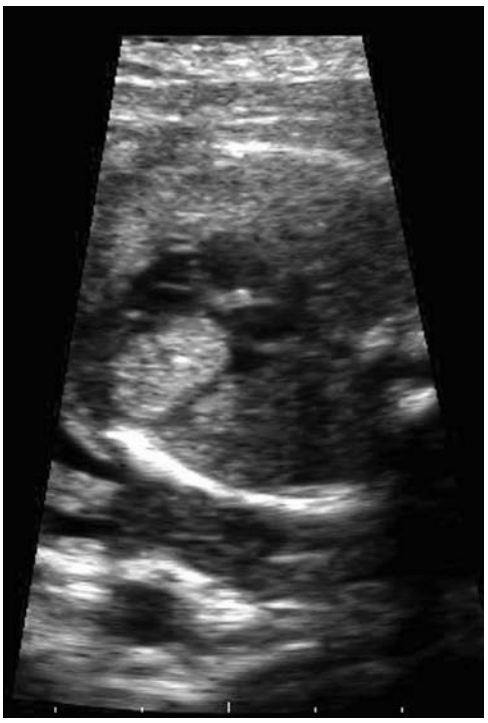


FIGURE 3.22 Cardiac rhabdomyoma secondary to tuberous sclerosis.

Whereas a mutation in SHH may have a high recurrence risk as a parent with mild features may be a carrier with a 50% risk of passing this on in a variable form. Hence identifying the cause is important but this could wait until after the baby has been terminated or born depending on parental wishes. Identification of the underlying cause of a fetal abnormality may alter only the recurrence risk in future pregnancies but not the prognosis for the present pregnancy.

Non-Invasive Methods of Prenatal Diagnosis

Ultrasound

Ultrasound is the most widely used and safest investigation undertaken during pregnancy. The identification and interpretation of abnormal features identified depend both on the quality of the ultrasound machine and on the expertise of the scanner. Protocols exist in many countries to aid identification of abnormalities by systematic analysis.

Fetal Dysmorphology

Fetal dysmorphology has been discussed in Chapter 2.

Identification of a single abnormality on ultrasound will automatically require the fetus to be examined in greater detail to try and identify further abnormalities. The fetus should be referred for a scan to be undertaken by an expert in fetal scanning. The expert may be able to look for known associations with the original abnormality. An example of this would be the identification of an encephalocele, polydactyly and polycystic kidneys, which would be associated with Meckel Gruber Syndrome which is a lethal disorder with a 1:4 recurrence risk.

3D/4D ultrasound may give greater clarity for certain abnormalities but should be used as adjunct to standard 2D ultrasound rather than as a replacement. For example, micrognathia may be part of the Pierre–Robin sequence and be caused by Treacher Collins syndrome which will show abnormal ear morphology which is much more clearly seen on 3D ultrasound.

Fetal MRI

Fetal MRI scanning can now be undertaken to clarify the presence of some abnormalities. This is particularly useful following the identification of brain abnormalities on ultrasound. The identification of CNS abnormalities is very gestation dependant and therefore it may not be possible to offer reassurance to a couple until the third trimester.

Ultrasound and MRI are complimentary. Normal values such as cerebellar size are much better established for ultrasound than fetal MRI, but fetal MRI is much better at looking at the developing gyral pattern of the brain, which is gestation specific as well as looking for neuronal migration defects. Agenesis of the corpus callosum (ACC) is associated with mental retardation in 30% of cases with isolated ACC but probably 100% if there are additional brain abnormalities. Mild ventriculomegaly will have a normal developmental outcome in over 95% cases if isolated. However, if associated with a neuronal migration defect, it would be very unlikely that the baby would have a normal developmental outcome. Normal developmental maturation can potentially vary within a two-week window and repeating MRIs may be necessary to identify true delayed maturation. Normal values are available in Garel's atlas.

Prenatal care now routinely involves the identification of abnormalities on ultrasound. High risk women of carrying babies with genetic disorders may be able to be offered early testing by a number of different procedures involving different technologies to allow antenatal choices to be made. As technology improves the underlying cause of ultrasound abnormalities is becoming increasingly possible. As more children are identified with gene mutations the possibility of preventing the birth of further affected children by either standard prenatal diagnosis as discussed above or by Pre-implantation Genetic Diagnosis (PGD) becomes increasingly possible. It is important to remember with this increasing technology, a number of ethical dilemmas and to many women termination of pregnancy is not an option. Invasive techniques continue to risk the pregnancy by causing miscarriage. The patients need to be involved in discussions for the reason and risk of all investigations. Their views must always be respected within the legal and ethical framework of the country in which the tests are being undertaken.

Important Points

- Prenatal invasive testing of a fetus for a suspected abnormality can be performed from 11 weeks using CVS, 16 weeks onwards using amniocentesis, 18 weeks onwards using fetal blood sampling or by fetal biopsy.
- Structural chromosomal abnormalities may be addition (trisomy, triploidy), loss (deletion, monosomy), re-arrangement (translocation, ring chromosomes) or problems with imprinting.
- A standard karyotype can only identify a 5–10 Mb deletion. A smaller deletion is not visible on light microscopy, and requires molecular bases tests. QFPCR is used to provide rapid results for aneuploidy.
- Techniques for identification of smaller chromosome abnormalities include FISH, MLPA, BACS and BOBs, CGH. A potential disadvantage of these techniques is identification of variations of uncertain clinical significance. Counselling of future parents is problematic.
- Free fetal DNA can be used as a non-invasive test for the detection of aneuploidy. It can also be used for diagnosing single gene disorders.
- Molecular techniques are necessary for identification of mutations in single gene disorders. They include Sanger sequencing, ARMS and next generation sequencing.
- As more and more gene mutations are identified, pre-implantation genetic diagnosis is potentially useful.

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DATABASES AND USEFUL RESOURCES

Orphanet Journal of Rare Diseases
www.ojrd.com
OMIM - Online Mendelian Inheritance in Man
www.omim.org
Decipher
https://decipher.sanger.ac.uk
Gene Reviews
www.genereviews.org
Unique - The Rare Chromosome Disorder Support Group
www.rarechromo.co.uk
MetBio.Net: National Metabolic Biochemistry Network
www.metbio.net

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Chapter 4

Fetal Infections

Francesco D'Antonio and Amarnath Bhide

Chapter Outline

INTRODUCTION

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. An infection can be transmitted from mother to the fetus in many ways. Transplacental transmission during embryonic and fetal development (prenatal) and the one occurring by direct contact between the fetus and maternal tissues during the delivery (perinatal transmission) represent the two commonest ways of interaction between the infectious agent and the fetus (See Box 4.1).

The likelihood for transmission from the mother to the fetus depends upon the time and type of maternal infection and the maternal immune response, whereas the severity of fetal damage once infection has established is strictly related on the interaction among the fetal immune response and pathogenicity of the infectious agent. Fetal damage can be induced by a direct destruction of fetal cells by the infectious agent or, alternatively by an exaggerated immune response developed by the fetus itself against its own or maternal tissues (See Box 4.2).

The time and the type of fetal infection are the most important factors in determining the rate of transmission and the likelihood of an adverse perinatal outcome. An *infection* is defined as primary when is acquired for the first time and non-primary or secondary when the host has already had the infection in the past, but contracts the infection again as a consequence of a reactivation of a previously latent infective agent or an infection with a different strain. Only the first infection, except in the case of cytomegalovirus, may potentially be transmitted to the fetus, while secondary infections are usually not dangerous. The rationale behind this assumption is that maternal viremia, which is a prerequisite for the transmission of the infection from the mother to the fetus, is usually more prolonged and substantial during a primary infection. Moreover, the maternal immune system during a secondary infection is promptly able to induce an immune response against the infective agent by producing immunoglobulin G (IgG) that can easily cross the placenta and induce a state of passive immunization in the fetus. Conversely, during the first infection, the immune response of the mother is slow and it is characterized by the production of IgM that cannot cross the placenta, while the production of IgG occurs later during the course of infection. In this scenario, the fetus is more susceptible to damage if it acquires the infection because its own immune system is not completely developed, and it has to rely on passive maternal immunization in order to protect itself from an infection. Gestational age at delivery is another fundamental factor determining the prognosis of congenitally infected fetuses. Fetal infection acquired at an early gestational age leads to greater damage to the fetus. Prenatal diagnosis of fetal infection is fundamental in order to counsel the parents about the outcome of the pregnancy and to tailor a proper prenatal intervention. Several factors influence the effects of infection on the fetus (Box 4.3).

BOX 4.1 The Routes of Transmission to the Fetus

- Transplacental transmission (haematogenous).
- Transcervical transmission (relatively uncommon).
- Direct contact at birth.

BOX 4.2 Fetal Effects of Infection

- Teratogenic – Malformations such as congenital heart disease, microcephaly.
- Disruption – Destructive brain damage, coagulation failure.
- Growth restriction – Reduced cell numbers, placental damage.
- Missed miscarriage and stillbirth.

BOX 4.3 Factors Affecting Effects of Infection on the Fetus/Neonate

- Infecting dose
- Type and virulence of the organism
- Maternal response
- Route of infection
- Time (in gestation) of infection

Screening for some infections (but not others) is routinely recommended (Table 4.1).

Routine screening is not recommended if the false positive rate is high, there are risks in confirming fetal infection, where there is no treatment or if fetal infection is not the synonymous with affection.

TABLE 4.1 Screening for Infections

Agent	Routine (Elective) Screening
Rubella	Yes
Syphilis	Yes
Hepatitis B	Yes
HIV	Yes
Cytomegalovirus (CMV)	No
Toxoplasma	No
Parvovirus	No
Group B streptococcus	Yes/No (See later)
Varicella	No
Herpes	No
Malaria	No

In clinical practice, there are three ways in which infection can be present as a possibility. These are the following:

1. Maternal exposure to infection or maternal infection.
2. Infection as a possible cause following ultrasound scan findings.
3. Positive TORCH test result.

In this chapter, we will discuss the most common and important fetal infections caused by bacterial, viral and protozoan agents. The following fetal infections will be dealt with in this chapter:

- Cytomegalovirus
- Toxoplasmosis
- Parvovirus B19
- Rubella (German measles)
- Varicella (Chicken-pox)
- Syphilis
- Group-B Streptococcus
- Viral Hepatitis
- Herpes
- HIV infection
- Malaria

CYTOMEGALOVIRUS (CMV)

Virology

Cytomegalovirus is a double-stranded DNA virus member of the family of herpes virus. The main feature of these viruses is their capacity to establish a state of latent infection in the host after primary infection has occurred and that is usually permanent through life. The virus can be occasionally reactivated thus leading to reinfection; reactivation is usually induced by immunological or hormonal changes in the host.[1]

The structure of CMV is similar to that of other herpes viruses, with an icosahedral protein capsid that contains the double-stranded DNA, while the capsid is surrounded by a proteinaceous tegument and an outer lipid envelope.[1] CMV enters the cell through fusion of the outer membrane of the cell and glycoproteins on the lipid envelope of virions. The DNA-containing protein capsid and the tegument proteins are released into the cell after the event of fusion. CMV infection recognizes two different stages: lytic and latent. During the lytic infection, there is the expression of proteins that induce viral DNA replication and modulate the host cell environment and stimulate the expression of viral early genes.[2] The viral-immediate early genes produce proteins that are responsible for replicating the double-stranded viral genomic DNA; after DNA replication, structural components of the virion are assembled thus allowing the viruses to leave the infected cell. Latent infection is characterized by minimization of viral gene expression, inhibition

of the assembly and egress of new viral progeny.[3] Latent infections can reactivate into a lytic infection upon certain environmental stimuli, which causes disease and allows viral spread.

Epidemiology

CMV is the most common cause of fetal infection occurring in 0.5–2% of all live births.[4] Pregnant women usually acquire CMV infection by exposure to children in their home or from occupational exposure to children and infection can potentially occur from close contact with different body fluids such as saliva, blood, semen, urine and cervical secretion.[5] Maternal infection is usually asymptomatic and the mother is generally unaware of being infected with CMV. A small proportion of patients may experience a mononucleosis-like syndrome with symptoms such as malaise, fever, generalized lymphadenopathy and hepatosplenomegaly. Patients who are immune-compromised may develop extremely serious sequelae of infection, including chorio-retinitis and pneumonitis.

Screening for maternal infection during pregnancy is not recommended, although in some countries such as Italy and France serologically screening in the first half of pregnancy is performed. The reasons of this choice include lack of an effective and proven treatment for reducing the rate of transmission and its effects. Hygienic intervention for preventing maternal infection seems appropriate, although it requires confirmation in randomized trials.[5]

Implication for Fetal Infection

Fetal infection with CMV is most common due to a transplacental passage of the virus, although transmission at delivery due to contact of cervical secretions or blood or after birth via breast milk is possible. Fetal infection can occur during both primary and non-primary maternal infection.[6] Non-primary infection can be the result of a reactivation of the virus in the host or reinfection with a different CMV strain. The outcome of the fetus/newborn is directly correlated to the type and timing of infection, with the most severe forms occurring as the result of a primary infection contracted in the first two months of pregnancy.[7]

The risk of transmission from the mother to the fetus is 30–50% during a primary infection. Of those infected, 90% of the fetuses are usually asymptomatic at birth while 10% may manifest signs or symptoms related to CMV infection. Of the 10% of fetuses showing signs of infection, 30% experience a fetal or neonatal demise, while the remaining 70% survive. Among the survivors, 50% present major sequelae, while 10% are normal. Among asymptomatic fetuses, 10% may experience sensorineural hearing loss. Transmission from the mother to the fetus is considerably lower in a non-primary infection and occurs in around 1% of the cases.[7-9] It is important to remember that, although the rate of transmission is reduced in non-primary compared to primary infections, the course of fetal disease once infection has established is no different, and cases of severe abnormalities in non-primary maternal infections have been reported.[10]

Transmission from the mother to the fetus can occur as the consequence of maternal primary or non-primary infection. CMV can be transmitted to the fetus even if maternal infection occurs in the pre or peri-conceptional period. Revello and coworkers reported that maternal CMV infection before 3 months of conception carries a risk of transmission of about 9%, whereas the transmission for an infection occurred within 4 weeks after was of about 30%.[2,11]

CMV has a particular tropism for the neuronal cells of the periventricular zone of the brain. In normal pregnancies, these cells migrate from this zone towards the cortical plate between 12th and 24th weeks of gestation thus allowing the formation of the brain fissure.[12] The degree and the extent of CMV-related brain damage is directly related to the time of infection. During early pregnancy, the damage of the neurons of the peri-ventricular zone results in an extensive damage of the brain. Later in pregnancy, white matter abnormalities are more common when the gross development of the brain is completed and myelination is occurring.[13]

Ultrasound Signs and Symptoms

The CMV affinity towards neuronal cells manifests in a wide range of congenital brain malformations that can be potentially detected at a detailed ultrasound examination. Although less common, extra-cerebral malformations, especially those involving the gastro-intestinal tract, can co-exist with brain anomalies or be found in isolation.

The main ultrasound features detected in fetuses with congenital CMV infection have been listed in Box 4.4.[14–18]

BOX 4.4 Ultrasound Features of Congenital CMV

- CNS (ventriculomegaly, intra-ventricular haemorrhage, intra-ventricular adhesions, periventricular echogenicities, sub-ependymal cysts, periventricular leukomalacia, microcephaly, lissencephaly, porecephaly, cerebellar agenesis, hypogenesis, hypoplasia and haemorrhage, microphthalmia).
- Intrauterine growth restriction (IUGR).
- Placental enlargement.
- Gastrointestinal tract (Hepatomegaly, splenomegaly, echogenic bowel, intrabdominal and liver calcification, ascites).
- Heart (cardiomegaly, pericardial effusions and calcifications).
- Non-immunehydrops.

CMV is the most common infective cause of congenital brain abnormalities. The pathogenesis of brain damage related to infection includes a direct cytopathic effect of the virus on neurons or the induction of an inflammatory response. Alternatively, destruction of placenta may impair the delivery of oxygen to the fetus, thus damaging the brain tissue. Ventriculomegaly is a common brain findings detected at the routine anomaly scan. The cause of ventriculomegaly, progression of ventricular dilatation and presence of other brain abnormalities are the main factors determining the prognosis of a fetus with an antenatal diagnosis of ventriculomegaly. Ventriculomegaly may be associated with CMV infection although other US signs such as microcephaly usually co-exist in this scenario. The rate of CMV infection in fetuses with isolated mild ventriculomegaly has been reported to be around 6%, thus a serological assessment of the mother is warranted when dealing with a fetus presenting with apparently isolated ventriculomegaly at the scan, especially if a recent history of flu-like symptoms is reported. Intra-cranial calcification is also relatively commonly associated with congenital CMV infection. Their distribution is usually around the periventricular zone, whereas brain calcifications associated with toxoplasma infection are scattered throughout the brain. Although in the setting of CMV infection brain malformations are common, extra-cerebral abnormalities can be detected in isolation in around 30% of the cases. Echogenic bowel and bowel dilation are the most common extra-cerebral findings detected at the scan in an infected fetus and are the result of viral enterocolitis. Hepatosplenomegaly and multiple liver calcifications are also seen.[14-18]

Although ultrasound has a low sensitivity in detecting congenital CMV infection even in patients at risk,[14] presence of ultrasound signs is an independent poor prognostic factor.[7,19] Therefore, a detailed ultrasonographic assessment in centres of excellence is warranted. It is important to state that a negative ultrasound scan in the second trimester does not exclude fetal infection. CMV infection is a progressive disease and structural abnormalities associated with infection, especially those involving the cortical fissures, may manifest only later in gestation. It is therefore important that serial follow up scans are arranged. Magnetic resonance imaging (MRI) has a better spatial resolution compared to ultrasound and may be helpful in detecting additional brain abnormalities especially late in gestation.

Congenital CMV infection may cause a wide range of neurological disabilities including mental retardation, cerebral palsy, autism, epilepsy, blindness or visual deficits and learning disabilities.[20] CMV is also the main cause of sensorineural hearing loss during childhood that is present in about 10–15% of all infected babies with the risk being greater if the infection was symptomatic in the neonatal period.[21]

Laboratory Investigation

Because clinical diagnosis of maternal CMV infection is unreliable, laboratory tests represent the first step for diagnosing CMV infection in pregnancy.[22]

The main aims of laboratory investigation for CMV infection in pregnancy are not only to diagnose the infection, but also to define the type (primary vs. non primary) and the time of the infection. The risk of transmission is higher with primary infection, and the outcome worse in cases of early infection.

The gold standard of serological diagnosis of CMV infection is maternal seroconversion or the presence of anti-CMV IgM antibodies combined with anti-CMV IgG antibodies of low avidity. When multiple serum sample from early pregnancy are available, the diagnosis of CMV is facilitated by the documentation of seroconversion to CMV specific antibodies, defined as the presence of anti-CMV IgM and IgG antibodies in a previously negative patient. Because screening for CMV is not currently recommended, diagnosis of CMV via seroconversion is only occasionally achieved and mothers are usually screened for CMV infection only if fetal abnormalities, suspicious of CMV infection, are detected at the scan or maternal flu-like syndrome is reported.

Detection of anti-CMV IgM antibodies is the most widely adopted screening test for CMV and usually indicate an acute or recent infection. When interpreting a serological test for a suspected CMV infection, it is important to remember that a rise in IgM antibody titre may indicate a reactivation or reinfection with CMV. This is particularly important because the rate of vertical transmission during a non-primary infection is significantly lesser compared to a primary infection. Moreover, IgM antibodies can be produced for months after the acute phase of infection. False positive results are possible due to the cross reaction of the antibodies with other infections (Epstein Barr) or autoimmune diseases. Since the detection of IgM does not necessarily imply the presence of a primary and acute infection, other investigations should be carried out for typing of the virus and timing the infection.[23,24]

CMV avidity test is currently the most reliable laboratory tool to identify primary infection.[24] Avidity refers to the strength with which an antibody binds to an antigen. Increasing avidity reflects progressive maturation of the human immune response. During the early stage of infection, IgG antibodies show a low avidity for the antigen that progressively increases with time and becomes high after 16–18 weeks.[24] The knowledge of CMV avidity allows a good estimation of CMV infection with high sensitivity in the late first and early second trimester.[24] However, the predictive value of avidity is lower after 20 weeks of gestation.[24] Viral detection in maternal blood with the use of polymerase chain reaction (PCR) does not play a major role

in the diagnosing of maternal infection and the positive detection of virus in maternal blood does not seem to increase the risk of adverse outcome.[24]

Women with positive anti-CMV IgM antibodies and low avidity are the ones who are at increased risk of transmitting infection to the fetus. In this case, laboratory diagnosis of CMV infection is usually accomplished by the detection of the virus in the amniotic fluid or fetal blood by PCR. It is important to wait at least 6 weeks between maternal infection and invasive procedure or to delay the latter till after 20 weeks of gestation when undertaking a prenatal invasive testing for the detection of fetal CMV infection. The rationale for this approach relies on the fact that viral shedding by fetal kidneys is reduced in the first 20 weeks of pregnancy due to reduced fetal dieresis.[25,26]

Increased in IgG antibody titre with or without the presence of IgM antibodies and high avidity usually represents a non-primary CMV infection.

Management

The likelihood of vertical transmission is higher in case of positive IgM antibodies titre combined with low avidity test result. Confirmation of fetal infection through an invasive test (amniocentesis or fetal blood sampling) should be offered to the parents. Fetal infection is unlikely if CMV is not detected in a fetal sample obtained at least 6–8 weeks after maternal infection or after 20 weeks of gestation. Isolation of CMV in the amniotic fluid by PCR confirms the diagnosis of fetal infection, but does not predict the outcome of these babies at birth.[24] In this case, viral load assessment through the use of quantitative PCR may be useful. A low viral load in the amniotic fluid (defined as the presence of $<10^3$ copies/ml) is usually associated with asymptomatic infection and a favourable neonatal outcome, whereas a high viral load is more likely to indicate a symptomatic infection.

Recently several authors have tried to correlate antenatal virological, biochemical, haematological and imaging parameters with the likelihood of an adverse outcome following confirmed fetal infection using for fetal blood biochemistry. Benoist and coworkers found that thrombocytopenia and abnormal findings at ultrasound were predictors of poor neonatal outcome while Romanelli found that higher levels of transaminases and IgG were detected in fetal blood of symptomatic babies.[15,27]

There is currently no proven prenatal treatment for congenital CMV infection. The use of CMV hyper-immune globulin or antiviral drugs given to the mother has been proposed to reduce the course of infection and the rate of vertical transmission. Nigro and coworkers,[28] in a non-randomised prospective study, reported that maternal treatment with hyper-immune globulin was associated with a smaller chance (3%) of symptomatic babies compared to 50% of the control group. Jaquemard and coworkers proposed that antenatal Valacyclovir given to the mother reduces the viral load in fetal blood.[29] Randomized clinical trials are needed in order to clarify the role of antenatal treatment with immunoglobulins or anti-viral drugs in congenital cytomegalovirus infection.

Postnatal Management

Postnatal diagnosis of congenital CMV infection relies on the isolation of the virus in the urine or saliva of the baby in the first two weeks of life. Neonatal prognosis is directly related to the timing of the infection, presence of ultrasound signs and viral load as detected in the amniotic fluid or fetal blood. About 10% of infected babies present with symptoms related to CMV. Congenital CMV infection is a multiorgan disease especially involving the brain and the reticulo-endothelial system and clinical presentation are related to the extent of the damage. Symptoms of fetal infection include hepato-splenomegaly, jaundice and petechiae. Presence of neurological symptoms is dependent upon the degree of brain damage and includes hypotonia, lethargy and seizure. Not all newborns presenting with symptoms related to congenital infection have a poor neurological outcome and one-third of these babies has been reported not to have severe neurological impairment.[12] Microcephaly and abnormal brain findings at postnatal imaging are highly correlated with adverse neurodevelopmental outcome.[24]

In view of the fact that neurological impairment, hearing and visual loss may be not evident immediately after birth, babies with a confirmed congenital CMV infection should be assessed sequentially during childhood by a multidisciplinary team including a paediatric neurologist, ophthalmologist and ENT surgeon.

CMV Infection: Indian Experience

Broor and coworkers 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.[30,31] In a more recent survey of 1300 newborns by Deorari and coworkers at AIIMS, the incidence of detection of CMV specific IgM antibodies was 0.6% and in a study at AIIMS by Broor and co workers on the saliva of 550 newborns, CMV was detected by PCR in 7 out of 550 newborns (1.4%).[31,32]

TOXOPLASMOSIS

Microbiology

Toxoplasma gondii is an obligate intracellular protozoan, whose lifecycle is characterized by a sexual phase occurring

only in cats and an asexual phase taking place within virtually all warm-blooded animals, including humans. During its reproductive cycle, Toxoplasma can take different forms: the oocyst, the tachyzoite and the cyst.[33]

Epidemiology

Mother acquires infection by ingestion of uncooked or raw meat containing toxoplasma cysts. Water or food contaminated by oocysts excreted in the faeces of infected cats represents another source of infection.[34] After ingestion, toxoplasma acquires its active form and invades intestinal epithelial cells, thus spreading in the circulation.[35]

Maternal infection is usually asymptomatic and only a small percentage of patients develop a 'mononucleosis-like syndrome' with low-grade fever, malaise, lymphadenopathy. In a small percentage of patients, toxoplasma infection manifests primarily as chorioretinitis. Transmission from the mother to the fetus occurs almost exclusively during a primary maternal infection, although in rare cases it may be due to reactivation of toxoplasma in immune-compromised patients.

Implications for Fetal Infections

The frequency of vertical transmission increases with the gestational age and is around 70% in the third trimester, while being as low a 5–6% in the first trimester of pregnancy. In contrast, the damage to the fetus is higher in the earlier stages of pregnancy and it has been estimated that the risk for developing symptoms or sequelae at birth after an infection acquired in the first trimester of pregnancy is about 80% with a risk of perinatal death of around 5%, while the corresponding figures for a fetus infected in the third trimester are 10% and 0%, respectively (Please see figure 4.1). At no point is the overall risk of a symptomatic infection lesser than 5–8%. At the moment, there are no large data about the impact of infection acquired in the periconceptional period and risk of fetal transmission and infection.

Ultrasound Signs and Symptoms

Ultrasound is recommended for detecting structural abnormalities in fetuses with a prenatal suspicion or diagnosis of congenital toxoplasmosis.[36]

The main ultrasound features in a fetus presenting with congenital toxoplasmosis are shown in Box 4.5.

The outcome of fetuses with congenital toxoplasmosis is worse when structural abnormalities are detected at the scan.

Recently the role of prenatal ultrasound for the prediction of the outcome in congenitally infected fetuses has been investigated. Berrebi has reported that the outcome of

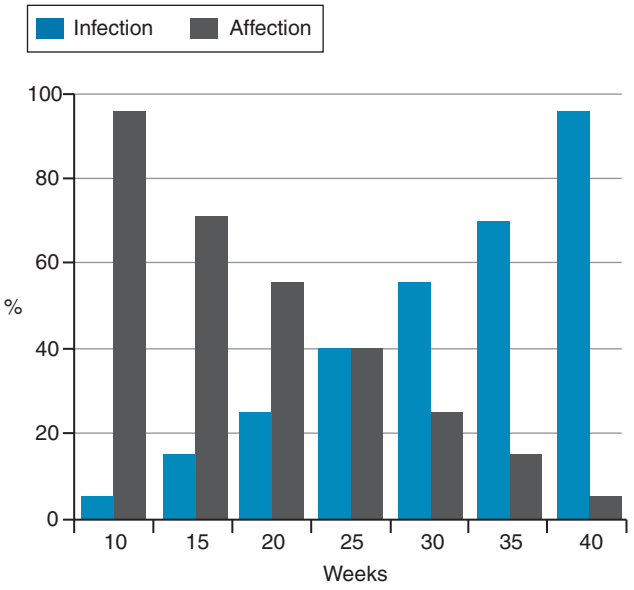

FIGURE 4.1 Risk of fetal infection with toxoplasmosis and the risk of being symptomatic if infected.

BOX 4.5 Ultrasound Features of Congenital Toxoplasmosis

- CNS abnormalities (ventriculomegaly, calcifications in the brain parenchyma, periventricular zone and caudothalamic zone, periventricular echogenicity or cysts.
- Ocular abnormalities (cataracts).
- GI abnormalities (hepatomegaly, liver calcifications, ascites).
- Placental enlargement/thickening.

fetuses at two years of age whose mothers acquired the infection during the first trimester of pregnancy and where a prenatal scan showed no structural abnormalities suggestive of infection, was not significantly different form that of fetuses whose mothers were infected later in pregnancy.[37]

Laboratory Investigation

Although feasible, screening for toxoplasma infection in pregnancy is not routinely performed in many countries, thus diagnosis of fetal infection in pregnancy is usually considered if the mother is symptomatic or if structural abnormalities are detected at the scan.

Serology represents the first step in order to establish whether and when the infection has occurred. As for CMV, the gold standard for diagnosing toxoplasma infection by using a serological test is the presence of sero-conversion. However, mostly only one serum sample is available for the analysis, thus precluding the documentation of seroconversion. Detection of specific anti-toxoplasma IgM and IgG

in the maternal serum is the most commonly adopted technique for diagnosing maternal infection. A negative result for both IgM and IgG indicates that the mother is non-immune and thus potentially susceptible to infection during pregnancy. A positive IgG and a negative IgM result in the first or second trimester is usually suggestive of an infection acquired before pregnancy. However, if the results come from a serum sample obtained in the third trimester of pregnancy, the result is more difficult to interpret because it might indicate an infection acquired early in pregnancy and characterized by an initial increased in IgM titre followed by its decrease to non-detectable levels within a short-time interval. The presence of positive IgM and negative IgG or both positive IgM and IgG usually reflects a recent infection. These results should be interpreted with caution because the mother can produce anti-toxoplasma IgM even for more than one year after the acute infection.[35] Therefore, any positive test needs confirmation in reference laboratories. Toxoplama IgG avidity test is usually performed as a confirmatory test in case of positive results at serology. The presence of high avidity antibodies indicates that the infection is acquired >16 weeks earlier, thus allowing an optimal estimation of the probability of vertical transmission. Parents with a high avidity IgG results in the first trimester of pregnancy can be reassuring suggesting. They indicate past infection and that it is unlikely to harm the fetus. However a positive result in the second or third trimester of pregnancy cannot completely exclude the possibility of transmission. In this case, invasive testing should be offered to parents in order to completely rule out fetal infection. Isolation of toxoplasma in the amniotic fluid by PCR represents the gold standard for the diagnosis of fetal infection.[38]

Invasive prenatal tests should always be performed after 18 weeks of gestation, when sensitivity and specificity for the diagnosis of infection are significantly higher than in earlier gestations.[38]

Management

Once serological tests have confirmed that a recent maternal infection has occurred especially in the first 18 weeks of gestations antenatal administration of spiramycin to the mother should be considered and invasive prenatal diagnosis of fetal infection should be offered to the parents.

Spiramycin is a macrolide antibiotic that has been reported to reduce the rate of vertical transmission by 60%, especially if administered in the first trimester of pregnancy.[39,40] Spiramicin is particularly indicated for mothers contracting the infection in the first 18 weeks of gestation and should be started at the dose of 1g (3 million units) every 8 hours. Spiramycin should be continued even in the presence of negative PCR results on amniotic fluid and/or normal findings at the scan.

Although routinely administered to prevent vertical transmission when maternal infection is confirmed, the effectiveness of spiramiycin is controversial and recent systematic review has failed to find a strong association between maternal administration of spiramycin and prevention of fetal infection,[41,42] thus calling for large randomized controlled trials.

In patients in whom fetal infections is confirmed by positive PCR on amniotic fluid, in fetuses presenting abnormalities suggestive of fetal infection at the scan or in mothers acquiring infection after 18 weeks of gestation a combination of pyrimethamine (50 mg every 12 hours for 48 hours followed by 50 mg daily), sulfadiazine (75 mg/kg, followed by 50 mg/kg every 12 hours) and folinic acid (10–20 mg daily) is another alternative. Pyrimethamine crosses the placenta and it should not be used in the first trimester of pregnancy due the possibility of teratogenicity. The rational of this multi-drug therapy is mainly to cure rather than prevent fetal infection.[35] However, the rate of serious neurological sequely or death in treated cases is no better than those without treatment.[42]

Postnatal Management

The majority of newborns with congenital toxoplasmosis do not show any clinical signs of the disease at birth. When present, clinical manifestations include epilepsy, psychomotor or mental retardation, blindness, strabismus, petechiae due to thrombocytopenia and anaemia.[43] Babies should be carefully examined at birth by a multidisciplinary team involving a paediatric neurologist and ophthalmologist. MRI or CT imaging should be used to assess normality of neonatal brain. Babies that are asymptomatic at birth should undergo a prolonged follow up. It has been reported that some manifestations of congenital toxoplasmosis such as chorioretinitis can occur even after as long as 12 years of age.[44] Treatment with pyrimethamine should be continued until 1 year of age.

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%.[45,46] 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.[47] 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[48]; significant hearing loss[49]; and eye lesions like microphthalmia, cataract, necrotizing chorioretinitis. About 50% suffer from visual impairment.[50]

RUBELLA (GERMAN MEASLES)

Virology

Rubella virus (RV) is a single stranded RNA virus member of the family togaviridae. It is a species-specific virus infecting only humans and is formed by RNA surrounded by a capsid and a lipoprotein envelope. The lipoprotein envelope contains glycoproteins E1 and E2, which are responsible for the immune response against the virus.[51]

Epidemiology

Before the introduction of vaccination programme, RV was an endemic infection. The contact between the virus and the host usually occurs through respiratory droplets. After infection, viraemia occurs for about 7 days before the rash and the virus can be detected until 7–12 days after the onset of rash. After incubation period of 14 (range 12–23) days, a maculo-papular rash appears on the face and then rapidly spreads to the trunk and limbs. The rash is usually associated with lymphadenopathy of the cervical area that may persist for up to two weeks after the rash has disappeared. Non-specific symptoms such as headache, sore throat, low-grade fever and conjunctivitis may also be present. Although the disease has usually a mild course with up to 50% of infections being asymptomatic, rarely it can cause serious complications such as encephalopathy and bleeding disorders due to thrombocytopenia especially in immucompromized patients or when associated chronic conditions are present. Primary infection confers life-long immunity. In countries where rubella immunization is routinely offered, the occurrence of congenital rubella syndrome is exceedingly rare.[52,53]

Implications for Fetal Infection

The risk of transmission from the mother to the fetus and the rate of congenital defects have been reported to be 80% and 85%, respectively with a high risk of birth defects if the infection occurs in the first 8 weeks of pregnancy.[54] The rate of miscarriage in the first trimester of pregnancy is around 20%.

The risk of fetal infection progressively reduces after the first trimester of pregnancy and rates of 54% and 25% have been reported between 13 and 16 weeks and at the end of second trimester respectively.[52,55] The risk of fetal compromise is negligible if infection occurs after the second trimester of pregnancy, although isolated cases of deafness have been reported.[51]

RV induces a characteristic pattern of multi-organ disease in the fetus, known as *congenital rubella syndrome (CRS)*.[34]

The main features of CRS are shown in Box 4.6.

Pathogenesis of CRS has not been completely elucidated yet. CRS is not associated with the presence of an inflammatory response of the host against the virus and suggested mechanisms for fetal damage include apoptosis, tissue necrosis and viral interference with the cell cycle.[34] After the second trimester of pregnancy, the developing fetal immune system is able to induce an immune response against the virus, thus explaining the lower rate of congenital abnormalities and adverse outcome.

It is important to remember that conditions such as diabetes and ocular abnormalities may manifest even in the second year of life or later. Thus a proper follow up is warranted, even if the newborn is apparently normal at birth.[56]

Ultrasound Signs and Symptoms

CRS is associated with the presence of multiple abnormalities at US examination. Although US is not highly specific in diagnosing CRS, this has to be considered when facing to a fetus presenting with multiple abnormalities and normal karyotype. Early gestational age at fetal infections is

BOX 4.6 Features of Congenital Rubella Syndrome

- Heart defects (pulmonary stenosis, patent ductusarteriousus)
- Neurological deficits (neurodevelopmental delay, speech defect, psychomotor retardation).
- Eye defects (cataracts, microphthalmia, retinopathy).
- Sensorineural or central deafness.
- Haematological abnormalities (thrombocytopenia, purpura)
- Hepato-splenomegaly.
- Diabetes

associated with an increased likelihood of detecting structural malformations in the fetus.[57,58]

The main ultrasound features associated with CRS are shown in Box 4.7.

Because the risk of congenital abnormalities is higher during the first trimester of pregnancy, early US examination is warranted in women with a confirmed RV infection on the basis of a serological diagnosis.

Laboratory Investigations

Clinical diagnosis of rubella infection is unreliable. Therefore, it is fundamental that mothers undergo serological examination, if they are non-immune to RV and present with rubella-like symptoms or exposed to individuals with rubella infection in the first 16 weeks of pregnancy. Although rubella vaccination confers a high degree of immunization, women with a history of rubella vaccination or with a previous positive test for rubella antibodies should be retested in the presence of a significant exposure to the virus. Positive rubella IgG and negative IgM in sera obtained before the incubation period, are indicative of maternal immunity, while women with negative or low level 8<10 IU/mL) results, should be retested in 7–10 days until 4 weeks after the contact to exclude seroconversion. Positive Rubella IgM in the presence of rubella-like symptoms or a history of contact with patients showing a macopapular rash or a fourfold increase of IgG antibody titre obtained 2 weeks apart are suggestive of maternal infection. If multiple serum samples obtained at different intervals during the first or early second trimester of pregnancy are available, they should be retested.

It is important to remember that false positive IgM results, especially in the absence of change in IgG concentration or absence of maternal symptoms may occur and that rubella IgM antiboides may persist for several years after the primary infection. In this scenario, use of rubella avidity test may be helpful in timing the occurrence of maternal infection if the time of exposure is unknown with low avidity rubella IgM and IgG suggesting a recent infection.[54]

Although RV infection or rubella vaccination confer a lifelong immunity after primary infection, reinfection is possible especially in immune-compromised patients. A significant increase in rubella IgG titre in a woman known to be immune indicates reinfection. It is important to differentiate a primary infection from a reinfection because the risk of fetal compromise occurs almost exclusively in mothers with a primary rubella infection.

BOX 4.7 Ultrasound Features of Congenital Rubella Syndrome

- CNS abnormalities (ventriculomegaly, microcephaly, intra-cranial calcifications, intra-ventricular adhesions, sub-ependymal cysts).
- Ocular abnormalities (microphtalmia, cataract).
- Heart defects (pulmonary artery stenosis and hypoplasia, atrial septal defect, ventricular septal defect, cardiomegaly).
- Intrauterine growth restriction
- Hepatomegaly
- Hydrops
- Polyhydramnios
- Ascites
- Hyper-echogenic bowel
- Placental enlargement

Management

Because the risk of fetal infection and compromise is higher in the first trimester of pregnancy, women with a serological diagnosis of RV infection in the first trimester should be counselled about the likely occurrence of an adverse outcome of the pregnancy. If the infection has occurred after the first trimester of pregnancy, the parents may be reassured that fetal infection is unlikely between 13 and 18 weeks and negligible after 18 weeks of gestation.

Diagnosis of rubella infection in the fetus is possible and can be accomplished either by performing a CVS, amniocentesis or FBS according to the different gestational age at presentation. Prenatal diagnosis of RV infection may be particularly useful after 12–13 weeks of gestation or in the first trimester of pregnancy in the absence of clear structural abnormalities detected at ultrasound or when serological tests are equivocal. PCR is the technique of choice in confirming fetal infection. An invasive test should be performed at least 7–8 weeks after infection or after the 21th week of gestation if the parents opted (Mace M). A positive PCR in the first trimester, especially if associated with the presence of structural abnormalities at the scan, usually indicates a poor outcome. If a positive PCR is not associated with any structural abnormalities especially in the second trimester, the parents should be explained the need for a careful and prolonged follow up after birth because functional defects cannot be ruled out by ultrasound. A negative PCR indicates no infection, although false negatives are possible.[59]

A detailed ultrasound assessment in centres with high skills in fetal medicine should be carried out if the parents declined invasive prenatal diagnosis in order to detect structural abnormalities associated with CRS. An early fetal echocardiography is also warranted. Currently, there is no evidence that giving rubella hyper-immune globulins to the mother reduce the rate of transmission or the course of fetal infection, although it may modify maternal disease.[60]

Post-natal Management

After birth, the baby should be examined carefully in order to rule out the presence of CRS. Blood and urine have to be obtained and tested for the presence of the virus if a prenatal work-up was not available. The baby should be examined for the presence of CSN, eye and cardiac abnormalities. Specific treatment depends upon the clinical manifestations, which may develop or progress over time, and a longer follow up is needed.

On the basis of the high morbidity and mortality associated with RV infection in pregnancy and of the lack of a cure if infection has establishes, it is important that women of child-bearing age are confirmed to be immune and that RV vaccine should be offered to all who are susceptible. A pregnancy should be avoided for at least 1 month after vaccination.

Although pregnancy represents a contraindication to rubella vaccination, the rate of congenital abnormalities does not appear to increase if vaccination was inadvertently administered during pregnancy.[61]

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.[62-70]

Table 4.2 displays wide differences in rubella immunity in different parts of the country. Until universal and 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.

PARVOVIRUS B19 (PB19)

Virology

Parvovirus B19 (PB19) is a single stranded DNA virus, member of the parvoviridae family. The PB19 genome consists of about 2500 base pairs and encodes for three major proteins: two structural proteins (VP1 and VP2) and one non-structural protein (NS1). While VP1 and VP2 form the viral capsid, NS1 proteins is involved in viral replication and is thought to be responsible for viral cytotoxicity presumably by inducing apoptosis of the host cells.[71,72]

Erythroid precursors, myocardial and endothelial cells are the major targets of PB19 infection (Chisaka) through the interaction between viral proteins and several cellular receptors,[72] the most known of which is globoside or P-antigen. B19-infected erythroid-lineage cells show apoptosis, which is thought to be caused by the non-structural protein, NS1, of B19. B19 infection also induces cell cycle arrest at the G1 and G2 phases of the cellular cycle. This causes lyses of the erythroid precursors leading to anaemia.

TABLE 4.2 Incidence of Seropositivity in Population Surveys

Authors	Place and Year	Prevalence (IgG Seropositivity)
Seth et al.[63]	North India three	80% seropositive
Yadav et al.[67]	New Delhi; 1995	55% seropositive
Chakraborty et al.[68]	Kolkata; 1973	56% seropositive
Bhaskaram et al.[69]	Hyderabad; 1991	95% seropositive
Verma and Gulati[70]	Faridabad; 2004	85% seropositive
Shanmugham et al.[66]	Kerala state; 1982	64% seropositive

Epidemiology

PB19 epidemics tend to occur every 4 years with a yearly peak of incidence in spring. Risk of PB19 infection is higher in day-care personnel and among women of child-bearing age with young children. Maternal infection usually occurs through respiratory droplets, although infection through blood and blood-derived product is also possible. Maternal viraemia reaches its peak approximately 7 days after the infection and IgM antibodies are detected in maternal blood between 7 and 14 days, while IgG antibodies are produced between 14 and 21 days.[71] Maternal infection is usually asymptomatic, although symptoms such as mild fever, headache, arthralgia and erythema infectiosum may occur. Pregnant women who are immune-compromised or those with pre-existing haematological problems such as sickle cell disease are more likely to develop transient aplastic crisis. They are at a higher risk of serious morbidity or even mortality.[71-74]

Implications of Fetal Infection

Fetal infection is the consequence of the transplacental passage of the virus during primary infection. No vertical transmission has been reported if the mother is immune at the time of exposure. The chance of vertical transmission from the mother to the fetus is related to the presence of maternal viraemia and occurs in 30–50% of the cases, while the risk of adverse fetal outcome is 10%.[70] Fetal infection with PB19 infection might be linked with miscarriage,[74] intrauterine fetal death, fetal anemia and non-immune hydrops fetalis. Thrombocytopenia is another possible complication of fetal infection.[75] The pathophysiology of PB19 cell-related damage is due to the destruction of erythroid precursors leading to fetal anaemia, high output cardiac failure, hydrops fetalis and eventually death. The risk of fetal hydrops is higher during the hepatic stage of haematopoiesis (8–20 weeks) because of

the shorter half-life of the erythrocytes compared to the later bone marrow and splenic stages.[76]

Apart from causing anaemia, PB19 may directly affect myocardium, which can cause arrhythmias or even cardiac arrest without evidence of anemia, cardiac failure or hydrops. Rarely, PB19 may be responsible of structural malformations, especially those involving the CNS. Perivascular calcifications involving the cortex, basal ganglia and thalami have been described in congenitally infected fetuses and newborns.[76]

Ultrasound Signs and Symptoms

The ultrasound features observed in fetuses with PB19 infection are consistent with the occurrence of fetal anaemia and high-output cardiac failure leading to hydrops. Increased nuchal translucency and abnormal flow in the ductus venosus may be the only signs linked to PB19 infection in the first trimester. Fetal anemia due to PB19 infection is suspected in the presence of an increased peak systolic velocity (PSV) in the middle cerebral artery (MCA) of the fetus, in mothers known to be positive for the Rh antigen and who have been in contact with patients with suspected PB19 infection.[76-80]

Fetal anemia progressively leads to high-output cardiac failure and fetal hydrops. At this stage, the ultrasonographic diagnosis is usually made in presence of the following signs: cardiomegaly, pericardial and pleural effusions, ascites, skin edema, placentomegaly and polyhydramnios. The peak incidence of fetal hydrops is between 17 and 24 weeks of gestations. In fetuses known to be at risk for PB19 infection, when planning an ultrasound examination it is important to remember that the interval between maternal infection and appearance of fetal hydrops is between 2 and 6 weeks.[76-80]

Laboratory Investigations

Serological examination of maternal blood is the first step for the confirmation of PB19 infection in patients at risk and laboratory detection is usually performed by enzyme immune assay.[81,82] PB19 IgM are detectable in maternal blood between 7 and 14 days, reach their peak at 10–14 days and then rapidly decrease within 2 or 3 months after maternal infection, while IgG antibodies are produced between 14 and 21 days.[83] A positive maternal IgM titer has a high sensitivity and specificity for the diagnosis of a recent PB19 infection. Alternatively, IgM/IgG ratio can be used, with a negative value indicating an infection taking place in the last month.[81] A precise estimate of the maternal contact is fundamental in interpreting the serological tests. After the contact between the mother and the virus there is a window of 7 days during which both IgM and IgG remain negative, leading to a false negative result if the mother is tested at that time. Anaemia due to PB19 infection progressively leads to the occurrence of fetal hydrops and eventually possible death. The interval between maternal infection and occurrence of hydrops is usually reported to be between 2 and 6 weeks. The rapid fall in IgM concentration usually after 2 or 3 months from maternal infection may lead to false negative diagnosis in the presence of a fetus showing sign of infection such as fetal hydrops.

In this scenario, polymerase chain reaction (PCR) analysis of maternal blood may help in the diagnosis. PCR is highly sensitive of PB19 infection compared to the commonly used serological tests, although the persistence of viral DNA in maternal circulation even for year after the primary infection may reduce the specificity of this test.[79-81]

Serological examination of amniotic fluid, fetal or neonatal blood is not reliable in detecting PB19 infection since most fetuses do not produce antibodies in response to infection. Therefore only PCR should be performed when analyzing fetal or neonatal samples.

Management

Pregnant women presenting with a rash should be tested for PB19 IgG and IgM. The patients can be reassured in case of negative IgM and positive IgG results, as this indicates past infection and maternal immunity. Women negative for both IgM and IgG should be considered at risk for infection and further serological testing should be carried out four weeks after the last contact or if signs of the disease develop. Finally, a positive IgM antibody test or a negative IgM/IgG ratio indicates a recent PB19 infection and an appropriate fetal follow up should be arranged. Infection with PB19 during pregnancy does not usually carry a high risk of maternal morbidity, although immune-compromised women or patients suffering pre-existing haematological conditions such as sickle cell disease should be monitored for the occurrence of aplastic crisis. No specific antiviral therapy or vaccine is available for PB19 infection.[75]

The fetus should be checked for the occurrence of anaemia or signs of hydrops within 4 weeks from the ascertained maternal infection. In case of negative ultrasound examination, additional follow up scans should be arranged every one or two weeks. If there is no fetal abnormality at or later than 30 weeks gestation, the mother can be reassured that there is unlikely to be any adverse sequelae from the PB19 infection. If ultrasound shows sign of anaemia or overt hydrops fetalis the patient should be referred to centers with a high level of expertise for an intrauterine transfusion. Fetal blood transfusion is warranted in these fetuses and it has been associated with an improved fetal outcome compared to expectant management.

There is some evidence suggesting a higher rate of adverse neurodevelopmental outcome if hydrops develops, irrespective of prenatal treatment. Thus a close ultrasound

follow up is needed after maternal infection is confirmed in order to detect anaemia in its earlier stages.[84]

Post-natal Management

Infection can be confirmed by detecting specific anti-Parvovirus B19 IgM in neonatal blood. Alternatively, viral isolation by PCR can be used to diagnose infection. A full blood count should be requested at birth in order to assess the degree of anaemia and thrombocytopenia in the newborn.[85-86] It has been recently suggested that neurodevelopmental and psychomotor disabilities in congenitally infected fetuses are associated with the infection per se, rather than the degree of fetal anaemia.[84]

VARICELLA ZOSTER (CHICKENPOX)

Virology

Varicella zoster virus (VZV) is a highly contagious human alpha-herpes virus which causes varicella (chickenpox) and herpes zoster. While Chickenpox is the consequence of a primary infection with VZV, herpes zoster is caused by the reactivation of the virus from its latency in the nucleus of the paraspinal cells usually due to immunosuppression, age or hormonal changes. The VZV virion consists of a nucleocapsid surrounding a core that contains a double-stranded DNA genome; a protein tegument separates the capsid from the lipid envelope, which incorporates the major viral glycoproteins.[87]

Epidemiology

VZV infection occurs in a worldwide distribution although its incidence varies according to the latitude and climate, with a peak during late winter and early spring in temperate climes. VZV is a highly contagious and readily transmissible infective agent with more than 90% of household contacts becoming infected after exposure. VZV is a highly species-specific virus with only humans being infected. The first contact between the virus and the host is usually through the conjunctivae and the mucous membranes of the nasopharynx.[88] After an incubation period of 15 days (range 10–21), non-specific prodromal symptoms such as fever, headache and malaise usually precede the macopapular rash, which becomes vesicular before crusting usually after five days.[89] The host can potentially transmit the infection from 2 days before to 5 days after the onset of the rash, until the vesicles crust over (7–10 days). Pneumonia represents the most serious complication of maternal infection, occurring in about 5–10% of the case with a mortality rate of $<1\%$. Although primary infection provides lifelong immunity, the virus persist in a latent form in the nucleus of the paraspinal cells and can potentially reactivate, especially if immunodepression co-exist. Although contraindicated in pregnancy, Varicella vaccine does not seem to be harmful for the fetus, if accidentally administered.

Implications of Fetal Infection

The mechanism of fetal infection has not been completely elucidated yet, but a reactivation of the VSV in utero as a consequence of the immature fetal cell-mediate immunity has been proposed.[90,91] The fetus can be infected only during a primary maternal infection. The risk of transmission following herpes zoster (reactivation) is negligible.

The rate of vertical transmission during the first and the second trimester has been reported to be at around 8–9% and congenital varicella syndrome occurs in about 10% of the fetuses developing infection (0.4–2% of all infected mothers), especially if maternal infection is acquired before 20 weeks of gestation. The risk of congenital varicella syndrome is negligible if maternal infection occurs after 20 weeks with only sporadic cases reported in the literature.[92,93]

Congenital varicella syndrome is characterized by features shown in Box 4.8.

Varicella is particularly dangerous for the fetus if delivery occurs between 5 days before and two days after the onset of the rash. In this scenario, the lack of an adequate immune response from the mother results in low levels of IgG in fetal blood, thus predisposing the fetus to neonatal varicella that occurs in up to 30% of the cases. Neonatal varicella is characterized by the presence of neurological, ocular, muscular, cutaneous, gastrointestinal and genitourinary abnormalities and leads the newborn to death in approximately 7% of the cases.[94,95]

Herpes zoster does not pose risk of fetal infection due to the presence of protective IgG from the mother and the shorter viraemic phase following reactivation of infection.

Ultrasound Signs and Symptoms

The main US findings associated with an increased likelihood of congenital varicella syndrome in a woman at risk are shown in Box 4.9.[96,97]

Some abnormalities associated with congenital varicella syndrome such as cutaneous and neuronal lesions are not usually diagnosed with ultrasound, thus highlighting the importance of a detailed post-natal assessment.

BOX 4.8 Features of Congenital Varicella Syndrome

- CNS abnormalities (mental retardation due to microcephaly and cortical atrophy)
- Limb hypoplasia
- Skin scarring
- Ocular abnormalities (cataracts, chorioretinitis)

BOX 4.9 Ultrasound Features of Congenital Varicella Syndrome

- Anomalies of the CNS (ventriculomegaly, microcephaly, intra-cranial calcifications, cerebral hypoplasia, porencephaly).
- Ocular abnormalities (microphthalmia, cataract)
- IUGR
- Limb hypoplasia
- Skeletal abnormalities
- Placental anomalies
- Hydrops fetalis
- Skin lesion (cutaneous scarring, Mandelbrot L)

Laboratory Investigations

Maternal varicella is usually diagnosed based on clinical findings. Detection either of specific IgM, or isolation of varicella virus by PCR in maternal blood confirms the diagnosis. Isolation of the virus by PCR in the amniotic fluid confirms the presence of fetal infection. An interval of at least 5 weeks between maternal onset of the rash and prenatal invasive tests is required in order to avoid false negative test.[98]

Management

Women exposed to varicella zoster infection and found to be seronegative should receive VZV IgG within 72–96 hours of exposure in order to attenuate maternal symptoms, while it has no effect once infection has established.

Women who develop varicella, should receive oral acyclovir (15 mg/kg every 8 hours) within 24 hours the onset of the rash in order to treat the disease and to reduce the rate of severe complications, such as pneumonia, that can occur in up to 10% of the infected mothers. If the maternal infection develops within 20 weeks of gestation the parents should be counselled about the presence of a small risk for congenital varicella syndrome (0.4–2%). Serial antenatal scans should be arranged and an amniocentesis may be offered to the parents. In the presence of a negative result at amniocentesis and a normal scan, parents should be reassured about the positive outcome of the pregnancy. If fetal infection is confirmed by a positive PCR on the amniotic fluid, serial ultrasound scans should be arranged in order to detect specific abnormalities associated with congenital varicella syndrome. If ultrasound is normal, parents may be counselled about a likely good outcome of the pregnancy. A complete detailed post-natal examination is required in order to rule out those abnormalities, such as cataracts, chorioretinitis and skin scarring, not detected at ultrasound. Abnormal ultrasound suggests the presence of congenital varicella syndrome and carries a poor prognosis or the fetus. If maternal varicella occurs in the third trimester of pregnancy and the delivery takes place between 5 days before and 2 days, an attempt to delay the delivery should be made in order to prevent neonatal varicella. Women presenting with varicella complicated by pneumonia should be admitted to the hospital and intravenous acyclovir should be administered.[99]

Post-natal Management

Newborn with a confirmed diagnosis of varicella infection in the amniotic fluid should undergo a detailed anatomical examination even if prenatal scan was negative, in order to exclude abnormalities not detected prenatally such as cataracts, skin scarring a chorioretinitis.

VZV IgG should be given to the baby if maternal varicella occurs in the third trimester of pregnancy and the delivery takes place between 5 days before and 2 days after the onset of the rash. Acyclovir should also be used if neonatal infection is confirmed.[99]

SYPHILIS

Microbiology

Syphilis is the result of the infection of *Treponema pallidum*, a gram-negative bacterium, 6–15 μm in length, not visible by light microscopy but readily identifiable by dark field microscopy. *T. pallidum* genome contains a single circular chromosome embedded in two membranes; the inner membrane mainly contains lipoproteins, while the outer membrane contains only rare transmembrane proteins, which are responsible for the induction of the inflammatory response by inducing cytokine release from monocytes.[100]

Epidemiology

The incidence of congenital syphilis is significantly greater in underdeveloped than in industrialized countries. 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.[101] World Health Organization (WHO) estimates that approximately 1.3 million pregnant women have active syphilis infection annually.[8] This leads to a substantial burden of preventable morbidity and mortality including over 200,000 stillbirths and fetal losses and more than 90,000 neonatal deaths.[102]

Syphilis is mainly transmitted by sexual contact and the risk of infection has been estimated to be around 30% per sexual contact with an infected partner.[103] The *Treponema* enters the body through small abrasions of the skin or the genital mucosa. A primary lesion known as chancre appears after an incubation period of approximately 3 weeks. The chancre is a painless, red, round ulceration with an indurated

base and well-formed border. Local-regional painless lymphoadenopathy is always present.

The chancre disappears spontaneously in 3–8 weeks even if untreated. If the immune response is unable to eradicate the infection, the *Treponema* multiplies locally and spreads through the perivascular lymphatic system to the systemic circulation, causing genital and extra-genital lesions known as *secondary syphilis*. These lesions occur mostly in ectodermal tissues such as skin and mucous membranes. The clinical picture of secondary syphilis resolves even if untreated, and most of the infected patients remain in an asymptomatic or latent phase. This stage is characterized by serologic evidence of syphilis without signs or symptoms of primary or secondary disease. 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. 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 at which point latent syphilis begins.[104]

Implication for Fetal Infection

Treponema pallidum can cross the placenta and causes congenital fetal infection at any time during pregnancy. The degree of fetal involvement is more severe if infection is acquired during the early stages of pregnancy. *T. pallidum* is responsible for a multiorgan disease in the fetus and the clinical scenario is highly dependent upon the gestational age at infection, degree of fetal involvement and time of maternal treatment. Congenital syphilis may cause stillbirth, preterm labour, growth retardation, fetal hydrops, and neonatal infection. Hepatosplenomegaly is frequent and can lead to hypo-albuminaemia and ascites. Anaemia and thrombocytopenia are otherwise frequent. Hydrops is usually the result of high-output congestive heart failure induced by severe anaemia. Skeletal involvement such as osteomyelitis, osteochondritis or periostitis is otherwise frequent.[105]

In live-born infants, the clinical symptoms of congenital syphilis can be divided into early and late signs. Early signs usually appear within two years of life and include respiratory symptoms, generalized lymphoadenopathy, hepatosplenomegaly, abnormal liver function, jaundice, hepatitis, anaemia, thrombocytopenia, osteochondritis or periostitis and maculopapular rash involving hands and feet. Central nervous system involvement is also frequent and may manifest with meningitis like symptoms. Late manifestations of congenital syphilis occur usually after two years of life. Although uncommon in treated patients, it can occur in up to 40% of untreated survivors. Typical manifestations of late congenital syphilis include facial and bone deformities, teeth abnormalities, keratitis and deafness.[105]

Ultrasound Signs and Symptoms

The main ultrasound findings described in fetuses with congenital infection are shown in Box 4.10.[106]

The degree of fetal involvement is directly related to the time of fetal infection and stage of maternal infection. Primary and secondary syphilis carry a higher risk of fetal compromise.

Laboratory Investigations

Antenatal screening has been shown to significantly reduce the rate of adverse perinatal outcome associated with congenital syphilis infection.[105,107] Although clinical diagnosis of the infection is feasible, serologic tests are necessary to confirm the diagnosis, especially in patients with secondary and latent syphilis. 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.[105]

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. 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 non-pregnant status. The FTA-ABS test and the MHA-TP tests are used to verify a positive screening test.

BOX 4.10 Prenatal Ultrasound Features of Congenital Syphilis

- IUGR
- Hydrops, ascites, pleural and pericardial effusion, generalized skin edema
- Placental thickening
- Hyper-echogenic bowel, hepatic calcifications
- Hepato-splenomegaly
- Shortening of the long bone
- Bone deformity (bowing, curvature and thickening)

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. False positive VDRL results may occur in patients with autoimmune diseases. Women who have persistent unexplained false positive VDRL results are at high risk for anti-phospholipids syndrome. 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.[104]

Management

Parental penicillin G represents the drug of choice for all the stages of syphilis and maternal treatment should be started soon after serological confirmation of infection according to the stage of the disease. Timing of antenatal care interventions makes a significant difference in the risk of having an adverse outcome due to syphilis and women treated in the first two trimesters of pregnancy are more likely to have a healthy infant, compared to women screened and treated in the third trimester.[104]

Penicillin is effective in preventing the transplacental transmission of the *Treponema* from the mother to the fetus and to treat fetal infection once established.

Antibiotic treatment in patients with confirmed syphilis infection is shown in Box 4.11.[108]

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.[109]

BOX 4.11 Antibiotic Treatment of Syphilis Infection

- **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.

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.

Postnatal Management

Babies of mothers with syphilis infection should be considered at high risk of congenital infection, irrespective of maternal antibiotic treatment during pregnancy. 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. An RPR or VDRL titer in the neonate four times greater than the maternal titer is also consistent with congenital syphilis. Penicillin treatment should be started only after serological confirmation of neonatal syphilis and these babies should be followed up closely for the occurrence of signs and symptoms of congenital infection (see above). Long-term follow up is needed in order to detect the late consequences of the infection.[105]

GROUP B STREPTOCOCCUS

Group B streptococcus (GBS) is a Gram-positive diplococcus that is beta-haemolytic, showing complete haemolysis on blood agar plates. Group B streptococcus (*Streptococcus agalactiae*, or GBS) can exist as a commensal in the lower genital and gastro-intestinal tracts, but is capable of causing particularly severe sepsis in the newborn. GBS also causes maternal infection, in particular chorioamnionitis, postpartum endometritis, wound infection, and sepsis and is an important cause of intrauterine asphyxia.[110]

GBS is recognized as the most frequent cause of severe early onset (at less than 7 days of age) infection in newborn infants. Group B streptococcus is the cause of a severe congenital infection that affects 0.5 to 1 neonate out of every 1000 live births every year in USA. The incidence of early onset GBS disease is reported to be 0.5/1000 births in the UK. Intrapartum antibiotic prophylaxis (IAP) with penicillin in GBS carrier mothers reduces the risk of early onset GBS disease. IAP has not been shown to have any impact on late onset (after the first 7 days but before 28 days of birth) neonatal sepsis.

GBS differs from group A streptococcus (*Streptococcus 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.[110]

Risk Factors for Early Onset GBS Sepsis

Some risk factors and their likelihood ratios are shown in Table 4.3.

Other risk factors for early onset GBS sepsis are the following:

- GBS bacteriuria
- Previous history of early onset GBS sepsis
- Multiple digital examinations in labour
- Prolonged labour
- Early onset GBS disease in a previous pregnancy

Maternal and Neonatal Colonization and Infection

GBS colonizes the genitourinary tract of 15–25% 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 ethnicity. The prevalence of colonization varies with the screening methods and is higher when specialized culture media (selective broth) rather than agar plates are used as the culture medium and when samples are taken from the lower third of the vagina and the rectum.[110] The rectal sample is of particular importance because colonization of the birth canal is secondary to colonization of the ano-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 15–25% 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.

TABLE 4.3 Risk Factors for Early Onset GBS Sepsis

Risk Factor	Prevalence	Likelihood Ratio for Early Onset GBS Sepsis
Known positive GBS carrier status	15–25%	4.6
Preterm delivery (<37 weeks)	7.9%	4.6
Preterm delivery (<35 weeks)	4.0%	5.6
Intrapartum pyrexia (>38°C)	1.9%	10.5
Prolonged pre-labour rupture of membranes (>18 hours) at term	9.4%	3.6

Antepartum cultures are predictive of intrapartum colonization only if they are obtained close of delivery.[111] 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.

Early onset GBS infection is a particularly virulent disease. A vast majority of infants (89–94%) who develop EOGBS infection, develop signs within the first 24 hours after birth. The majority of such infants (65–67%) will have had one or more 'conventional' risk factors that can be identified in or before labour. Therefore, infants at risk of EOGBS should be observed for the first 12–24 hours after birth with regular monitoring of general well-being, feeding, heart rate, respiratory rate and temperature. The overall mortality of early onset GBS disease is 9–10%. Whereas it is 5% for neonataes born at term, it is 20% for those born preterm.

GBS infection is also an important cause of stillbirth, particularly before 28 weeks of gestation 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.[112,113]

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 bacteraemia is present, GBS is identified by blood cultures in approximately 15% of the cases).[114]

Screening

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.[115] 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 staining. 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 with a positive predictive value of 100% and a negative predictive value of 98.8%.[116] 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. A UK study concluded that screening using a rapid test was not cost-effective based on its current sensitivity, specificity and cost.[117]

Prevention of Neonatal Infection

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 labour was effective in preventing early onset disease.[118] However, the systematic use of antepartum prophylaxis only started in 1996 when the Center for Disease Control (CDC) produced a set of recommendations to prevent early onset GBS neonatal infection.

There are essentially three strategies for early onset GBS disease.

1. Screen every pregnant woman, and offer intrapartum antibiotic prophylaxis (IAP) to the carriers – This approach is recommended by USA and Canada.
2. Do not routinely screen, but offer IAP to women with risk factors of GBS disease – This approach is recommended in the UK.
3. Routine screening and IAP offer to those who screen positive and also have risk factors for GBS disease.

The Royal Australian College makes no recommendations, and acknowledges that regional differences may exist in Australia. The initial CDC recommendations asked clinicians to adopt one of the first 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 labour, defined as a temperature of over 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[119] The study by Schrag[120] and coworkers 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 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). These recommendations lead to a 70–80% decline in the incidence of early neonatal GBS infection that reached a low frequency of 0.5 per 1000 live births.[120]

Screening of all pregnant women for GBS carrier status is not uniformly practiced all over the world. The UK NHS recommends that all pregnant women not be screened for GBS. They recommend a 'risk-factor' based approach (See Box 4.12). This difference from the policy of universal screening in USA is based on lower carrier prevalence in the UK.

IAP is not necessary if delivery is by pre-labour Caesarean section with intact membranes. In the USA, prophylaxis is not offered if previous pregnancy had a positive GBS screening culture but negative screening during the

BOX 4.12 Indications for Intrapartum Prophylaxis

Currently in the UK, IAP is recommended for the following:

- Previous baby with invasive GBS infection.
- GBS bacteriuria in the current pregnancy.
- Vaginal swab positive for GBS in current pregnancy.
- Pyrexia (>38°C) in labour (give broad-spectrum antibiotics to include GBS cover).
- Chorioamnionitis (give broad-spectrum antibiotics to include GBS cover).

present pregnancy, and when carrier screening is negative at 35–37 weeks' gestation in the present pregnancy, regardless of intrapartum risk factors. The details of intrapartum GBS prophylaxis can be seen in Box 4.13.

GBS resistance to penicillin or ampicillin are very rare, but have been reported. 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. Ampicillin may be a better choice for prophylactic treatment because it is transported easily through the placenta into the fetus and into the amniotic fluid. 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 or clindamycin every 12 hours until delivery. Erythromycin and clindamycin are thought not to be as good a choice 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 sub-therapeutic levels of the drug in the fetus and the amniotic fluid.[118]

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 misses women delivering preterm, which is the group at highest risk. Despite these problems, GBS prophylaxis has been successful and has 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.[121] 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.

BOX 4.13 Intrapartum Prophylaxis for GBS Infection

Penicillin 5 mU IV initial dose followed by 2.5 mU IV every 4 hours until delivery

Or

Ampicillin 2 g IV initial dose followed by 1 g every 4 hours until delivery.

Patients with non-anaphylactic reaction to penicillin:
Cefazolin 2 g IV initial dose followed by 1 g IV every 8 hours until delivery.

Patients with severe allergic reactions to penicillin:
Vancomycin 150 mg IV every 6 hours until delivery.

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, 1-2 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.[118]

Immunization

Active immunization against GBS using a vaccine is an attractive proposition. However, the results of vaccination trials have been disappointing and only 57% of vaccinated pregnant women have an adequate serum antibody response.[122] The design of vaccines capable of eliciting a stronger induction of antibodies is an area of active research at the present time. Moreover, women who deliver newborns who develop early onset disease seem to be unresponsive to the immunologic challenge posed by the GBS infection and may not respond to vaccination.[123]

Group B Streptococci Infection: Indian Experience

Daftary and Desai reported that these organisms can be isolated from the vagina and rectum or both in 15–40% of obstetric patients.[124] 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 labour. Morbidity and mortality is much higher in these preterm infants.

VIRAL HEPATITIS

There are at least five different types of viral hepatitis: A, B, D, C and E. All hepatitis viruses except B are RNA viruses. Vertical transmission of Hepatitis A is not seen. 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 co-existing infection with hepatitis B. Hepatitis E has similar characteristics to hepatitis A, but is a more serious condition predominant in countries with sub-optimal 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.[125]

Hepatitis A

Hepatitis A is uncommonly diagnosed during pregnancy because signs and symptoms are non-specific and the majority of infected individuals are asymptomatic. The virus is non-teratogenic 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 is supportive and consists of rest and adequate nutrition.[125]

Hepatitis B

Virology

The hepatitis B virus (HBV) is a virus with a diameter of 42 nm, formed by a nucleocapsid containing the core antigen (HBcAg) surrounded by inner and outer envelopes. HBV genome consists in a long circular DNA molecule that is partially double stranded. The surface antigen (HBsAg) and the 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 persistence indicates chronic infection. The HBeAg is a marker of infectivity and viral replication.[126]

Epidemiology

Chronic HBV infection affects about 350 million people worldwide, half of whom acquire the infection either prenatally or in early post-natal period.[126-128] 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. Although the infection remains stable in a vast majority of patients, it can progress towards cirrhosis and liver cancer in a up to 40% of infected individuals. 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.

Maternal Infection

In most cases, acute or chronic HBV infection in pregnancy is not different from that occurring in non-pregnant women. 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, 5–10% would become chronic carriers, and less than 1% manifest a lethal fulminant hepatitis.[129]

Seven of each 10 chronic HBV carriers have chronic persistent hepatitis (CPH), whereas the remaining three 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.[129]

The outcome of maternal infection is strictly dependent upon the stage of the disease; patients with advanced cirrhosis may experience rupture of oesophageal varices in up to 25% of the cases. Other conditions such as liver failure, jaundice and rupture of splenic aneurism are not uncommon in this scenario.[129]

Implications for Fetal Infection

HBV infection may be transmitted from the other to the fetus. Transplacental infection of the fetus is rare and viral DNA is rarely found in the amniotic fluid and cord blood.[130] Most neonatal infections are the result of contact with infected maternal blood and vaginal secretions during parturition or acquired during breast-feeding. The rate of vertical transmission is highly dependent on the gestational age of maternal infection, with rates of vertical transmission of 10% and 80–90% if maternal infection occurs in the first/second or third trimester, respectively. Without prophylaxis, transmission is very high and strictly dependent upon maternal antigenic status. The rate of vertical transmission is higher for HBeAg-positive others (70–90%) compared to HbeAg-negative/HBeAb-negative (25%) and HbeAg-negative/HBeAb-positive (12%).

Ultrasound Signs and Symptoms

HBV is not a teratogen, and therefore ultrasound cannot diagnose the infection. Furthermore, maternal infection is

not responsible for an increase in fetal mortality compared to the general population, although an increased incidence of low birth weight and prematurity has been reported in the acute phase of infection.[127]

Laboratory Investigations

HBsAG appears in maternal serum 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 serologic 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.[129]

Management

Currently routine screening for Hepatitis B infection is recommended. All pregnant women, irrespective of their vaccination history, should be screened for HBV infection in the first trimester of pregnancy. If the mother is positive for the infection in early pregnancy, the status of the disease needs to be established. An active disease is defined by the presence of high viral load and elevated ALT. In this case, therapy should be initiated irrespective of the gestational age at diagnosis. A non-active disease is defined by the presence of low ALT levels and low viral load. In this case, surveillance is warranted and HBV DNA should be repeated in the late second trimester of pregnancy. If the viral load is $>10^6$ copies/mL antiviral prophylaxis should be started in the third trimester.[129]

There is no general consensus of which antiviral drug should be used to prevent neonatal HB infection. Lamivudinen has been shown to be a safe and effective drug in preventing perinatal transmission of the virus.

The use of cesarean delivery for the prevention of neonatal infection in HBV carriers is controversial, but generally not recommended. 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.[131] Vaccination for HBV infection can be performed during pregnancy and is advisable in sero-negative women at high risk for infection. The currently available vaccines are highly immunogenic and are prepared from yeast cultures using recombinant DNA technology.

Postnatal Management

Infected newborns are usually asymptomatic but approximately 85% will develop chronic infectionif they are untreated. 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. Neonatal infection can be prevented by screening of the entire obstetrical population, and by administration of hepatitis B immunoglobulin and hepatitis B recombinant vaccine to babies 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 reduced by subsequent breast-feeding.[132]

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. 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.[133]

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 co-exist 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.[134] HCV is rarely transmitted by breast-feeding.

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 the mother to the 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%.[135] HEV is the main cause of non-A, non-B hepatitis, whilst HCV is not an important cause of acute viral disease.[136] Infective hepatitis is endemic to our country and assumes epidemic proportions particularly during the rainy season when contamination of drinking water sources is highest.[137] 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 4.4).[138-141]

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.[137] The mortality is 3.5 fold higher during pregnancy (an immunocompromized state) than in non-pregnant women.

Various workers analyzing the problem of hepatitis complicating pregnancy have reported wide variations in maternal mortality from the disease in India (Table 4.5).[142-148]

TABLE 4.4 Prevalence Rates of HBsAg During Pregnancy in India

Authors	Year	Prevalence Rates
Gupta et al.[138]	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.
Mittal et al.[139]	1996	HBsAg positive in 6.34% (micro-ELISA) HBeAg positive in 18% of above
Sharma et al.[140]	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 per cent of babies born to HBsAG positive mothers were healthy.
Ahmad et al.[141]	2001	HBsAg positive in 9.0%

TABLE 4.5 Maternal Mortality Due to Viral Hepatitis in India

Authors	Years	Maternal Mortality (%)
Patel et al.[142]	1994–1997	3.6
Doke and Salunkhe[143]	1987–1990	24.0
Roy et al.[144]	1990–1998	4.8
Shankar and Seetharam[65]	1988–1997	12.4
Sharma[145]	1987–1996	5.4
Kulkarni and Huilgol[146]	1988–1997	9.4
Khare[147]	1985–2000	25.0
Bedi et al.[148]	1991–1996	7.1

GENITAL HERPES (HSV)

Virology

HSV are DNA viruses belonging to alpha-herpesviridae, a subfamily of Herpesviridae. There are two main antigenic types of HSV, HSV-1 and HSV-2. HSV-2 is sexually transmitted and is responsible of most of the genital herpes, while HSV-1 is transmitted via non-sexual contact and is mainly responsible for the occurrence of oral herpes. However, HSV-1 can also be responsible for genital herpes, especially in developed countries and among college-age population. Both viruses infect epithelial mucosal cells and migrate along the nerves to reach the local-regional ganglia. Peculiar feature of these viruses is to persist throughout the life of their hosts in a latent phase, from which they can occasionally reactivate thus causing recurrent infection outbreaks.[149]

Maternal Infection

Genital HSV infection may or may not be symptomatic. Symptomatic infections are characterized by the presence of ulcerative lesions in the external genitalia, the cervix and in the perineum causing pain, vaginal discharge, dysuria and regional lymphadenopathy. Systemic symptoms such as fever, myalgia and headache are usually present, and in a small percentage of cases, represent the only clinical manifestation of the disease. Severe complications of HSV infection are rare and include meningitis, encephalitis, disseminated

skin lesions, hepatitis and haematological disorders. The occurrence of severe systemic symptoms is more common in pregnant compared to non-pregnant patients.[150,151]

Although asymptomatic patients do not show the classical clinical manifestations of the disease, they are infectious, thus representing an important source of transmission. After the first episode of the infection, the virus persists in a latent phase in the regional nerve ganglia from which it can periodically reactivate and induce recurrent infections.

Clinical diagnosis of genital HSV infection during pregnancy is inaccurate because 75–90% of HSV-2 infected individuals are unaware of having the infection. Approximately 70% of new HSV infections among pregnant women are asymptomatic or unrecognized.[152] The other 30% have clinical symptoms that range from minimal lesions to severe presentation. The reason for this is that, most sexual transmissions occur during episodes of sub-clinical reactivation in persons who are unaware of their infection. 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%.

Implication for Fetal Infection

HSV infection of the newborn can be acquired in utero, during labour or postnatally. Intrauterine HSV infection before delivery is uncommon, and accounts for about 5% of the infected neonates. It typically occurs in pregnant women with disseminated HSV-2 infection before 20 weeks of gestation, and usually leads to miscarriage, stillbirth and congenital malformations, especially those involving the CNS, skin and eyes.[151] 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.[153]

The most important route of transmission 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 labour 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 (usually more than 4 hours) has also been associated with neonatal infection, 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 women with active genital herpes at the time of delivery is markedly reduced, if the infant is delivered by cesarean section. In the past, it was thought that after 4 hours the possibilities of fetal infection were pretty significant and cesarean probably ineffective. Therefore, a period of 4 hours after rupture of the membranes was considered to be the threshold for performing cesarean section. 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 considered irrespective of the duration of ruptured membranes. The risk of acquiring HSV infection appears to be similar whether the infant is term or preterm. Transplacentally acquired antibodies against HSV may protect the infant from disseminated HSV infection but do not protect against localized disease, which may be fatal.[151,153]

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 non-specific 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 frequently involved organs 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. Cutaneous, oral or ocular lesions are often associated with disseminated disease. Encephalitis may occur as a part of disseminated herpetic infection or as a predominant manifestation. It is characterized by non-focal, 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 3 and 14 days of life is the most prominent feature of the infection.[151,153]

Ultrasound Signs and Symptoms (Box 4.14)

Intrauterine infection of HSV before labour is rare, and accounts for 5% of infected newborns. The ultrasound features of infected fetuses are highly variable and dependent upon the

BOX 4.14 Ultrasound Features of Congenital Herpes Infection

- CNS (severe ventriculomegaly, hydranecephaly, microcephaly, enlarged cisterna magna).
- Non immune fetal hydrops
- Abdominal calcification especially within the liver
- IUGR
- Skin scarring

extent of fetal involvement. The most common ultrasound features in congenital HSV are shown in Box 4.14.[154]

Laboratory Investigations

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. 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. Similar 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. Cytologic techniques are a readily available and rapid means of identification of HSV infection. Cell scrapings are obtained from the base of lesions as well as from the cervix 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 extra-genital (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.[150]

Viral 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.

Management

All women with a history of HSV genital infection are considered to be at risk and would benefit from viral suppressive therapy during the last 4 weeks of gestation. Most individuals with HSV-2 infections are asymptomatic and unaware of their infection and may have asymptomatic viral shedding during pregnancy.[150] To prevent neonatal infection, before labour onset, it is necessary to identify women with negative history who are at risk of genital HSV-2 infection and women who are infected but are unaware of their infection, who may shed the virus in the peri-partum period. To achieve this objective, serologic screening of all asymptomatic pregnant women without history of herpes and their partners at the end of the second trimester of pregnancy may be helpful. 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 much less, approximately 2.4%.[155] 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 labour. Absence of antibodies in both members of the couple indicates no risk for primary infection.

Prevention of vertical transmission in women at risk 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.[156]

Women presenting in labour with herpetic genital lesions or with prodromal symptoms suggestive of genital herpes should be deliver by cesarean section. The beneficial effect of cesarean has been demonstrated in prospective cohort studies and is greater in the absence of ruptured membranes.[152] 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 labour, because the results of these tests are not available in time to influence clinical decisions. Women with no history of herpes genital infection or on suppressive antiviral therapy should be examined, and if no herpetic lesions are present, they should be allowed to deliver vaginally.

HSV Infection: Indian Experience

Deepika Deka from AIIMS, New Delhi (India) has extensive experience in the field of maternal fetal medicine.[49] 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, hydrencephaly, 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 labour (35%) and intrauterine growth restriction (IUGR). Since all organs are susceptible to

infection, multiple abnormalities can arise. Clinical markers of HSV include abortion, preterm labour, 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.[49]

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Virology

The human immunodeficiency virus (HIV) is the cause of the acquired immune deficiency syndrome (AIDS).

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, 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), a 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 of these cells by the HIV-1 virus causes 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.[157]

Epidemiology

According to the WHO globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012. This is an increase from previous years, as more people are receiving the life-saving antiretroviral therapy. There were 2.3 (1.9–2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. 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.

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 users. Rarely, maternal infection results from the administration of blood or blood products, especially if they were received before April 1985, after which individuals from high-risk groups were 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 users, have multiple sexual partners, and have intercourse with partners at high risk.[157]

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 detected. 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* (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 candida, CMV, herpes, histoplasma, cryptococcus, and pneumocystis carinii or develop Kaposi's sarcoma, lymphoma of the brain, or multiple recurrent bacterial infections.

Prospective studies have demonstrated that pregnancy does not affect the progression or the survival of HIV-infected women.[158] 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.

Implications for Fetal Infection

Approximately 15–25% 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 labour and delivery and the rest occurs antepartum.[159]

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 copies of HIV RNA 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. 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.[160] 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[159] and cesarean delivery has a protective effect.[161] An important factor associated with the frequency of vertical transmission is the use of maternal combination antiretroviral therapy. The frequency of mother–infant transmission decreases drastically if the pregnant woman is being treated with highly active antiretroviral therapy (HAART) or receives intrapartum treatment. HAART lowers the frequency of transmission irrespective of the maternal viral load, and vertical transmission is a rare event when the viral load reaches undetectable levels.[162] 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.[162]

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 non-infected newborns will be seronegative. The presence of positive serology secondary to passive transmission of antibodies makes the diagnosis of HIV infection difficult in the newborns. In this situation, viral cultures and PCR testing should be performed to confirm or exclude infection.

Diagnosis

The diagnosis of HIV infection is serologic, by virus culture, or by detection of viral genetic material 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 indeterminate. A positive test is indicative of infection. The probability of a false positive diagnosis is almost non-existent, 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 is possible and every month thereafter. Viral cultures are rarely used for diagnosis of HIV infection. Cultures are labour-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 labour 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 labour and delivery suite when the specimen is whole blood. A negative rapid HIV test result is reliable and indicates absence of infection. A positive test requires confirmation by Western blot and antiretroviral prophylaxis is started without waiting for the results of the confirmatory test.[164]

Ultrasound Signs and Symptoms

Ultrasound features of fetal infection are non-specific and include[163,164]

- IUGR
- Microcephaly
- Cranio-facial anomalies (hypertelorism, prominent forehead, flat nasal bridge)

It has been suggested that fetal infection does not result in a specific pattern of fetal abnormalities, but that the ultrasound signs found in infected fetuses might be the result of maternal co-morbidities, such as concomitant infections, poor nutrition and drug abuse, rather than HIV infection per se.[165]

Management

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 is to have HIV testing at the first prenatal visit and offer the test later in pregnancy if the patient initially declines.[166]

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 women will be provided by social workers, nutritionists, paediatric 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 limited. One important task for the obstetrician is to advise these women about the option of termination if the gestational age is less than the legal age for termination. The woman should have a CD4 cell count every trimester and serial ultrasound scans in order to assess the longitudinal growth pattern of the fetus if she decides to continue with the pregnancy.[166]

The evolution of the disease during pregnancy is followed with periodic assessments of the viral load and the CD4 cell count, usually every month. Box 4.15 lists the drugs used in HIV infection. Drug therapy is not different from that provided to non-pregnant 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.

One of the principles governing treatment during pregnancy is to include zidovudine (ZDV) as a component of the HAART regimen whenever possible.[161] Some of these drugs have overlapping toxicities, or reduced 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 drug 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 labour. Women with HIV infection should be scheduled for induction of labour or cesarean delivery at 38 weeks of gestation. The reason for this timing of delivery is to avoid rupture of the membranes or labour

BOX 4.15 Drugs Used for HIV Infection

Antiretroviral drugs		
Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors	**Non-Nucleoside Reverse Transcriptase Inhibitors**	**Protease Inhibitors**
Azidothymidine (AZT)	Nevirapine	Indinavir
Zalcitabine	Delavirdine	Ritonavir
Didanosine	Efavirenz	Saquinavir
Stavudine		Nelfinavir
Lamivudine		Amprenavir
Abacavir		Lopinavir/
Tenofovir DF		Ritonavir

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. 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. Paediatric 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 therecommended discussing and advising cesarean delivery for women with viral loads >1000 copies/ml.[160] Women 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 women may choose between cesarean or vaginal delivery. For women who chose vaginal delivery, avoiding the use of fetal scalp electrodes is recommended to decrease the contact between fetal blood and vaginal secretions.

Intrapartum treatment with ZDV is of fundamental importance to reduce 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.[160]

Postnatal Management

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 important.

HIV in Pregnancy: Indian Experience

Damania and Tank from India made a pertinent observation that HIV infections lowered patient's resistance to disease[167]; 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 and coworkers 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.[168] 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 and coworkers from Chandigarh reported a low incidence of HIV of 0.036%.[169] 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 and coworkers 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 centres.[170] Madhivanan and coworkers from Chennai reporting on the profiles of HIV positive pregnant women reported that heterosexual contact was the main route of transmission.[171] 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 and coworkers from Indore documented that 33 out of 500 pregnant women tested HIV positive.[172] The age group of 25–34 was mainly affected; the mean age was 28.5 years. About 75–80% of women were infected through hetero-sexual 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 and co-workers from Mumbai reported an incidence of HIV positive in 3.9% of the pregnancies with a vertical transmission incidence of 36.4%.[173] Asha Dalal from Mumbai 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.[174] Although, ideally breast-feeding is contraindicated, in poor and low resource countries this requires a critical reappraisal.

MALARIA

Microbiology

Malaria is caused by protozoan parasites belonging to the genus plasmodium.[175] The following causative organisms have been recognized: *P. vivax, P. falciparum, P. malariae,* and *P. ovale.* Of these, *P. falciparum* is responsible for most severe disease and mortality. Resistant strains are posing major clinical problems in controlling the disease.

Malaria can be transmitted by several species of female anopheles mosquitoes that differ in behaviour. This contributes to the different epidemiological pattern of

Malaria observed worldwide.[175] The organism invades and damages the red blood cells leading to a decrease in the haemoglobin. The damaged red cells become sticky and adherent. This results in sequestration in vital organs leading to a disturbance in the microcirculation, which in turn leads to disturbed metabolism. The two classical presentations of malaria in non-pregnant women are cerebral malaria and severe anemia. In pregnancy, trophoblastic infection leads to impaired function leading to a peculiar clinical scenario.

Epidemiology

Over 50 million of pregnant women are exposed to the risk of Malaria in pregnancy and it has been reported that Malaria infection is directly responsible of 75,000–20,00,000 perinatal deaths every year.[176-178] Pregnant women are more susceptible to infection especially during the first and second trimester of pregnancy. The peculiar immunological and hormonal change taking places in pregnancy are thought to be responsible for this susceptibility.

Implication for Maternal and Fetal Infection

The pathophysiology of fetal and maternal malaria infection is thought to be the result of an impaired trophoblastic function induced by *Plasmodium*. Infected erythrocytes accumulate in the inter-villous space causing damage to placental angioarchitecture and immunological changes the leads to impaired placental function.[177]

The clinical manifestations of malaria in the mother are directly related to the immunological status, *Plasmodium* strain and presence of associated co-morbidities such as HIV infection. Immunological changes occurring in pregnancy predispose to an increased severity and frequency of the attacks.

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. Delirium sets in in severe cases. Hemolytic jaundice and anaemia are common. Cerebral malaria is a life-threatening condition requiring intensive care. The risk of severe anaemia, jaundice, hypoglycaemia, hyperpyrexia and convulsions is also increased in pregnant women.[177]

Involvement of the fetus is common, occurring in up to 60% of the cases. The effect of the infection of the fetus depends upon the balance of the time of infection, *Plasmodium* strain and maternal immunity. Miscarriage, stillbirth, preterm birth and IUGR are the most common clinical manifestations during pregnancy. IUGR is determined by severe placental insufficiency induced by the *Plasmodium*, usually leading to fetal hypoxemia, academia and death. Severe maternal anaemia may also play a role in this scenario.

Ultrasound Signs and Symptoms

IUGR represent of the most severe and common fetal complications occurring during malaria infection.[179,180] IUGR is thought to be the consequence of impaired trophoblastic function induced by the parasites progressively leading to fetal hypoxemia and academia. Dorman and coworkers[179] has previously reported that Malaria infection at 32–35 weeks of gestation was associated with abnormal uterine artery flow velocity waveforms and that this association persisted after controlling for pre-eclampsia.[7] Furthermore, the authors reported that abnormal utero-placental blood flow was also predictive of poor perinatal outcome, including low birth weight, preterm delivery and perinatal death. Longitudinal assessment of fetal growth is therefore warranted in pregnancy affected by Malaria infection.[179,180]

Laboratory Investigation

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.

Management

WHO recommends two doses of intermittent preventive treatment at least 4 weeks apart, starting at about 18–20 weeks of gestation.[181] Although the risk of teratogenicity is reduced, malaria during trophoblast invasion or placentation is not treated. Moreover, if the two doses of sulphadoxine–pyrimethamine intermittent preventive treatment are completed by 28 weeks of pregnancy, this could leave women susceptible to malaria in the third trimester, which is the peak growth period of the fetus. Longitudinal assessment of fetal growth is warranted in order to detect fetuses affected by IUGR.[181]

Infection as a Possible Cause Following Ultrasound Scan Findings

A specific scan finding may raise the suspicion of fetal infections. Table 4.6 lists such findings. A TORCH test is often requested in response (Please see below).

TABLE 4.6 Ultrasound Scan Findings Commonly Seen in Infections

Infection	Head/Central Nervous System	Cardiac	Abdominal	Placenta/Amniotic Fluid	Other
Toxoplasmosis	VM, microcephaly, calcifications, cataracts		Hepatomegaly, splenomegaly, ascites, echogenic bowel	Placentomegaly, hydramnios	Hydrops, IUGR
Syphilis			Hepatomegaly, splenomegaly, ascites, dilated bowel	Placentomegaly, hydramnios	Abnormal long bones, IUGR
Rubella	Microcephaly, microphthalmia, cataracts, VM	VSD, ASD, coarctation	Hepatomegaly, splenomegaly, Meconeum peritonitis		IUGR
CMV	VM, microcephaly, IC calcifications	Cardiomegaly	Hepatomegaly, splenomegaly, ascites, echogenic bowel, parenchymal calcifications	Placentomegaly, hydramnios, oligohydramnios, small placenta	IUGR, hydrops
Herpes	VM, IC calcifications, microcephaly, microphthalmia		Hepatomegaly, splenomegaly		IUGR, limb deformities
Varicella	VM, IC calcifications, microphthalmia		Hepatomegaly, ascites, parenchymal calcifications	Hydramnios, oligohydramnios, small placenta	IUGR, limb deformities, hydrops
Parvovirus	Increased MCA PSV	Cardiomegaly, biventricular regurgitation	Hepatomegaly	Polyhydramnios	Hydrops, skin oedema

VM = Vetriculomegaly, IC = Intracranial, VSD = Ventricular septal defect, ASD = Atrial septal defect. MCAPSV = Middle cerebral artery peak systolic velocity

Positive TORCH Test Result

Blood testing is often carried out to check for maternal infection, and collectively, the tests are often referred to as '*TORCH*'. The important ones include serological test for Toxoplasma and Cytomegalovirus infections. Serology for rubella and syphilis is tested at booking. Performing a TORCH test without a clear indication is generally a bad idea. Test detects antibodies, but is unable to distinguish between a recent and a past infection. Majority of positive test results are as a result of past infection (which usually indicates immunity). In the UK, approximately 50% pregnant women are immune for CMV, 5–15% for Toxoplasma, 60% for Parvovirus, over 95% for Rubella, and 90% for Chicken-pox (Varicella). Although presence of antibodies of the IgG type generally means immunity from infection, fetal infection with cytomegalovirus in immune mothers has been documented (Reactivation or re-infection). The following steps are necessary in order to assess the impact of possible infection:

1. Assess maternal susceptibility
2. Confirmation of maternal sero-conversion
3. Identify fetal infection
4. Assess impact of fetal infection (Affection)

Important Points

- 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.
- Several approaches are available for the prevention of early-onset GBS infection. The favored approach in the US for the prevention of early-onset GBS infection is based in screening for ano-genital 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.
- 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.

- 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.
- 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.
- 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.
- 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.
- The best contribution of the obstetricians to the prevention of congenital rubella is postpartum vaccination of nonimmune individuals.
- 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.
- 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.
- 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.
- 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%.
- Pregnant women exposed to varicella should have their immunity evaluated. If the patient is not immune she should be treated with VZIG.
- 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%.
- 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.
- 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.
- 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.
- 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.
- 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.
- The following steps are necessary in order to assess the impact of possible infection: Assess maternal susceptibility, confirm of maternal sero-conversion, identify fetal infection and assess impact of fetal infection (fetal affection).

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Chapter 5

Fetal Growth Restriction

Giorgio Pagani and Amarnath Bhide

Chapter Outline

CONCEPT

In every population, fetal size shows a normal distribution at a given gestation. Consequentially, a fraction of fetuses is large for gestational age (LGA) and another fraction is small for gestational age (SGA) regardless of their own growth potential. Fetuses at the extremities of the distribution may have either grown physiologically or may have overachieved (LGA) and underachieved (SGA) their own growth potential.

DEFINITION

Fetal growth restriction (FGR) is a pathological condition in which a fetus has not achieved his genetic growth potential, regardless of fetal size. It is important to understand that a fetus does not need to be small to be growth restricted and that FGR and SGA are not synonymous. It is estimated that the majority of FGR fetuses are SGA, while 50–70% of SGA fetuses have grown appropriately but are constitutionally small.[1]

Overall, structurally normal SGA fetuses are at an increased risk for perinatal mortality and mobility. However, majority of the adverse outcomes are encountered in the growth-restricted group. Fetal growth restriction represents the second primary cause of perinatal mortality, accounting for 30% of stillbirths, besides determining a higher frequency of premature births and intrapartum asphyxia.[2] Fetal growth restriction is also associated with neonatal complications, including meconium aspiration, metabolic and haematological disorders, cognitive dysfunction, and

cerebral palsy.[3-6] Some epidemiological studies also report a higher incidence of coronary diseases, arterial hypertension and diabetes in adult life.[7] Nonetheless, FGR is not always detected during the prenatal period, making this disorder one of the main challenges of obstetrics.

Although FGR as a concept is easy to define, it is impossible to quantify the growth potential of an individual fetus, and objective criteria for identification are not available. Small for gestational age if often used as being a proxy for being growth restricted. Smallness is often defined as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th centile and severe SGA as EFW or AC less than the 3rd centile. Fetal growth restriction is sometimes defined as SGA with abnormal Doppler indices such as umbilical artery (UA), pulsatility index (PI) above the 95th centile or mean uterine artery (UtA) PI above the 95th centile.[8] However, SGA fetus with normal uteroplacental Dopplers may still not have reached its growth potential. Consequently, not all small fetuses are growth restricted and not all growth-restricted fetuses are SGA.

TYPE OF SMALLNESS

A fetus can appear to be small for the following four reasons:

1. Error in pregnancy dating.
2. SGA: Constitutionally small.
3. SGA: Fetal disease/anomaly/infection (Non-placenta-mediated smallness)
4. SGA: Placental insufficiency

Error in Pregnancy Dating

It is easy to understand that if the pregnancy is dated inappropriately, a fetus can be misclassified as SGA. Pregnancy should be dated according to Crown rump length (CRL) until 13^{+6} weeks' gestation or to head circumference (HC) from 14 weeks' gestation.[9]

Symmetry and Asymmetry

The concept of symmetry means that all fetal segments (head, abdomen, long bones) are small and that the centiles of their measurements are comparable (Fig. 5.1). Asymmetry is related to a more accentuated reduction of the abdomen, compared to the other fetal segments (Fig. 5.2).

Constitutionally Small Fetuses

Constitutionally small fetuses are small because they are genetically programmed to be so. Historically, they are considered 'symmetrically' small.

Generally speaking, they (a) are small from the second trimester, (b) are symmetrically small, (c) have low first trimester risk for aneuploidy, low or normal placental hormones (PAPP-A/hCG), (d) maintain their growth velocity across gestation, (e) have normal feto-placental Doppler patterns.

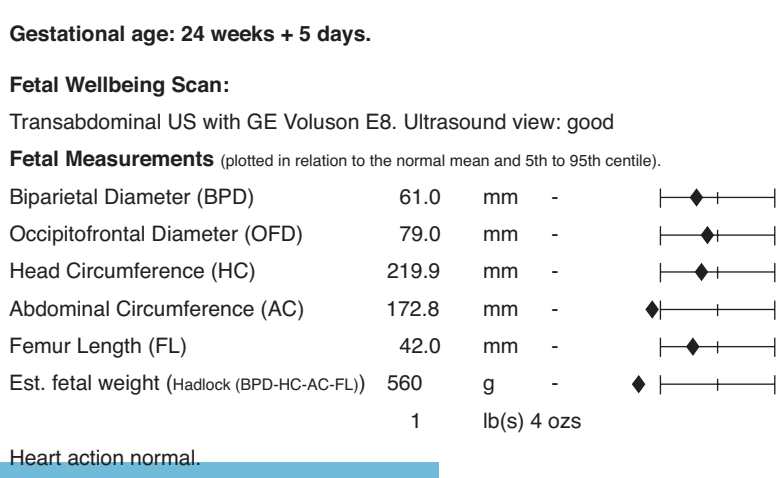
Structural or Chromosomal Abnormality

Another group of small fetuses is the one that includes structural or chromosomal abnormalities.

Trisomy 18 is one of the most common causes of SGA among chromosomal defects and it is usually associated to multiple structural abnormalities visible on the scan.

One example of structural abnormality (not associated to chromosomal defects) that leads to SGA is gastroschisis because of the abdominal wall defect, the bowel is out of fetal abdomen and abdominal measurements are consequently smaller. In this condition Doppler examination is essential in order to exclude/detect fetal growth restriction due to placental insufficiency.

This group of SGA can (a) be small from the first early second trimester, (b) be symmetrically or asymmetrically



Gestational age: 24 weeks + 5 days.

Fetal Wellbeing Scan:

Transabdominal US with GE Voluson E8. Ultrasound view: good

Fetal Measurements (plotted in relation to the normal mean and 5th to 95th centile).

Biparietal Diameter (BPD)	61.0	mm	-
Occipitofrontal Diameter (OFD)	79.0	mm	-
Head Circumference (HC)	219.9	mm	-
Abdominal Circumference (AC)	172.8	mm	-
Femur Length (FL)	42.0	mm	-
Est. fetal weight (Hadlock (BPD-HC-AC-FL))	560	g	-
	1	lb(s) 4 ozs	

Heart action normal.

FIGURE 5.1 Asymmetrically small fetus.

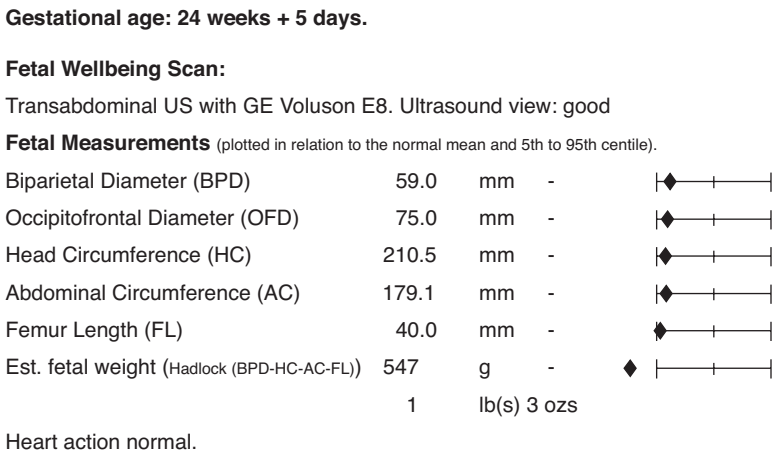


FIGURE 5.2 Symmetrically small fetus.

small, (c) have high first trimester risk for aneuploidy and low placental hormones (PAPP-A/hCG), (d) maintain or reduce their growth velocity, (d) have normal feto-placental Doppler patterns.

Fetal Infection

Several pathogens such as cytomegalovirus, rubella, *toxoplasma gondii*, *plasmodium malariae* and *Treponema pallidum* are associated to SGA unrelated to placental insufficiency. When passed from the mother onto the fetus, these pathogens lead to placental inflammation, lesions of the vascular endothelium and fetal viraemia, with direct inhibition of cellular multiplication, obliterating angiopathy, chromosome ruptures and cytolysis.

This group of SGA (a) is small since infected, (b) is usually asymmetrically small, (c) has low first trimester risk of aneuploidy and normal placental hormones (PAPP-A/hCG), (d) shows a deceleration in growth velocity unless the infection is cured, (d) has usually normal feto-placental Doppler patterns.

Placental Insufficiency

Interactions between maternal and fetal circulations in the placenta are necessary for an adequate exchange of oxygen and nutrients. It is thought that this adaptation occurs due to a continuous physiological process often referred to as 'waves of trophoblast migration'. Trophoblastic tissue invades the muscular layer of maternal arteries, thereby converting them from high- to low-resistance vessels.

Inadequate placentation is consequent to the absence of destruction of the muscle and elastic portion of the spiral arteries in the trophoblast migration. When this happens, it leads to a territory with high resistance to blood flow and decreased nutrition of the intervillous space. This has been associated to a greater frequency of pre-eclampsia and SGA.

This group of SGA (a) may start from the second trimester, (b) is asymmetrically small, (c) has low first trimester risk of aneuploidy but low placental hormones (particularly PAPP-A), (d) shows a progressive deceleration in growth velocity, (d) likely to show abnormal feto-placental Doppler patterns.

RISK FACTORS

Risk factors for placental insufficiency have been extensively studied and can be used to tailor prenatal care and customize the follow-up.

Placental transfer of nutrients can be affected either by maternal factors such as low pre-pregnancy weight, undernutrition, substances abuse, severe anaemia or medical conditions that can affect placental implantation and trophoblastic invasion such as pre-eclampsia, chronic hypertension, diabetes with vascular disease (Table 5.1–5.4).

Maternal Characteristics (Assessed at Booking and During Pregnancy)

Several maternal risk factors have been shown to be associated with an increased risk for SGA (Table 5.1). These are (a) maternal age ≥35 years with a further increase after 40 years, (b) Afro-Caribbean and Indian/Asian ethnicity, (c) nulliparity, (d) social deprivation, (e) unmarried status, (f) low pre-pregnancy weight (body mass index [BMI] $<20 kg/m^2$) and obesity (BMI>30 kg/m^2), (g) intense daily exercise.

Table 5.1 summarizes maternal risk factors that maintain their effect adjusted for other associated factors.

Maternal Medical History (Assessed at Booking)

Many medical conditions have been shown to be associated to increased risk for SGA. Among them, (a) diabetes with

TABLE 5.1 Maternal Risk Factors for SGA

Maternal Risk Factor	Definition of Risk	Odds Ratio Point Estimate	95% CI of Odds Ratio
Age	Maternal age ≥ 35 Maternal age ≥ 40	1.4 3.2	1.1–1.8 1.9–5.4
Parity	Nulliparity	1.9	1.8–2.0
Body mass Index (BMI) kg/m^2	<20 20–24.9 25–29.9 ≥30	1.2 1.0 1.2 1.5	1.1–1.3 n/a 1.1–1.3 1.3–1.7
Maternal substance Exposure	1–10 cigarettes per day ≥11 cigarettes per day Cocaine	1.5 2.2 3.2	1.4–1.7 2.0–2.4 2.4–4.3
IVF	IVF singleton pregnancy	1.6	1.3–2.0
Exercise	Daily vigorous exercise	3.3	1.5–7.2
Diet	Low fruit intake pre-pregnancy	1.9	1.3–2.8

IVF=in vitro fertilization; BW=birth weight; OR=odds ratio; AOR=Adjusted Odds ratio; CI=confidence interval. Outcome measured: BW < 10th centile population

TABLE 5.2 Medical Historical Risk Factors for SGA

	Definition of Risk	Odds Ratio Point Estimate (95% CI)
Maternal medical history		
SGA	Maternal SGA	2.6 (2.3–3.1)
Hypertension	Chronic hypertension	2.5 (2.1–2.9)
Diabetes	Diabetes and vascular disease	6 (1.5–23.3)
Renal disease	Renal impairment	5.3 (2.8–10)
APLS	Antiphospholipid syndrome	6.2 (2.4–16.0)
Paternal medical history		
SGA	Paternal SGA	3.5 (1.2–10.3)

SGA=small for gestational age; FGR=fetal growth restriction; APLS=Antiphospholipid syndrome; BW=birth weight; OR=odds ratio; AOR=Adjusted Odds ratio; RR= relative risk; ARR= adjusted relative risk; CI=confidence interval. Outcome measure: BW < 10th centile population

vascular disease, (b) renal impairment (especially when associated with hypertension), (c) antiphospholipid syndrome (APS) and (d) chronic hypertension (CH) have been demonstrated to be the most important ones.

For other conditions such as systemic lupus erythematosus (SLE) and congenital heart defect, the risk for SGA has not been quantified, although the condition has been observed to be more likely.

Table 5.2 summarizes maternal medical risk factors that maintain their effect once adjusted for the other associated factors.

Obstetric History (Assessed at Booking)

Risk factors for SGA that can be found in obstetric history investigation are (a) previous SGA birth(s), (b) previous stillbirth and (c) previous pre-eclampsia.

In particular, a woman that has had a SGA has a two-fold increase in the risk for recurrence; this risk is increased further after two SGA. Furthermore, if one of the parents was SGA at birth, the risk for the fetus to be SGA is increased.

Previous stillbirth is associated with a six-fold increase in the risk for SGA. Moreover, a short (<6 months) or long

TABLE 5.3 Previous Pregnancy Related Risk Factors for SGA

Previous Pregnancy	Definition of Risk	Outcome Measured	Estimate Measure	Point Estimate (95% CI)
Previous SGA	Previous SGA newborn	BW < 10th centile customized	OR	3.9 (2.1–7.1)
Previous stillbirth	Previous stillbirth	BW < 10th centile customized	OR	6.4 (0.8–52.6)
Previous pre-eclampsia	Pre-eclampsia	BW < 10th centile population	AOR	1.3 (1.2–1.4)
Pregnancy interval	< 6 months ≥ 60 months	SGA not defined SGA not defined	AOR AOR	1.3 (1.2–1.3) 1.3 (1.2–1.4)

SGA=small for gestational age; BW=birth weight; OR=odds ratio; AOR=Adjusted Odds ratio; CI=confidence interval.

TABLE 5.4 Risk Factors for SGA Related to Current Pregnancy Findings/Complications

Current Pregnancy	Definition of Risk	Outcome Measured	Estimate Measure	Point Estimate (95% CI)
Threatened miscarriage	Heavy bleeding similar to menses	BW < 10th centile population	AOR	2.6 (1.2–5.6)
Down syndrome screening	PAPP-A <0.4 MoM	BW < 10th centile population	OR	2.6
Ultrasound findings	Echogenic bowel	BW < 10th centile population	AOR	2.1 (1.5– 2.9)
Pregnancy-induced hypertension	Mild	BW < 10th centile population	RR	1.3 (1.3–1.4)
	Severe	BW < 10th centile population	RR	2.5 (2.3–2.8)
Pre-eclampsia	Pre-eclampsia	BW < 10th centile customised	AOR	2.26 (1.2– 4.2)
Maternal weight gain	Low weight gain*	BW < 10th centile population	OR	4.9 (1.9–12.6)
Unexplained APH	Unexplained APH	'IUGR' not defined	OR	5.6 (2.5–12.2)
Exposure in III trimester	Caffeine ≥300mg/day	BW < 10th centile population	OR	1.9 (1.3–2.8)

(>60 months) interpregnancy interval and heavy vaginal bleeding during the first trimester have been shown to increase the risk for SGA.

On the contrary, the evidence regarding recurrent miscarriage is conflicting, likely because of the vast spectrum of causes.

Historically, the concept of primipaternity has been associated with an increase risk for SGA; however, a recent systematic review by Shah and coworkers has demonstrated inconclusive evidence.[10]

Obstetric risk factors that maintain their effect after adjusting for other associated factors are summarised in Table 5.3.

Current Pregnancy Findings/Complications

Several pregnancy findings/complications have been described as risk factors for SGA. Among them the most important are (a) heavy bleeding similar to menses in the first trimester, (b) PAPP-A <0.4 MoM at Down syndrome first trimester screening, (c) echogenic bowel, (d) pregnancy-induced hypertension, (e) pre-eclampsia, (f) low maternal gain (<11kg and <7kg for maternal BMI less and more than 30 kg/m^2, respectively).

In addition, maternal exposure to domestic violence during pregnancy (Adjusted OR [AOR] 1.53, 95% CI 1.28-1.82) has been shown to be associated with SGA.

Table 5.4 summarizes current pregnancy findings/complications that increase the risk for SGA once adjusted for the other associated factors.

Substance Abuse (Assessed at Booking and During Pregnancy)

Smoking and cocaine exposure have been described as risk factors for SGA with OR proportional to the amount of substance assumption (Table 5.1).

Furthermore, caffeine consumption ≥300 mg (i.e., ≈3 espresso) per day in the third trimester has been described as a risk factor (Table 5.4).

SCREENING FOR SGA DUE TO PLACENTAL INSUFFICIENCY

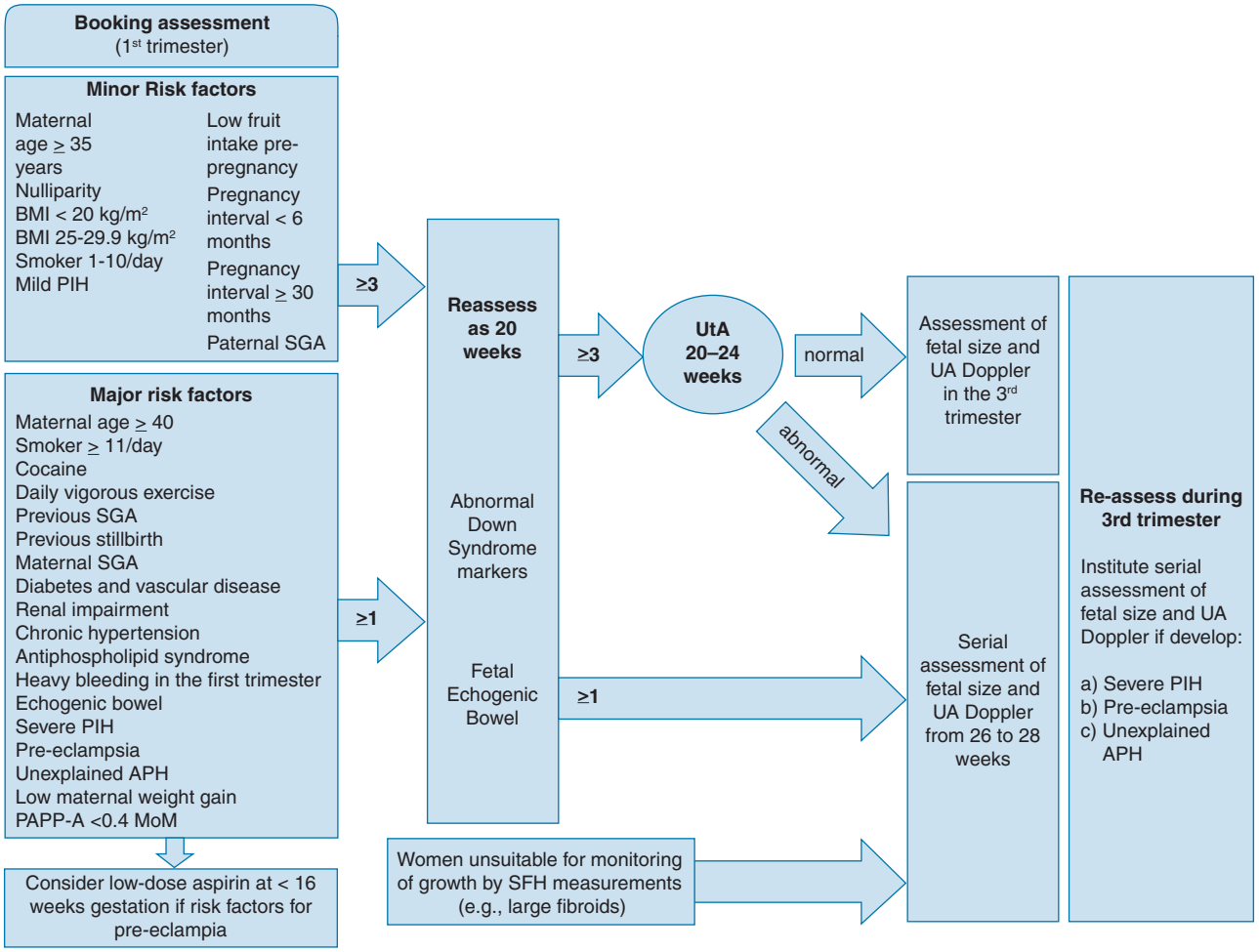
Uterine Artery Doppler

Uterine artery (UtA) Doppler reflects directly the involvement of trophoblastic invasion and can be used as a screening tool for all high-risk pregnancy for the prediction of pregnancy outcome (Hernandez-Andrade, Vergani, Frusca, Malchiorre, D'Antonio).[11-16] The role of such technique in the first trimester screening remains under investigation, UtA Doppler assessment in the second trimester represents a valuable tool to assess trophoblastic invasion.

A recent meta-analysis involving 61 studies (total of 41,131 patients) has shown that for overall fetal growth restriction, the second trimester uterine artery Doppler Pulsatility Index (PI) has shown a sensitivity and specificity of 18% (95% CI 16–19%) and 95% (95% CI 92–97%), respectively. Second trimester uterine artery Doppler screening has shown a sensitivity and specificity of 67% (95% CI 53–80%) and 95% (95% CI 94–96%) respectively for severe growth restriction defined as birth weight below the 5th or the 3th centile.[17]

In conclusion, UtA Doppler assessment at 20–24 weeks' gestation can be offered in women who have one major risk factor (Odds Ratio [OR] >2.0) or three or more minor risk factors (Odds Ratio [OR] ≤2.0) for SGA (Table 5.1–5.4).

Flowchart 5.1 summarizes the screening for SGA proposed by the RCOG Green-top guideline No.31.



FLOWCHART 5.1 Summarises the screening for SGA proposed by the RCOG Green-top guideline No.31. BMI = body mass index; PIH = pregnancy-induced hypertension; SGA = small for gestational age; APH = ante-partum haemorrhage; SFH = symphisys-fundal height; UtA = uterine arteries; UA = umbilical artery; MCA = middle cerebral artery, DV = ductus venosus.

DIAGNOSIS

Ultrasound Biometry

A number of different criteria have been used to detect SGA. The Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 31 suggests fetal AC or EFW <10th centile for GA as recommended cut-offs for the diagnosis of SGA.[18]

Alternative criteria include EFW or AC under 3rd, 5th and 15th centile as well as less than 2SD below the mean for that given population. It is important to remember that overly strict criteria may have very high positive predictive values, but may miss a significant number of under-grown fetuses. Using the 10th centile has shown better sensitivities and specificities than other commonly used criteria.[19,20] Two meta-analyses have shown that in a high-risk population, fetal AC<10th centile has a sensitivity of 72–94% and specificity of 50–83%. On the other hand, sensitivity and specificity for EFW<10th centile are 33–89% and 53–90%, respectively.[19,20]

It is important to underline that in a low-risk population, for any given parameter, sensitivity drops to 0–10% and specificity rises to 66–99%.[19,21]

The deceleration in AC or EFW growth velocity is another commonly used criterion (Fig. 5.2). Although 'eyeballing' a chart of individual AC and EFW measurements may give an impression of SGA, a more objective definition has not been establish yet, nor the number of centiles to be crossed for the diagnosis of SGA, if AC and EFW are plotted between the 10th and 90th centiles.[22,23]

Umbilical artery (UA) Doppler alone has been shown to be of moderate accuracy for diagnosis of SGA infants, even in a high-risk population (LR+ 3.76, 95% CI 2.96-4.76; LR- 0.52, 05% CI 0.45-0.61).[24] Therefore, UA Doppler should not be used alone for the diagnosis of SGA.[18]

Clinical Examination

Symphysis-fundal height (SFH) should be measured from the fundus to the pubic symphysis with the cm markings hidden from the examiner.[25] Measurements should be plotted on customized centile charts and women with a single SFH, which plots below the 10th centile, or serial measurements that show slow or static growth should be referred for further investigation. However, there is no evidence to determinate the number of centiles to be crossed for referral.[18]

Cohort and case-control studies, performed in low-risk population, have shown that abdominal palpation is of limited accuracy in the detection of both SGA (sensitivity 19–21%, specificity 98%) and severe SGA infants (if BW<2.3rd centile, sensitivity 28%).[26,27] In mixed risk population, the sensitivity increases to 34–44% and in high-risk population, sensitivity reaches 37% and 53% for SGA and severe SGA, respectively.[28,29]

Biophysical Tests

Biophysical tests such as amniotic fluid volume, cardiotocography (CTG) and biophysical profile (BPP) scoring have been shown to be poor diagnostic tests for SGA.[18,30-32]

Investigations to be Undertaken for Differential Diagnosis

Invasive Prenatal Diagnosis

The incidence of chromosomal abnormalities in severe SGA has been reported to be close to 19–20%. Among them the most likely are triploidy and trisomy 18. The risk for chromosomal defect is higher if (a) the diagnosis is made before 23–26 weeks' gestation, (b) there are associated structural abnormalities, (c) amniotic fluid volume is normal, (d) head circumference/abdominal circumference ratio is high or (e) uterine artery Doppler is normal.[33]

Karyotype should be offered in severe SGA fetuses with structural anomalies and in those detected before 23 weeks' gestation, especially if uterine artery Doppler and amniotic fluid are normal.[18]

Test for Maternal/Fetal Infection

Fetal infections are responsible for up to 5% of SGA fetuses. The most common pathogens are reported to be cytomegalovirus (CMV), toxoplasma, syphilis and malaria, although a recent multicentre study found no association between congenital toxoplasmosis and incidence of SGA infant.[34] Malaria is known to be a significant cause of preterm birth and low birth weight worldwide, therefore should be considered in women who have travelled in endemic areas.[18]

Different ultrasound finding can be suggestive, but not diagnostic, for fetal infection (see chapter on fetal Infection), however their absence does not exclude infection.

Serological screening for *CMV and toxoplasmosis* infection should be offered in severe SGA. Test for malaria and syphilis should be undertaken in high-risk populations. If the screening results positive, the only way to assess fetal infection is PCR on amniotic fluid (see chapter about Infections).[18]

Doppler Assessment

Fetal-maternal Doppler assessment has been shown to be the gold standard to assess placental development and function.

As previously said, UtA Doppler reflects trophoblastic invasion that is completed at 23–24 weeks' gestation. On the other hand, UA Doppler reflects placental function and becomes abnormal if placenta is working ≤50% of its capacity. UtA and UA Doppler assessment should be performed at

SGA diagnosis in order to detect placental insufficiency and FGR.

FETAL SURVEILLANCE

Fetal Biometry

Serial assessments of fetal biometry can identify the worsening in growth velocity in fetuses diagnosed as SGA. Mongelli and coworkers have shown that the false positive rate for SGA (defined as not apparent growth in fetal AC between two consecutive examinations) was increased by shortening the interval of examination (30.8%, 16.9%. 8.1% and 3.2% for intervals of 1, 2, 3 and 4 weeks, respectively.[35] Their findings suggested that to estimate growth velocity should be used measurements at minimum of 3 weeks apart in order to minimize the false positive rate. This recommendation does not preclude more frequent ultrasound measurements.[18]

Doppler Assessment

Doppler examination is essential to drive the differential diagnosis to placental insufficiency (FGR) and to stratify the risk in this subset of fetuses.

Uterine Artery Doppler

If the value of UtA in the Doppler in the second trimester has been well-described, its role to predict adverse pregnancy outcome in the third trimester is still under discussion.

There is moderate evidence that in women with abnormal UtA Doppler at 20–24 weeks' gestation, subsequent normalization at 26–28 weeks is still associated to a higher risk for SGA compared to women with normal findings since the second trimester.[36] Furthermore, the risk for SGA is significantly higher in women with persistent abnormal UtA findings (32% vs 9.5%, $p = 0.007$).[36] Despite these data, repeating uterine artery Doppler, in women with abnormal findings in the second trimester, is considered of limited value.[18]

Reference range for uterine artery Doppler pulsatility index (PI) during 14–41 weeks have been listed in Table 5.5.[8]

TABLE 5.5 Reference Range for Uterine Artery Doppler Pulsatility Index (PI) from 14 to 41 Weeks[8]

Gestational Age (weeks)	5th Centile	Mean	95th Centile
14	0.99	1.49	2.24
15	0.94	1.41	2.11
16	0.89	1.33	1.99
17	0.85	1.27	1.88
18	0.81	1.20	1.79
19	0.78	1.15	1.70
20	0.74	1.10	1.61
21	0.71	1.05	1.54
22	0.69	1.00	1.47
23	0.66	0.96	1.41
24	0.64	0.93	1.35
25	0.62	0.89	1.30
26	0.60	0.86	1.25
27	0.58	0.84	1.21
28	0.56	0.81	1.17
29	0.55	0.79	1.13
30	0.54	0.77	1.10
31	0.52	0.75	1.06
32	0.51	0.73	1.04
33	0.50	0.71	1.01
34	0.50	0.70	0.99
35	0.49	0.69	0.97
36	0.48	0.68	0.95
37	0.48	0.67	0.94
38	0.47	0.66	0.92
39	0.47	0.65	0.91
40	0.47	0.65	0.90
41	0.47	0.65	0.89

Umbilical Artery Doppler

If UtA Doppler reflects trophoblastic invasion and placental development, umbilical artery (UA) Doppler reflects placental function and indicates the degree of placental insufficiency.

High UA PI (above the 95th centile per GA) with positive end-diastolic flow, absent end-diastolic flow (AEDF) (Fig. 5.3) and reverse end-diastolic flow (Fig. 5.4) reflect that placental insufficiency is ≥50%, ≥70% and ≥90%, respectively.[37] It is important to remember that there is significant difference in Doppler indices obtained at the intra-abdominal portion, feta-end, free-loop or placental-end of the umbilical cord. Appropriate reference ranges should be used according to sampling site. When comparing repeated measurements longitudinally, recordings from fixed sites (i.e., fetal end, placental end, intra-abdominal portion) may be preferable because more reliable.[38]

Regardless the sampling site, there is compelling evidence that UA Doppler is a useful tool in the management of high-risk pregnancies. The predictive ability for pooled

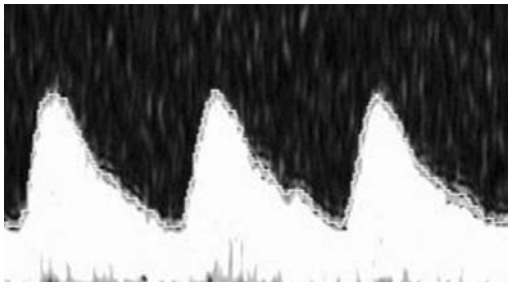


FIGURE 5.3 Absent end-diastolic flow in umbilical artery Doppler.

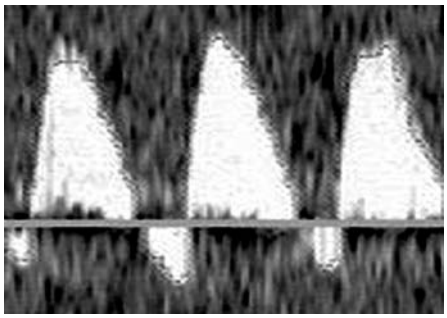


FIGURE 5.4 Reversed end-diastolic flow in umbilical artery Doppler.

adverse fetal/neonatal outcome of this technique was found to be LR+ 4.37 (95% CI 0.88-21.8) and LH- 0.55 (95% CI 0.48-0.62).[39]

Reference range for umbilical artery pulsatility index (PI) sampled at free loop during 24–41 weeks have been listed in Table 5.6.[40]

TABLE 5.6 Reference Range for Umbilical Artery Pulsatility Index (PI) Sampled at Free Loop from 24 to 41 Weeks[40]

Gestational Age (Weeks)	5th Centile	Mean	95th Centile
24	0.86	1.12	1.47
25	0.83	1.09	1.44
26	0.80	1.06	1.41
27	0.77	1.03	1.38
28	0.75	1.00	1.35
29	0.72	0.98	1.32
30	0.70	0.95	1.29
31	0.68	0.93	1.27
32	0.66	0.90	1.25
33	0.64	0.88	1.22
34	0.62	0.86	1.20
35	0.60	0.84	1.18
36	0.58	0.82	1.16
37	0.56	0.80	1.14
38	0.55	0.78	1.12
39	0.53	0.76	1.10
40	0.51	0.75	1.09
41	0.50	0.73	1.07

Middle Cerebral Artery and Ductus Venosus Doppler

If UtA and UA reflect placental development and function, middle cerebral artery (MCA) and ductus venosus (DV) reflect how the fetus is coping.

Cerebral vasodilatation, also known as 'brain-sparing effect', is a response of the fetus to chronic hypoxemia and results in an increase in diastolic flow and in a decrease in Doppler indices. Therefore, reduced MCA PI and MCA/UA PI ratio (cerebro-placental ratio) are early signs of fetal hypoxemia in SGA fetuses.[41]

The 'brain-sparing effect' may develop in two scenarios: (a) in early onset SGA (before 32 weeks) where UA was already abnormal, for the worsening of placental circulation, (b) in late onset SGA (after 32 weeks) where UA is typically normal because fetal metabolic needs are greater than placental capacity even in absence of placental insufficiency (i.e., small placenta).[41] Predictive ability of adverse fetal/neonatal outcome is greater in the latter scenario where MCA PI <5th centile has shown an OR 9.0 (95% CI 1.25–295) for neonatal metabolic acidosis and OR 18.0 (95% CI 2.84–750) for caesarean section for non reassuring fetal status.[42]

According to these findings, the development of **brain sparing** effect should be considered for time to **deliver** in late onset **SGA** (>32–34 weeks) where UA is normal.[18]

Reference range for middle cerebral artery pulsatility index during 24–39 weeks has been listed in Table 5.7.

The ductus venosus (DV) Doppler flow velocity pattern reflects atrial pressure–volume changes during the cardiac cycle. As SGA worsen, velocity reduces in the DV a-wave owing to increase pre- and after-load, as well as increased end-diastolic pressure, resulting from the directs effects of hypoxia and/or academia and increased adrenergic drive. An increased PI (Fig. 5.5) and a retrograde a-wave in the DV reflect the onset of overt cardiac compromise.[43]

DV should be used for: (a) **surveillance** in preterm SGA fetuses with abnormal UA Doppler,[44] (b) **decision** of time **to delivery** in early onset **SGA** (<32–34 weeks).[18]

Reference range for ductus venosus pulsatility index for veins (PIV) during 24–39 weeks have been listed in Table 5.8.[45]

TABLE 5.7 Reference Range for Middle Cerebral Artery Pulsatility Index from 24 to 39 Weeks*

Gestational Age (Weeks)	5th Centile	Mean	95th Centile
24	1.38	1.86	2.52
25	1.44	1.94	2.62
26	1.50	2.01	2.71
27	1.55	2.06	2.78
28	1.58	2.11	2.84
29	1.61	2.15	2.88
30	1.62	2.16	2.90
31	1.62	2.16	2.90
32	1.61	2.14	2.87
33	1.58	2.10	2.82
34	1.53	2.04	2.74
35	1.47	1.96	2.64
36	1.39	1.86	2.52
37	1.30	1.75	2.38
38	1.20	1.63	2.22
39	1.10	1.49	2.05

*Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements. *Ultrasound Obstet Gynecol.* 2007;30:287–296.

TABLE 5.8 Reference Range for Ductus Venosus Pulsatility Index for Veins (PIV) from 24 to 39 Weeks[45]

Gestational age (weeks)	5th centile	Mean	95th centile
24	0.32	0.57	0.83
25	0.32	0.57	0.83
26	0.31	0.57	0.82
27	0.31	0.56	0.82
28	0.31	0.56	0.81
29	0.30	0.55	0.81
30	0.29	0.54	0.80
31	0.28	0.53	0.79
32	0.28	0.53	0.78
33	0.27	0.52	0.77
34	0.26	0.51	0.76
35	0.25	0.50	0.75
36	0.24	0.49	0.74
37	0.23	0.48	0.73
38	0.22	0.46	0.72
39	0.21	0.45	0.71

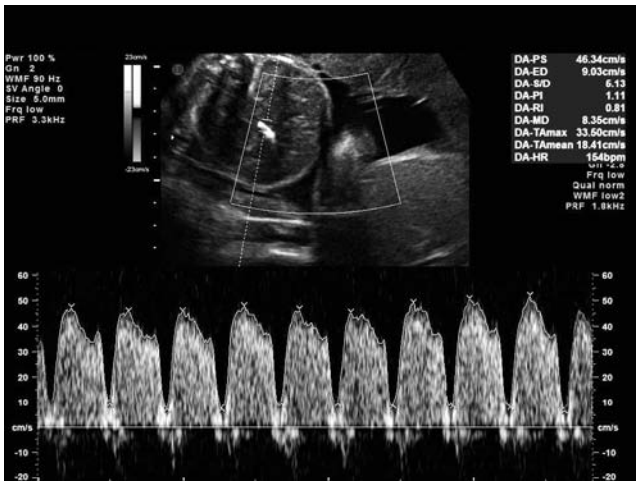


FIGURE 5.5 Increased pulsatility index of ductus venosus Doppler.

Amniotic Fluid Volume

Amniotic fluid volume reflects how the fetus has been coping during the previous 2–3 weeks. A recent Cochrane review involving five trials and 3226 women has shown that the use of amniotic fluid index ≤5cm compared to single deepest pool <2 was related to a higher rate of induction of labour (RR1.92, 95% CI 1.50–2.46) without an improvement in perinatal outcome.[46,47] Therefore, interpretation of amniotic fluid volume should be based on single deepest vertical pool. Values ≥2cm are considered normal.[18]

Biophysical Profile

The biophysical profile (BPP) includes four acute fetal variables: (a) breathing movement, (b) gross body movement, (c) cardiotocography and (d) amniotic fluid volume. Each variable assigns a score of 2 (if normal) or 0 (if abnormal). Scores ≤4 are considered abnormal.

A systematic review on effectiveness of BPP as surveillance in high-risk pregnancies found that the use of BPP was not associated to a better fetal/neonatal outcome.[48] Moreover, recent studies in preterm severely SGA fetuses suggest BPP as a poor predictor of fetal acidaemia.[49,50]

Therefore, BPP should not be used for fetal surveillance in preterm SGA fetuses.[18]

Cardiotocography

Conventional antepartum CTG is known to have high intra and inter-observer variability and when used alone has

been shown to do not improve perinatal mortality in high-risk pregnancies.[51] On the contrary computerized CTG (cCTG) has been shown to be objective and consistent.[52] Among all the variables, fetal heart rate (FHR) variation is the most useful predictor of fetal well-being in SGA fetuses[49,53]; a short-term variation ≤ 3ms (within 24 hrs of delivery) has been associated with higher rate of metabolic academia (54.2% vs 10.5%) and early neonatal death (8.3% vs 0.5%).[51]

A Cochrane review comparing traditional CTG to cCTG including two trials and 469 high risk fetuses showed a reduction in perinatal mortality with cCTG (4.2% vs 0.9%; RR 0.20, 95% CI 0.04-0.88).[51]

In conclusion: (a) CTG should not be used as the only surveillance tool in SGA fetuses, (b) cCTG should be preferred to conventional CTG in the surveillance of SGA fetuses, (c) interpretation should be based on short-term fetal heart rate variation.

INTERVENTIONS IN PRETERM SGA

According to the RCOG Green-top Guideline No. 31, women with a SGA fetus between 24 and 35^{+6} week's gestation, where delivery is being considered, should receive a single course of antenatal corticosteroids to accelerate fetal lung maturation and reduce neonatal death and morbidity.[54]

It is important to remember that a proportion of growth-restricted fetuses will be delivered preterm and consequently be at increased risk for cerebral palsy. Maternally administration of magnesium sulphate has been shown to have a neuroprotective effect and to reduce the incidence of cerebral palsy among preterm infants. Australian guidelines recommend administration of magnesium sulphate when delivery is planned before 30 weeks' gestation.[18]

Bed rest, maternal oxygen administration, dietary modification, NO-donors, plasma volume expanders, Ca^{2+}-antagonists, β-mimetic drugs and sildenafil have been evaluated as possible prenatal therapy for FGR; however, none have been shown to be of value.[18,55]

PREVENTION OF SGA

Antiplatelet agents during pregnancy are associated with moderate but consistent reductions in the relative risk for pre-eclampsia, birth before 34 weeks' gestation, SGA and other serious adverse outcomes.[56]

A recent systematic review and meta-analysis of nine trials involving 1317 women with abnormal uterine artery Doppler at 20 weeks' gestation concluded that aspirin started before 16 weeks of pregnancy reduced the incidence of both pre-eclampsia and SGA (RR 0.51, 95% CI 0.28–0.92; number needed to treat 10, 95% CI 5–50). On the other hand, when Aspirin was started after 20 weeks' gestation no reduction was observed.[57]

Another systematic review of five trials involving 414 women has suggested that, with respect to women at risk for pre-eclampisa, when aspirin was started before 16 weeks' gestation the RR for SGA was 0.47 (95% CI, 0.30–0.74) and the number needed to treat was 9 (95% CI 5.0-17.0).[58] No reduction was observed when aspirin administration was started after 16 weeks' gestation.

Smoking cessation has been shown to reduce the incidence of low-birth weight (RR 0.83, CI 95% 0.73–0.95).[59] There is emerging evidence that women who stop smoking by 15 weeks of gestation can reduce the risk back to that for non-smokers.[60]

Till date, there is no evidence that dietary modification, progesterone or calcium are useful to prevent SGA. Therefore, these interventions should not be used for this indication.[18,55]

TIMING OF DELIVERY

At the present, no intervention except delivery has been observed to be effective in altering SGA course. The timing of delivery remains a critical issue. Risks of prolonging the pregnancy (i.e., stillbirth) have to be balanced to risks due to prematurity.

Gestational age is critical in decision making. In SGA detected before 33 weeks' gestation, gestational age was found to be the most significant determinant of total survival and intact survival <27 and ≤29 weeks, respectively.[41]

The other critical issue in decision-making is the interpretation of surveillance tests that are used to predict perinatal outcomes such as death, major morbidity and neurodevelopmental delay. Several studies have investigated the sequence of changes in Doppler and BPP as SGA worsens.[61-64] While the majority of fetuses have shown a deterioration of arterial Doppler before the worsening of venous Doppler or BPP, the sequence of changes is still unclear.

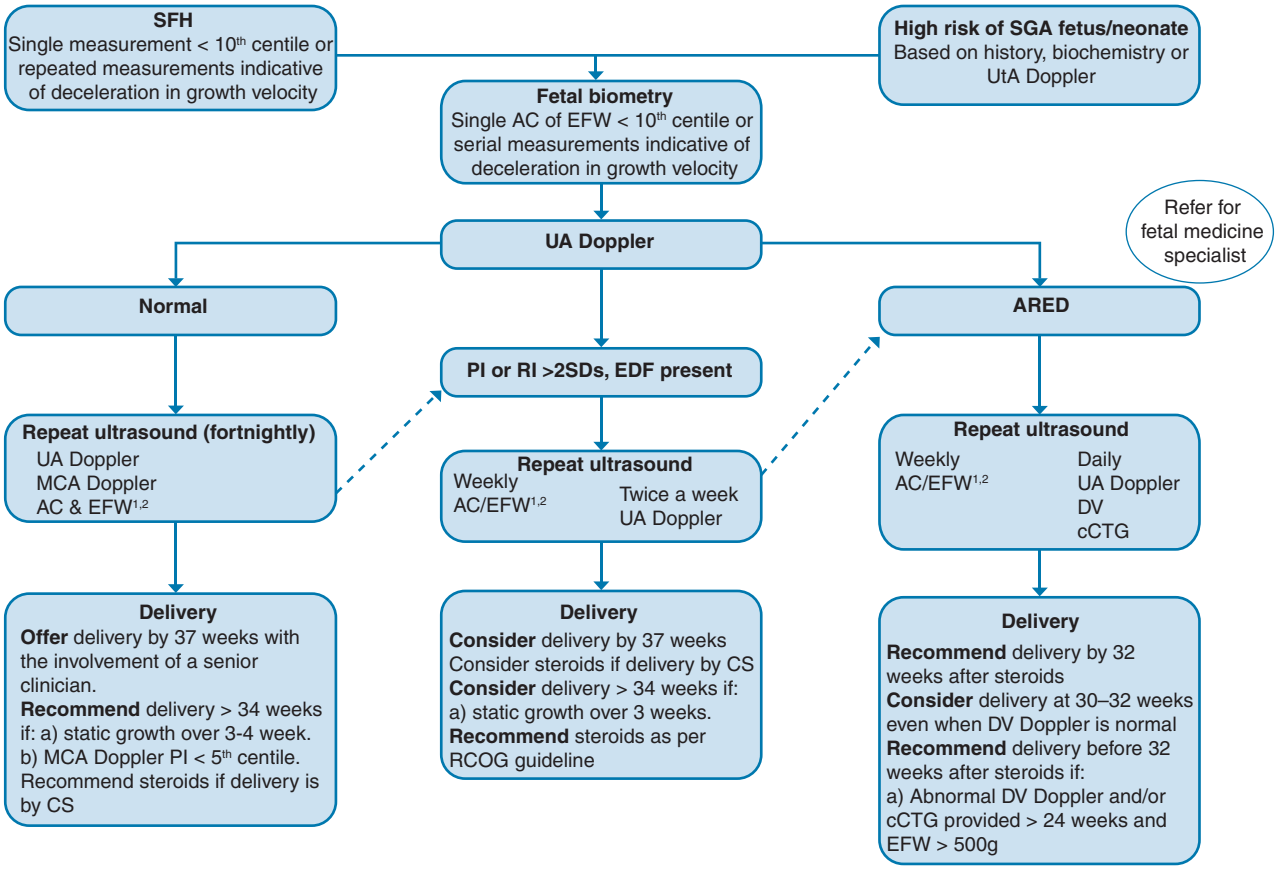
Flowchart 5.2 summarizes the management of SGA fetuses according to the RCOG Green-top guideline No.31, 2013.

FETAL AND NEONATAL PROBLEMS ASSOCIATED WITH FGR

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

Fetal Hypoxia and Acidosis

Perinatal and intrapartum hypoxia and acidosis are the most important and frequent complications of FGR



FLOWCHART 5.2 Summarises the management of SGA fetuses according to the RCOG Green-top guideline No. 31, 2013. CS = caesarean section; AC = abdominal circumference; EFW = estimated fetal weight; SGA = small for gestational age; cCTG= computerized cardiotocography; SFH= symphisys-fundal height; UtA= uterine arteries; UA = umbilical artery; MCA = middle cerebral artery, DV = ductus venosus; EDF = end-diastolic flow; ARED =absent/reverse end-diastolic flow. 1 = Weekly measurement of fetal size is valuable in predicting birth weight and determining size-for gestational age; 2 = If two AC/EFW measurements are used to estimate growth, they should be at least 3 weeks apart.

particularly when growth disturbance is due to placental insufficiency. This is the reason why only diagnosis and adequate surveillance of the pregnancy complicated by placental insufficiency is so important. When FGR fetuses are assessed with electronic fetal heart rate monitoring, non-reassuring signs as late decelerations, severe variable installations, beat-to-beat variability and episodes of bradycardia are more frequent than in normal fetuses and acidosis during labour occurs in as many as 40% of FGR fetuses as a result the incidence of caesarean delivery is high.[65]

Stillbirth

There is a clear relationship between FGR and stillbirths. One study found that approximately 20% of all stillbirths show signs of growth restriction.[66] Another study found that FGR gifted with and is probably responsible for 26% stillbirths among infants with the birthweight less than 1500 g.[67] Fetal death in FGR babies may occur at any time but is more frequent after 35 weeks 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 and coworkers, the incidence of FGR when the amniotic fluid volume was normal was 5% but when oligohydramnios was present, it increased to approximately 40%.[68] The cause of oligohydramnios seen in FGR babies is decreased fetal urine output secondarily to redistribution of the fetal blood flow with decreased renal perfusion and preferential shunting to the brain.

Intrapartum Complications

The main problem to labour fetuses with the growth restriction is the high incidence of intrapartum hypoxia and

essence. For this reason, labour in the 55 m closely monitored and delivery by caesarean should be performed, if there are non-reassuring at our patterns. The reader will find more information about this topic later.

Neonatal Complications

Diagnosis of FGR is easier after birth. After birth, an FGR infant shows signs of soft tissue wasting. The skin is loose and thin, and carries little subcutaneous fat. The abdomen is scaphoid, the ribs are protuberant and the muscle mass 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 AC. The birthweight and in most cases the placental weight is below the 10th percentile. Fetuses with pathological growth restriction frequently have thrombocytopenia, an elevated nucleated red blood cell count. In contrast, the normal AGA baby has symmetric development of the head and abdomen and a normal amount of subcutaneous fat.

Respiratory Distress Syndrome (RDS)

RDS is the main cause of co-morbidity and mortality in the preterm growth-restricted infant.

Meconeum Aspiration Syndrome

Passage of meconeum is more common in growth-restricted fetuses, and hypoxia can stimulate respiratory centre leading to aspiration of the meconeum stained amniotic fluid. Amnioinfusion has been used to attempt to dilute the meconeum and avoid aspiration of particulate meconeum into fetal airways. Amnioinfusion is only useful in settings where facilities for perinatal surveillance are limited, and leads to significant improvements in perinatal outcome. It is not clear if the benefits are due to dilution of meconium or improvement in the amniotic fluid volume.

Persistent Fetal Circulation

Persistent fetal circulation is a frequent sequel to perinatal hypoxia and acidosis. Pulmonary hypertension develops due to vasoconstriction in the vasculature of the lungs. The blood flow through the ductus arteriosus persists even after birth in this condition. The main indicators are hypoxia with mild hypercapnia, right to left shunting without evidence of structural heart defect and cardiomegaly. Treatment is adequate ventilation, minimal stimulation and the use of pulmonary vasodilators such as sildenafil.

Intraventricular Haemorrhage (IVH)

Grade II/II IVH and periventricular leucomalacia (PVL) are common complications seen in preterm growth-restricted fetuses.

Newborn Encephalopathy

Neonatal encephalopathy is a non-specific diagnosis to describe a variety of neurological signs and symptoms that frequently occur following hypoxic/ischaemic brain injury. The brain injury may range from cerebral oedema, intracranial bleeding to infarction. The symptoms include irritability, twitching, apnoea and seizures. It may be followed in some cases by permanent brain injury resulting in cerebral palsy. Neonatal encephalopathy is seen more often in growth restricted than in AGA infants.

Hypoglycaemia

Newborns are more prone to develop hypoglycaemia especially if born preterm. The cause is inadequate stores of glycogen and fat stores. The symptoms are non-specific: jitteriness, irritability, drowsiness, apnoea, tachypnoea and occasionally seizures. Hypoglycaemia is seen more commonly in growth-restricted infants due to inadequate stores, and monitoring of blood glucose levels is necessary in the first 24–48 hours.

Hypocalcaemia

Hypocalcaemia is also seen more commonly in growth-restricted infants. The symptoms are similar to those due to hypoglycaemia.

Hyperviscosity Syndrome

Chronic intrauterine hypoxia leads to stimulation of the fetal bone marrow, and a high haematocrit. The main sign is polycythaemia, defined as haematocrit in excess of 65%. Hyperviscosity can lead to sluggish blood flow particularly in smaller blood vessels. This can cause thrombosis in the vessels of the lungs and intestines leading to infarcts. Volume overload may lead to congestive heart failure and pulmonary oedema. Treatment involves partial exchange transfusions with plasma.

LONG-TERM OUTCOME

SGA fetuses born at term with or without growth restriction are associated with lower neurodevelopmental scores compared to normal term controls.[69] A recent systematic review by Arcangeli and coworkers involving 28 studies of SGA with a total of 7861 SGA and 91,619 AGA babies and three studies of FGR with a total of 119 FGR and 49 control AGA babies showed that among babies born at term, being SGA is associated with lower scores on neurodevelopmental outcomes compared to AGA control (0.32 SD (95% CI 0.25–0.38) below those of normal controls.

Although several possible explanations have been proposed, the real mechanism that leads to neurodevelopmental delay in such fetuses is still under debate.[69]

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.[70] It accounts for more than half of neonatal deaths.[71]

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 (anaemia, 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, 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.[72] 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 5.9 shows that IUGR infants are more prone to birth asphyxia, polycythaemia and metabolic disorders, whereas small, preterm babies are more prone to respiratory distress syndrome, birth injuries, infection and perinatal loss.

In another interesting study on the subject, from Pune,[73] comparing the perinatal outcome of patients with IUGR versus normal controls, the following observations were recorded (Table 5.10).

TABLE 5.10 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

The predominant indication for caesarean 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, diarrhoea, and respiratory infections.

Among the medical disorders contributing to poor intrauterine fetal growth, anaemia heads the list. In an interesting study from Indore on the subject of the effects of anaemia on perinatal outcome, Awasthi and coworkers reported the following observations (Table 5.11).[74]

Table 5.7 clearly points out the need to detect and treat anaemia 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.[75]

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

TABLE 5.9 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%
Hyperbilirubinaemia	6.49%	3.65%
Hypoglycaemia	4.70%	1.94%
Hypothermia	3.36%	2.53%
Hypocalcaemia	1.94%	2.53%
Septicaemia	1.05%	1.57%
Respiratory distress syndrome	4.10%	
Birth injuries	1.51%	3.37%
Perinatal mortality	4.85%	8.7%

TABLE 5.11 Perinatal Outcome in Mothers with Anaemia Complicating Pregnancy

Parameter of Comparison	Moderate Anaemia (Hb <8.0 g%)	Non-Anaemic 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

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 glycaemic control. Uncontrolled hypothyroidism also predisposes to low birth weight and congenital fetal malformation.[76]

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,[77] 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 colour 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 from Pune compared the sensitivity of individual ultrasonographic parameters for detecting fetal growth retardation (Table 5.12).[78]

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.[79] 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 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,[80] 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 reported that high BPP scores correlate well with fetal well-being.[81] 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 labour in suspected cases of IUGR.

In Lucknow, a study was undertaken to evaluate the usefulness of amnioinfusion during labour complicated with meconium.[82] The incidence of meconium staining of liquor amnii during labour 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 5.13.

TABLE 5.12 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

TABLE 5.13 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%

The above findings emphasize the need for resorting to amnioinfusion in cases of meconium-stained liquor detected in labour 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.[83] But later investigations revealed that 2–8 cm was normal 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.[84]

Important Points

- Growth restriction is a concept whereas SGA is an objective definition.
- Risk factors for SGA should be assessed at booking and during pregnancy in all women to identify those who require further investigations.
- Women who have a major risk factor (Odds Ratio [OR] >2.0) should be monitored with serial growth scans and Doppler assessments from 26 to 28 weeks' gestation.
- Women who have three or more minor risk factors (Odds Ratio [OR] ≤2.0) should be referred for uterine artery Doppler at 20-24 weeks' gestation.
- If a fetus is diagnosed as SGA at 18–20 weeks' gestation, a referral for detailed anomaly scan and uterine artery Doppler assessment by a fetal medicine specialist should be offered.
- Karyotype should be offered to fetuses with severe SGA, with structural anomalies and in those detected before 23 weeks' gestation, especially if uterine artery Doppler is normal.
- Serological screening for cytomegalovirus and toxoplasmosis infection should be offered in severe SGA.
- Test for malaria and syphilis should be reviewed in high-risk population, if severe SGA.
- Abnormal UtA or UA Doppler are likely pointer towards placental insufficiency.
- Single course of antenatal corticosteroids should be administrated to accelerate fetal lung maturation in SGA fetus between 24 and 35^{+6} weeks' gestation, where delivery is being considered.
- Magnesium sulphate should be considered when planning severe preterm delivery (typically delivery before 30 weeks' gestation)
- In women at high-risk for pre-eclampsia, low-dose aspirin should be started <16 weeks' gestation.
- Smoking cessation should be recommended and achieved <15weeks' gestation.
- Dietary modification, progesterone and calcium do not prevent SGA.
- In SGA fetuses with UA ARED detected before 32 weeks' gestation, delivery is recommended after completion of steroids when DV Doppler becomes abnormal or umbilical vein pulsations appear, provided that the fetus is viable. Even when DV is normal, delivery is recommended by 32 weeks' gestation and should be considered between 30 and 32 weeks' gestation.
- If MCA Doppler is abnormal, delivery should be recommended not later than 37 weeks' gestation.
- For SGA fetuses detected >32 weeks' gestation with normal UA, a senior obstetrician should be involved in determining the timing and mode of birth. In such cases, delivery should be offered at 37 weeks' gestation.

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Chapter 6

Early Pregnancy Complications

Parikshit Dahyalal Tank

Chapter Outline

INTRODUCTION

Though there is no accepted definition of the term "early pregnancy", it is generally used in the context of a pregnancy in the first trimester. Early pregnancy and the first trimester in particular is the time with the greatest likelihood of fetal demise and abnormal outcomes in a recognized pregnancy. About 20% of pregnancies may have some complication in the first trimester. Symptoms such as vaginal bleeding and pain are the most common presenting complaints which could indicate a pregnancy complication. A systematic approach is important to determine the status of the pregnancy and further care. The diagnosis depends on the period of pregnancy, clinical background and results of investigations. The management of early pregnancy bleeding is based on the diagnosis assigned at the particular time of presentation. The woman's anxiety towards the situation also needs to be addressed.

Physiological changes start as early as the first few weeks of pregnancy and they may cause symptoms which may be perceived as complications such as vomiting, lower abdominal pain, frequency of passing urine, etc. It is important to distinguish these from pathological conditions and manage them accordingly.

PRESENTATION-BASED APPROACH TO COMPLICATIONS IN EARLY PREGNANCY

An approach based on clinical presentation is useful to make a diagnosis and initiate clinical care in early pregnancy. The clinical presentations of interest are outlined in Table 6.1. Though the clinical presentations of all the possible complications are variable, this approach is a rule of thumb and should be used with the complete clinical picture in mind.

BLEEDING IN EARLY PREGNANCY

Causes of Bleeding in Early Pregnancy

In early pregnancy, vaginal bleeding could be due to causes related to and with a possible impact on the pregnancy. Such bleeding is usually from the uterus. Bleeding could also be due to cervicovaginal factors. The causes are outlined in Table 6.2. The diagnostic approach to a woman with early pregnancy bleeding is based on a clinical evaluation and results of tests—blood and ultrasound. The aim of the diagnostic evaluation is to look for conditions which require intervention and to guide the counseling process

TABLE 6.1 Clinical Presentations of Complications in Early Pregnancy

Vaginal bleeding
Vomiting and hyperemesis
Lower abdominal and pelvic pain
Physiological changes of pregnancy mimicking complications

TABLE 6.2 Aetiology of Early Pregnancy Bleeding

Related to Pregnancy	Unrelated to Pregnancy
Implantation bleeding	Cervical or vaginal pathology such as erosion, polyp, fibroids, cancer
Miscarriage	Trauma to the cervix or vagina
Ectopic pregnancy	
Gestational trophoblastic neoplasms	
Cervical insufficiency	

about further treatment and prognosis. The cardinal rule in the evaluation of early pregnancies with bleeding, especially in the early first trimester, is to have a high index of suspicion for an ectopic pregnancy. Clinicians need to "Think Ectopic" so as not to miss this potentially lethal diagnosis.

Clinical Evaluation of a Woman with Early Pregnancy Bleeding

The clinical evaluation sets the background on which the investigations should be added to complete the picture and guide further management.

The duration of the pregnancy should be determined from the cycle frequency, regularity and the last date of the menstrual period. This may not always be accurate but gives a working estimate of the gestational age. The history of bleeding should first determine if it is indeed vaginal. On occasion, hematuria and rectal bleeding may be mistaken for vaginal bleeding. The nature, quantity and duration of bleeding should be recorded. Of particular note is the history of passing large clots or a fleshy mass, which could indicate the passage of the products of conception. Pain accompanying the vaginal bleeding, if present, should be explored in detail. Symptoms indicating the possibility of sepsis may be present such as fever, chills and malaise.

Physical examination should begin with a determination of the vital parameters and their stability. They will be abnormal in a woman in shock from hemoperitoneum, excess vaginal bleeding or sepsis. Abdominal examination should be focused on eliciting tenderness in the iliac fossae and in the second trimester, of the uterus. Vaginal examination should be done to estimate the gestational age, elicit tenderness in the fornices or on cervical motion and assess the cervix. Cervical motion tenderness has long been thought to be an important sign for the diagnosis of ectopic pregnancies. However, it is seen only in half the women with an ectopic pregnancy.[1] However, this may not necessarily be seen in an ectopic pregnancy which is very early and not ruptured. On the other hand, a woman may appear to have tenderness in the fornices due to anxiety and pain of the vaginal examination. Other causes of forniceal tenderness include an associated corpus luteum hematoma in an intrauterine pregnancy, pelvic infection and other adnexal masses. This sign should not be relied on to make decisions especially those leading to an operative intervention if other modalities of investigation are available. Digital examination of the cervix is useful to assess the status of the cervical os and the presence of products or clots in the cervicovaginal canal.

Clinical methods to determine the presence of hemoperitoneum such as an abdominal paracentesis or culdocentesis have been described. Both these are invasive and subject to erroneous performance and interpretation. With the widespread availability of ultrasound, they are relegated to the footnotes. In situations where no imaging modalities are available or a rapid decision has to be made in view of a woman's deteriorating vital parameters, one may resort to these techniques.

In very early pregnancy, it may not be yet established that the woman is pregnant. A urine pregnancy test is the quickest way to determine this. It should be done for every woman with an unclear history or irregular cycles irrespective of age and contraception used.

Blood Investigations in Early Pregnancy Bleeding

A blood count and blood group with Rhesus factor determination should be done routinely for every woman with early pregnancy bleeding. Women who are Rhesus negative should be offered prophylaxis with anti-D immunoglobulin. The dose is dependent on the duration of pregnancy, nature and quantity of bleeding.

A variety of serum markers have been used to diagnose and determine the viability of early pregnancy. They are useful in the early part of the first trimester. Of all these markers, serum beta-hCG (S. β-hCG) and S. progesterone are commonly available and used.

hCG is secreted by syncitiotrophoblasts. False positive or negative results in terms of pregnancy detection are possible but exceedingly rare. With modern laboratory assays, detection levels of serum β-hCG are as low as 5 IU/L. The sensitivity of a urine pregnancy test is about

25 IU/L. The typical level in a healthy pregnancy on the day of the missed period is 50 to 100 IU/L. In a healthy intrauterine pregnancy, levels of serum β-hCG will double every 1.4 to 2.1 days and peak between 50,000 and 100,000 IU/L at 8 to 10 weeks of pregnancy. Compared to the pattern observed in healthy intrauterine pregnancies, the rate of increase between two serum β-hCG levels done 48 hours apart is slower (<50% increase) in pregnancies destined to miscarry or those in ectopic locations.[2] There are, however exceptions to the rule. Viable pregnancies may have slow rise in serum levels and ectopic pregnancies which are viable may mimic a healthy intrauterine pregnancy in terms of serum β-hCG levels. Also, interpreting levels and rates of rise are complicated in situations where the pregnancy is a result of assisted reproduction or a multiple pregnancy. Taking into view these considerations, paired serum β-hCG levels though useful, should be used in conjunction with transvaginal ultrasound to establish a diagnosis.

Serum progesterone has been suggested as a marker for viability and location in early pregnancy. Low levels are associated with abnormal pregnancies while high levels with normal intrauterine pregnancies. However, there is a wide overlap in levels and clinical outcomes. Serum progesterone levels greater than 20 ng/mL almost always indicate a normal intrauterine pregnancy while those lower than 5 ng/mL almost always indicate an unhealthy pregnancy (ectopic or intrauterine). Unfortunately, 50% of ectopic pregnancies and nearly 20% of pregnancies destined to miscarry and almost 70% of viable intrauterine pregnancies will have a serum progesterone level between 5 and 20 ng/mL.[3] However, in clinical practice, this test may be useful in ruling out a viable pregnancy.[4]

Transvaginal Ultrasound in Early Pregnancy Bleeding

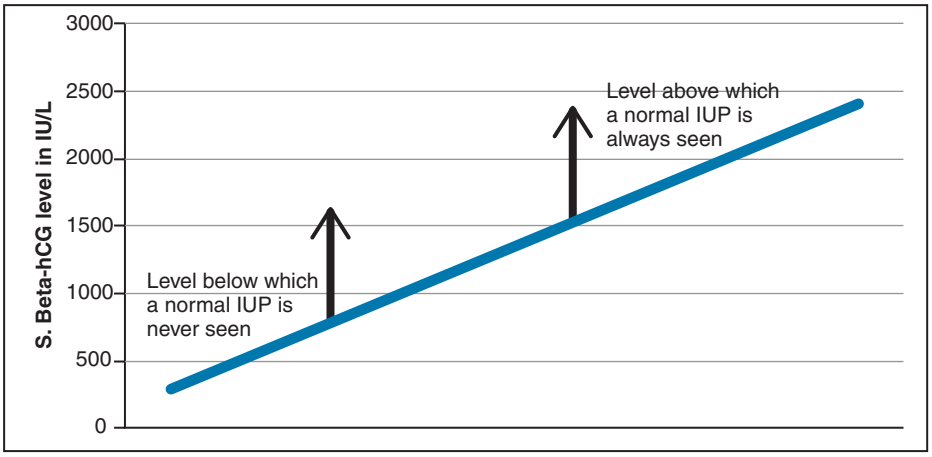
Ultrasonography is probably the single most important investigation in a woman with bleeding in early pregnancy.[5] It should generally be done transvaginally since the imaging quality and accuracy is superior to transabdominal route.[1] A pregnancy is usually seen with almost 100% accuracy at 5.5 weeks of gestation and usually at 5 weeks of gestation. This can be correlated to the serum β-hCG level. At levels higher than 1500 IU/L, a pregnancy should almost always be seen with a 6.5 MHz transvaginal probe. If an intrauterine pregnancy is not seen, an ectopic pregnancy should be strongly suspected. There is a level of serum β-hCG below which even a healthy intrauterine pregnancy is not seen. This is generally taken as 800 IU/L. The zone of serum β-hCG levels between 800 and 1500 IU/L is called the discriminatory zone (Figure 6.1). If the serum β-hCG is in this level, ultrasound imaging may not be conclusive. In the past, the discriminatory zone was wider and higher. It was generally accepted to be 3000 to 5000 IU/L. This was due to studies based on transabdominal rather than transvaginal ultrasound and older methods of measuring serum β-hCG.[6]

The normal developments of intrauterine pregnancy in the first few weeks are important to the understanding and interpretation of images to help establish a diagnosis in early pregnancy bleeding. This is described in Table 6.3.[7]

The diagnostic features of an ectopic pregnancy on ultrasound are variable. A clear diagnosis of an ectopic pregnancy can be made by visualizing a gestational sac with a yolk sac, fetal pole or cardiac activity outside the uterus. A single ultrasound at presentation is accurate in about 80% of women in diagnosing an ectopic pregnancy. At the other extreme of the spectrum, visualizing an intrauterine pregnancy rules out the diagnosis of an ectopic pregnancy barring the exceptionally rare circumstances of heterotropic pregnancies. Between these two extremes of absolute confirmation and ruling out an ectopic pregnancy, lies a gray zone. The following imaging results may confound interpretation:

- Non-visualization of pregnancy (intrauterine or extrauterine) – This situation is also called a PUL (pregnancy

FIGURE 6.1 Concept of discriminatory zone.



IUP = Intrauterine pregnancy

TABLE 6.3 Ultrasound Milestones in Normal Early Pregnancy Development – Sonoembryology*

Gestational Age	Mean Sac Diameter (in mm)	Crown Rump Length (in mm)	Ultrasound Imaging Feature
4 weeks			Thickening of the endometrium and deciduas
4 to 5 weeks			Gestational sac: appears as an echogenic ring in the decidua, usually placed eccentrically
5 weeks	8 mm		Yolk sac
5 to 6 weeks	20 mm	1–2 mm	Fetal pole/embryo
6 weeks	25 mm	5 mm	Fetal cardiac activity

*Modified from Reference 7.

of unknown location). Various outcomes are possible with a PUL as outlined in Table 6.4. Serum markers may be useful in resolving the question of location and viability of the pregnancy. It is important to follow up the PUL because, at least 25% of women with an ectopic pregnancy may have this finding before the diagnosis of ectopic pregnancy is made and about 15% of women who present with symptoms and have a PUL will eventually be diagnosed with an ectopic pregnancy.

TABLE 6.4 Possible Outcomes with a Pregnancy of Unknown Location (PUL)

Intrauterine Pregnancy	Extrauterine Pregnancy
Healthy intrauterine pregnancy in which the gestational sac has not developed to a size that can be seen on ultrasound	Extrauterine pregnancy which is not developed to a size that can be seen on ultrasound
Nonviable intrauterine pregnancy in which the gestational sac has not developed to a size that can be seen on ultrasound	Extrauterine pregnancy which has been expelled from the fallopian tube (tubal abortion)
Nonviable intrauterine pregnancy in which the sac has collapsed and cannot be seen	
Nonviable intrauterine pregnancy which has been completely expelled from the uterus (complete miscarriage)	

TABLE 6.5 Differential Diagnosis of an Adnexal Mass in Early Pregnancy Bleeding

Ectopic pregnancy with collapsed sac or blood clot
Corpus luteum with haemorrhage
Hyperstimulated ovary with multiple follicles
Pelvic inflammatory disease with hydrosalpinx
Endometrioma

- Visualization of an adnexal mass – The differential diagnosis of an adnexal mass in these circumstances is outlined in Table 6.5. Distinguishing between these may not always be possible on a single examination. One must consider the clinical presentation, serum markers and past sonographic findings (if available) to reach a diagnosis. Colour Doppler has been recommended as a tool to distinguish between an ectopic pregnancy and other pathologies. However, visualization of the typical "ring of fire" appearance is possible only when good trophoblastic activity is present and circulation is intact in an ectopic pregnancy.

When the location of the pregnancy has been established as intrauterine, the next issue is of fetal viability. If the fetal cardiac activity can be demonstrated, the diagnosis of a viable intrauterine pregnancy can be made. On the other hand, it may not be possible to make the diagnosis of a non-viable pregnancy with a single ultrasound examination. An algorithm to assess viability in an intrauterine pregnancy is presented in Figure 6.2.[1]

MISCARRIAGE – CLINICAL TERMINOLOGIES

A number of terms are used in clinical practice in the settings of a miscarriage. It is important to understand these and their implications to facilitate day-to-day communication. These terms are largely based on clinical presentation as outlined in Table 6.6.

MANAGEMENT OF THREATENED MISCARRIAGE (VIABLE INTRAUTERINE PREGNANCY WITH BLEEDING)

Most management strategies in this clinical situation are based on empiricism. Bed rest is no longer recommended since it is disruptive and difficult to cope with.[8] Women are generally advised pelvic rest (abstaining from intercourse, douching, tampon use and strenuous physical activity). A number of pharmacological agents have been tried historically but have not been shown to be of benefit such as

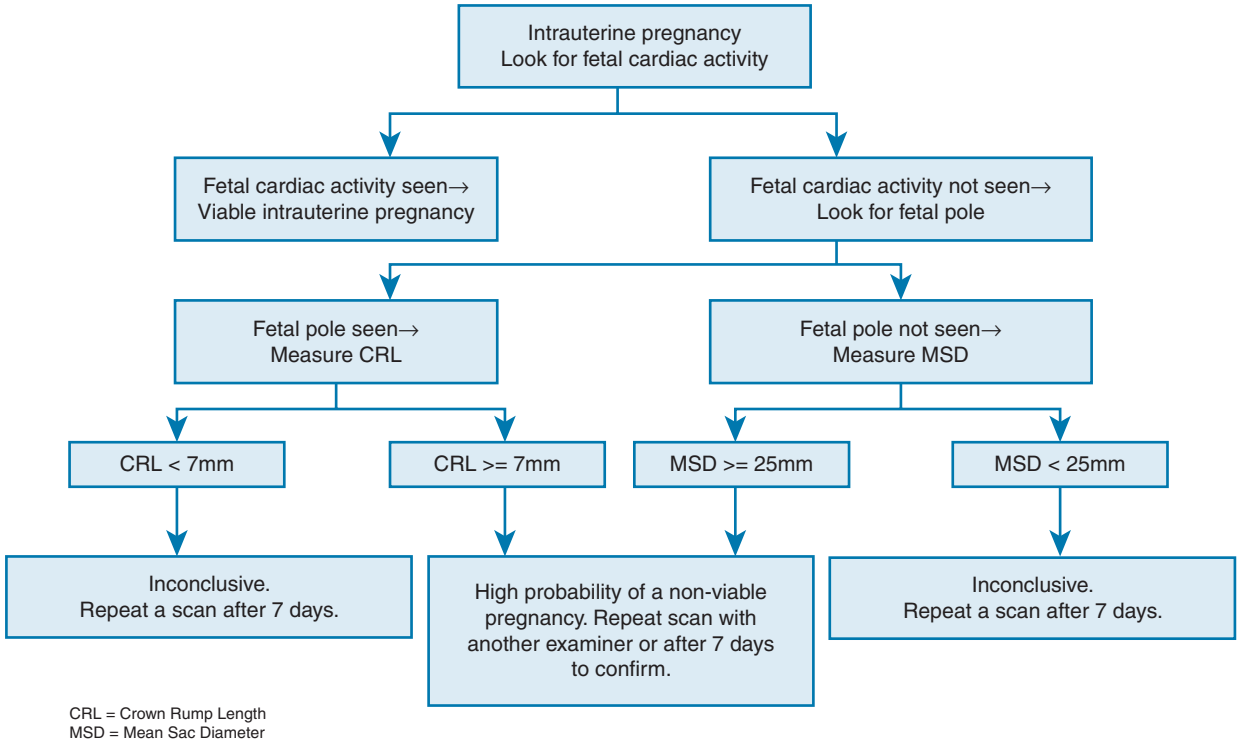


FIGURE 6.2 Algorithm to assess viability in an intrauterine pregnancy.[1] *(Reproduced from: National Collaborating Centre for Women and Child Health. Ectopic Pregnancy and Miscarriage. London: RCOG; 2012, with the permission of the Royal College of Obstetricians and Gynaecologists)*

TABLE 6.6 Clinical Classification of Miscarriage

Type and Definition	Bleeding	Colicky Pain or Cramps	Cervical Status	Uterine Size in Relation to Period of Amenorrhea	Tests
Threatened: Process of miscarriage has started but not progressed to the stage of irreversibility	Fresh, may start as spotting. Usually small quantity.	No	Os closed, no products felt	Corresponds	UPT positive. USG shows viable pregnancy or inconclusive scan.
Invevitable: Process of miscarriage has progressed to the stage of irreversibility	Fresh bleeding, some clots.	May be present	Present, products felt through the os	Corresponds	UPT positive. USG shows viable pregnancy or inconclusive scan.
Incomplete: A part of the products of conception are expelled	Fresh bleeding, significant quantity, clots passed. Shock may occur.	Present	Present, products felt in the cervical canal and vagina	Slightly smaller	UPT positive. Nonviable pregnancy in a state of expulsion on USG.
Complete: All the products of conception are completely expelled spontaneously	Fresh bleeding with clots which may have abated	Strong cramps followed by decrease in pain	Os closing down, no products felt	Smaller	UPT positive. Normal ultrasound with thick endometrium.
Missed: A non-viable pregnancy which has been retained in the uterus (for more than four weeks)*	Small quantity, often brown, altered colored	No	Os closed	Smaller	UPT may be negative. USG shows nonviable pregnancy.
Septic: Any of the above presentations with evidence of superadded pelvic or systemic infection	Variable	Variable	Variable os status. Cervical movements may be tender	Variable	Variable. Patient may be toxic due to sepsis.

UPT, urine pregnancy test; USG, ultrasonography.

*The criterion of four weeks to define a missed miscarriage is not realistic in clinical practice today due to the earlier recourse to ultrasound and interventions available.

human chorionic gonadotropins,[9] uterine relaxants,[10] multivitamins,[11] antiprostaglandins, thyroid extracts, ethamsylate, and tranexamic acid.

Progesterone has a controversial place in the management of threatened miscarriage. It may be administered parenterally (progesterone in oil intramuscular injections, natural micronized progesterone vaginally or rectally or progesterone gel vaginally) or by the oral route (dydrogesterone). Despite this condition being extremely common and the use of progesterone growing exponentially, the available evidence is of very low quality and the numbers of patients in these trials are very small. At the present time, the data from a Cochrane review suggest that the use of progestogens is effective in the treatment of threatened miscarriage with no evidence of increased rates of pregnancy-induced hypertension or antepartum haemorrhage as harmful effects to the mother, nor increased occurrence of congenital abnormalities on the newborn.[12] The application of this into clinical practice should be with the background knowledge that most miscarriages (nearly 80%) are a result of abnormal gametes or embryos and progesterone cannot correct this. The earlier mentioned limitations should also be borne in mind. The use of progesterone to prevent miscarriage in these settings is an area which urgently requires research attention.

MANAGEMENT OF OTHER MISCARRIAGE SCENARIOS (NONVIABLE INTRAUTERINE PREGNANCY)

The following principles should be kept in mind in managing women with a nonviable intrauterine pregnancy:

- Acknowledgement of loss of a pregnancy by the care provider and appropriate counseling
- Assessing the need for uterine evacuation
- Method of uterine evacuation – medical or surgical

In some situations, there is a definite need for uterine evacuation as an urgent measure. In most of these circumstances, surgical evacuation should be done. These are outlined below:

- Significant vaginal bleeding with shock or a change in haemodynamic parameters
- Evidence of infection
- Pain or discomfort

In addition, uterine evacuation should be offered as a first line option to women with the following features:

- Increased risk of haemorrhage (late first trimester)
- Previous adverse and/or traumatic experience associated with pregnancy (for example, stillbirth, miscarriage or antepartum haemorrhage)
- Increased risk from the effects of haemorrhage (coagulopathies or unable to have a blood transfusion)

The NICE guidelines[1] recommend an expectant line of care in all other situations besides the ones outlined above. Products of conception are likely to be expelled spontaneously in the first seven days from the diagnosis of a miscarriage. Most women may not need any intervention. However, in following an expectant line of management for a miscarriage, there are certain risks such as unscheduled bleeding. This must be factored into the decision making, considering the access to care and availability of emergency resources. It may be reasonable to offer uterine evacuation as the first line of management.

If an expectant line of management is chosen, and if symptoms suggest that the miscarriage process has been completed in the waiting period of 7 to 14 days, the woman should be advised to do a urine pregnancy test after 3 weeks. Interventions can be offered to women who are on expectant management if:

- No symptoms of bleeding or pain in the waiting period
- Ultrasound suggests no change in the status
- Pregnancy test is positive 3 weeks after miscarriage has been thought to be complete

Uterine evacuation can be carried out medically or surgically. In medical uterine evacuation, misoprostol alone is sufficient. Mifepristone need not be used for missed or incomplete miscarriages.[1,13] A single dose of 600 to 800 micrograms administered vaginally is adequate. If the vaginal route is not acceptable, misoprostol may be administered orally. The woman should be offered information about the process, pain relief and access to antiemetics. The dose of misoprostol may be repeated after 24 to 48 hours in case there are no symptoms of miscarriage after the first dose. In less than 5% of cases, there may be a need for urgent surgical intervention due to excessive bleeding, pain or infection. Surgical management can be offered as a manual vacuum aspiration procedure or suction evacuation. The choice depends on the patient's level of comfort, provider's experience with the technique and clinical presentation (size of pregnancy, bleeding, pain). Antibiotic prophylaxis is recommended for surgical uterine evacuation.

MANAGEMENT OF TUBAL ECTOPIC PREGNANCY

There has been a sea-change in the presentation and management options of women with ectopic pregnancy. Earlier, most women presented in a state of shock with haemoperitoneum and could only be managed by an emergency laparotomy and vigourous resuscitation. Today, with early diagnosis of ectopic pregnancy being the norm, a wider range of clinical presentations and treatment options have emerged. A tubal

ectopic pregnancy can be treated surgically or medically. Expectant management is offered only in rare, exceptional circumstances. Surgery may be performed laparoscopically or through a laparotomy. At surgery, the ectopic pregnancy is managed by a salpingostomy or salpingectomy. For patients treated medically, the most commonly used drug is methotrexate. This is usually administered systemically and requires constant vigilance of effect and evaluation by serial follow-up. The choice of therapy will be influenced by the clinical presentation, especially haemodynamic stability, S. β-hCG levels, size of the ectopic pregnancy and the woman's choice. We should consider treatment effectiveness, safety and impact on future fertility in counseling these women. An algorithm for the initial management of tubal ectopic pregnancy is presented in Figure 6.3.[1]

Medical Therapy – Methotrexate

Methotrexate is an antimitotic agent and acts on viable trophoblastic cells. It is the most widely used and studied agent in the medical therapy of ectopic pregnancy. Other agents such as mifepristone and prostaglandins have been studied, but are no longer used. Before a woman is administered this therapy, it should be ascertained that she meets the criteria for using methotrexate as given in Figure 6.3. The main advantage of medical therapy in this situation is to avoid surgery and anaesthesia and their possible complications. Counseling should include the possibility of a long resolution period, increased waiting time for future fertility if desired, possible side effects of methotrexate (gastritis, stomatitis, hair loss) and the possibility of emergency surgical intervention and unscheduled hospitalization. Laboratory parameters (blood count, liver and renal functions) should be confirmed to be normal. Systemic therapy with methotrexate is as effective as and simpler than locally administered methotrexate. A single dose of methotrexate is administered intramuscularly or as a slow intravenous infusion. A variety of protocols such as a two-dose and multi-dose protocol have been described but do not offer significant advantage over a single dose. The dose of methotrexate is 50 mg/m^2. Serum β-hCG levels should be done on Day 4 and Day 7 after giving the therapy. Up to Day 4, it is common to see a small increase in S. β-hCG level. Between Day 4 and 7, S. β-hCG level should be 15% lower than the pre-therapy level. After Day 7, a weekly S. β-hCG level should be done until it reaches zero. She should be advised to avoid a pregnancy for the next three months and take folic acid in the subsequent periconceptional period. If the S.β-hCG level between Day 4 and Day 7 does not fall by at least 15%, a repeat dose of methotrexate can be given. If S.β-hCG levels do not decline by 15% in each subsequent week, repeat methotrexate can be given for a maximum of three doses. Medical therapy should be abandoned if it has not worked or if there is evidence of rupture of the ectopic pregnancy in the form of haemodynamic instability or increasing pain. The main determinant of success of medical therapy is the pre therapy serum β-hCG level. Ninety-eight per cent of ectopic pregnancies will resolve when the pretherapy level is less than 1500 IU/L. When pre therapy level is over 5000 IU/L, success rates fall to 85%.[14]

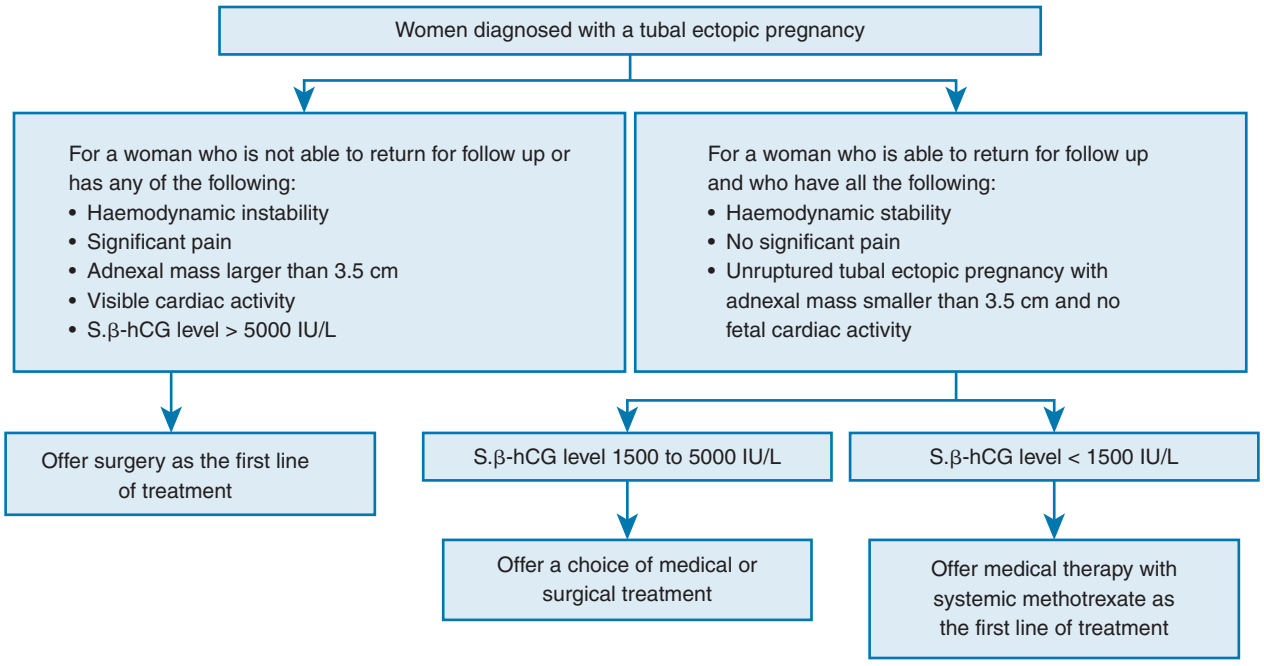


FIGURE 6.3 Algorithm for management of a tubal ectopic pregnancy.[1] *(Reproduced from: National Collaborating Centre for Women and Child Health. Ectopic Pregnancy and Miscarriage. London: RCOG; 2012, with the permission of the Royal College of Obstetricians and Gynaecologists)*

Surgical Therapy

Most tubal ectopic pregnancies are managed by laparoscopy, today. Laparotomy is reserved for exceptional situations such as:

- Haemodynamic instability and shock
- Intraoperative haemorrhage or other complications during laparoscopy
- Frozen pelvis with very difficult access to the pelvis

In such situations, the team effort to ensure adequate resuscitation, maintaining airway, breathing and circulation and replacement of the blood volume with crystalloids until blood becomes available are of vital importance.

The surgical methods for treating the ectopic pregnancy are salpingostomy or salpingectomy. Salpingostomy can be offered where future fertility is desired and there are risk factors for infertility such as a diseased opposite tube, endometriosis or pelvic adhesions. The advantage of a salpingostomy is the preservation of the tube and nonsignificant increase in future intrauterine pregnancies. However, salpingostomy is associated with increased operative time, bleeding during surgery, residual trophoblastic tissue requiring therapy and recurrent ectopic pregnancies. Where future fertility is not desired or in a woman who desires future fertility but does not have risk factors for infertility, salpingectomy is a more effective treatment option.

On introducing the laparoscope, the first step should be to survey the pelvis before handling the affected tube. The ectopic pregnancy should be grasped atraumatically to prevent rupture during surgery and bleeding. Good suction equipment and lavage should be available. Overzealous haemostasis should be avoided especially when a salpingostomy is being done.

If a salpingostomy is planned, ensure that there is complete evacuation of the trophoblastic tissue from the tube. Bleeding from the base should be identified and cauterized. After a salpingostomy, serum β-hCG should be repeated after a week to ensure complete evacuation. If the hCG level is above 1000 mIU/mL 7 days after surgery or is more than 15% of the original level at this time, persistent ectopic pregnancy (PEP) is nearly always present. If the day 7 hCG level is under 1000 mIU/mL or less than 15% of the initial value, PEP is very unlikely. About 10% of women will need methotrexate or re-operation due to PEP presenting as haemorrhage or persistent lower abdominal pain.

If a salpingectomy is planned, it is important to stay close to the fallopian tube and avoid devascularizing the broad ligament. This is to prevent a reduction in ovarian reserve. Also, the tube should be resected till the cornual end and there should be no stump left behind. After a salpingectomy, if a woman does not get a period after 4 weeks, she should take a urine pregnancy test and follow up if it is still positive.

Future Fertility after Ectopic Pregnancy

Women with ectopic pregnancies may have a history of infertility or may have conceived on treatment for the same. Therefore, future fertility is an important consideration in this situation. Whatever treatment modality is used, fertility prognosis after ectopic pregnancy is not correlated to the features of the protocol/method or the ectopic pregnancy but depends mainly on patient age, past history and state of her pelvis.[15] Hence the modality of management should be based on present clinical circumstances and criteria outlined in Figure 6.3 rather than considerations of future fertility.

MANAGEMENT OF ECTOPIC PREGNANCY (NONTUBAL SITES)

Over 95% of ectopic pregnancies occur in the fallopian tube. Various other sites of ectopic gestation have been documented such as the cornual region of the uterus, scar of previous uterine surgery, ovary, cervix, peritoneal cavity (abdomen) and various visera. The management of each is individualized. These pregnancies are at high risk for rupture and haemorrhagic complications because diagnosis is delayed, presentation is late and size is larger. If they are diagnosed early, medical therapy with methotrexate is generally the method of choice. It may also be used as an adjuvant. The various surgical approaches are aimed at minimizing the risk of bleeding, avoiding organ damage and fertility preservation where it is desired and found to be safe.

GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

Gestational trophoblastic disease is an unusual cause of early pregnancy bleeding. GTD includes hydatidiform mole (complete and partial) and gestational trophoblastic neoplasia (invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor). The incidence of GTD is higher in Asian populations, especially in Far East Asia and Japan.[16] The benign GTD essentially comprises of complete or partial molar pregnancies. The essential features are outlined in Table 6.7. The most common presentation of GTD is along the lines of a failed early pregnancy. The prominent features are irregular bleeding with a period of amenorrhea, positive urine pregnancy test, uterine size larger for dates, lower abdominal pain and hyperemesis. Rarely, the disease may present with metastatic features such as respiratory distress or seizures. Ultrasound is helpful in making the diagnosis. The typical features are an absent fetal pole and multiple cystic areas in the uterine cavity giving it a “snow storm” appearance. Theca lutein cysts may be present. These features are not always present. About 50% of molar pregnancies have a preoperative diagnosis of delayed miscarriage or anembryonic pregnancy.[17]

TABLE 6.7 Essential Features of Benign Gestational Trophoblastic Disease (GTD)

Feature	Complete Mole	Partial Mole
Karyotype	46 XX. The chromosomal complement is entirely of paternal origin – Androgenesis.	Triploid. Derived from two paternal and one maternal haploid set of chromosomes.
Embryo/fetus	Absent	Present
Theca lutein cysts	25% of cases	Rare
Trophoblastic proliferation	Diffuse, marked	Focal, mild
S.β-hCG levels	High, slow return to normal	Lower, earlier return to normal
Stromal oedema	Pronounced	Variable
Fetal vessels	Absent	Present
Malignant potential	20%	5%

Serum β-hCG levels higher than twice the median value for the gestational age may provide a diagnostic clue. The GTD is ultimately a histopathological diagnosis. It is not necessary to send products from every pregnancy termination for histopathology if fetal parts are identified. Histopathology should be obtained ideally for all evacuated products of anembryonic or missed miscarriages or at least in all cases where a repeat evacuation has been performed. The treatment for GTD comprises of evacuating the pregnancy followed by a rigorous watch for malignant sequelae and appropriate use of chemotherapy.

The best method for evacuating a GTD is by suction curettage. The procedure should be performed in an operation theatre with facilities for blood transfusion, resuscitation and emergency laparotomy available. Cervical preparation may be done, but prolonged use of prostaglandins should be avoided to reduce the risk of embolization of trophoblastic cells.[18] Medical therapy to evacuate the uterus is not recommended unless the size of the fetal parts in a partial mole preclude suction evacuation. Other methods such as hysterotomy or hysterectomy are rarely used for this purpose. Anti-D prophylaxis is required following evacuation of a molar pregnancy.

After evacuation, a weekly follow-up of serum β-hCG levels is recommended. Once serum β-hCG levels are negative on three occasions one week apart, testing could be reduced to once a month. It should be followed up for six months after uterine evacuation or after the levels have become normal, whichever is later. Women should be advised not to conceive until their follow-up is complete or for one year after the last chemotherapy regimen if it has been used. During the follow-up period, the couple should be advised barrier contraception. After the serum β-hCG levels have returned to normal, the woman can use hormonal contraception or an intrauterine device can be inserted. If there is a future pregnancy, serum β-hCG levels should be assessed 8 weeks after the pregnancy, irrespective of the outcome.

The need for chemotherapy after a complete mole is about 15% and after a partial mole is 0.5%. Ideally, they should be registered with a gestational trophoblastic neoplasia (GTN) registry wherever such facilities exist. Gestational trophoblastic neoplasia may be treated with single- or multi-agent chemotherapy based on the FIGO 2000 scoring system.[19]

NAUSEA, VOMITING AND HYPEREMESIS IN EARLY PREGNANCY

Nausea and vomiting are very common in early pregnancy and about 70% of women have these features. Though it is commonly called morning sickness, it may occur at any time through the day. It is thought to be due to the rise of pregnancy hormones generated by the placenta, particularly hCG and estradiol. Psychological factors play an important role through stressors as well as triggers to the emetic center in the midbrain. Typically, symptoms appear at 6 weeks of gestation and subside by 14 weeks. Usually, morning sickness does not produce any detrimental effect on a woman's health. Simple measures such as the following can be advised:

- Small frequent meals
- Start the day with simple food such as a few biscuits or dry toast
- Non-fatty, dry, high calorific food
- Avoid dehydration and keep sipping liquids through the day
- Avoid smell and taste triggers

If these measures do not bring relief, simple antiemetics such as doxylamine, pyridoxine, metoclopromide

or promethazine. Associated heartburn should be treated with antacids.

Hyperemesis is defined as vomiting in pregnancy that results in dehydration, ketonuria, significant weight loss and requires hospitalization and intravenous fluid therapy.[20] A number of aetiological factors have been described including:

- Hormonal – excessive hCG production as seen in GTD, multiple pregnancies
- Anatomical – rapid overdistension of the stomach and uterus
- Immunological
- Associated changes in thyroid physiology

Examination and investigations should be directed at assessing the severity of the problem, detecting complications and making certain that other pathological causes such as gastrointestinal infection, urinary infection (pyelonephritis), cholecystitis, ulcerative upper gastrointestinal disease and diabetes are not the cause of vomiting. Investigations should include:

- A daily weight chart
- Urine analysis to rule out infection and confirm ketonuria
- Blood count to rule out infections and assess dehydration
- Electrolyte levels, liver and renal function tests to look for metabolic complications
- Ultrasound to assess the pregnancy

Laboratory abnormalities such as low TSH, high free thyroxine and elevated liver function tests, amylase and lipase and alterations in the electrolyte levels from a loss of sodium, potassium and chloride may be seen in women with hyperemesis gravidarum.

Treatment is supportive and aimed at correcting dehydration, electrolyte imbalances, reducing the symptoms and preventing complications such as Wernicke encephalopathy. An infusion of Ringer's Lactate or normal saline with appropriately added potassium doses should be given. Dextrose containing solutions should be avoided. Parenteral antiemetics such as metoclopromide, promethazine or ondansetron can be used in a sequential manner. Corticosteroids (intravenous hydrocortisone followed by oral prednisolone in tapering doses) have been used, but their benefit is not clear. Parenteral antacids such as ranitidine should be added. Vitamins should be added in the intravenous infusion until oral route is tolerated. Dietary advice is important and a gradual introduction and sustenance till normal diet is established should be the goal. Rarely, complications to the mother such as Wernicke encephalopathy and central pontine myelinolysis may occur. It is more common to see psychological fallouts such as depression, anxiety and social issues such as economic problems from losing employment. It may very rarely be required to terminate a pregnancy affected by hyperemesis if the maternal condition is life threatening.

LOWER ABDOMINAL AND PELVIC PAIN IN EARLY PREGNANCY

The presentation of lower abdominal and pelvic pain may be due to physiological and pathological aetiologies. It is important to distinguish between these. The differential diagnosis is based on the associated complaints, if any, such as vaginal bleeding, urinary or gastrointestinal features. They are outlined in Table 6.8. Investigations are dictated by the clinical presentation. An ultrasound to establish pregnancy status is reassuring.

Adnexal Torsion

Torsion usually involves a preexisting ovarian cyst (most commonly a dermoid cyst), paraovarian cyst or the corpus luteum. Disruption of the blood supply produces ischaemia and pain. It is typically described to be a cramping pain which relents for periods of time. The diagnosis is made by ultrasound and colour doppler. The first line of management is analgesia, intravenous fluids, antibiotics and observation. If the pain worsens, surgical intervention

TABLE 6.8 Causes of Lower Abdominal and Pelvic Pain in Early Pregnancy

Usually with Vaginal Bleeding	Usually with Clinical Feature Related to an Organ System	Usually no Other Clinical Feature
Miscarriage	Acute urinary retention	Adnexal torsion
Ectopic pregnancy	Urinary tract infection	Ruptured corpus luteum with haemorrhage
Gestational trophoblastic disease	Urolithiasis	Ovarian hyperstimulation
	Appendicitis	Degenerating fibroid
	Bowel obstruction	
	Inflammatory bowel disease	

is required. Laparoscopic management is feasible. Traditionally, salpingoophrectomy was advocated as the treatment of choice in adnexal torsion. However, several case reports and case series support the option of detorsion and sparing of the affected ovary even in the presence of blue-black ischaemic changes.[21] In case, the ovary is removed or corpus luteum is damaged, pregnancy should be supported with progesterone until 9 weeks of gestation are completed.

Ovarian Hyperstimulation Syndrome (OHSS)

Ovarian hyperstimulation syndrome is a serious iatrogenic complication of assisted reproduction therapies. All methods and drugs used to induce ovulation can cause OHSS. However, it is more likely to occur in protocols where there is a downregulation with gonadotropin-releasing hormone agonists, stimulation with gonadotropins and trigger with hCG. Risk factors include young age, polycystic ovarian syndrome, low body mass index, past history of OHSS, high dose stimulation and high estradiol levels during stimulation. The presentation is usually of lower abdominal pain, bloating and in severe cases, respiratory distress. Investigations should include an ultrasound to assess ovarian size and rule out other causes of pain. A blood count, especially the haematocrit and biochemical parameters of renal and hepatic function should be obtained. Weight and urine output should be monitored. Outpatient care is adequate for mild cases. Adequate hydration and symptomatic relief of pain using analgesics other than nonsteroidal anti-inflammatory drugs is usually sufficient to treat mild OHSS. Admission is warranted for moderate or severe grades of OHSS. The principles of management are to maintain a fluid and electrolyte balance ensuring adequate urine output but preventing the risk of pulmonary oedema. Various agents such as albumin, hydroxyethyl starch and heparin have been used but are of doubtful benefit. Fluid may have to be drained from the peritoneum by paracentesis or from the pleural cavities by thoracocentesis under ultrasound guidance if symptoms are severe. Surgical intervention is rarely required.[22] The aim is to prevent OHSS with soft stimulation protocols, agonist trigger with antagonist downregulation, cycle cancellation, "freeze-all" strategies and the use of dopamine agonists.[23]

PHYSIOLOGICAL CHANGES AND SYMPTOMS MIMICKING COMPLICATIONS

Pregnancy is associated with considerable anatomical, physiological and biochemical adaptations which are necessary to maintain the pregnancy. These adaptations may give rise to symptoms which should be assessed and distinguished from pathological causes. The goal in managing these symptoms is to ascertain that they are physiological and offer advice and reassurance. The most common symptom is nausea with or without vomiting which has been discussed earlier. Other symptoms that may be seen in early pregnancy are:

- **Pica and ptyalism** – pregnant women may experience a craving for unusual foods and even non-foods. Iron deficiency anemia should be ruled out.
- **Urinary frequency** – as the uterus becomes an abdominal organ from its pelvic position, it presses on the bladder base and causes a sense of urinary urgency and results in frequency. Cystitis should be ruled out. Sensible fluid intake and avoiding excess fluids before bedtime is helpful.
- **Aches and pains** – with the expanding uterus and stretch on the round ligaments, women may experience backache or groin pain in the late first trimester. An ultrasound is useful in ruling out uterine, ovarian or pregnancy-related pathology. Local heat and simple analgesics will usually suffice. Postural modifications and footwear are helpful.
- **Palpitations, breathlessness, blackouts, fatigue** – due to the early haemodynamic changes and rise in progesterone levels, women may experience these symptoms in early pregnancy. The most prevalent pathological cause associated is anaemia. Cardiovascular and respiratory examination should be done. Unusual causes such as thyroid disorders should be ruled out. Reassurance and altering the sleeping position are useful.
- **Vaginal discharge** – due to the hormonal influences, women may have excess secretions which may be mistaken for a vaginal infection. In the absence of other symptoms such as itching, burning, pain and bleeding, most women will only need reassurance.

INDIAN PERSPECTIVE

In India, the urban, educated and well-informed woman does not pose any challenges significantly different from her Western counterpart in early pregnancy. Differences may arise in populations when there is lack of healthcare facilities or delay in access to care. Traditionally, women would access healthcare only close to seventh month of pregnancy. Typically, this situation is compounded by lower socioeconomic status, poor general health and associated risk factors. It would be common to see women presenting with prolonged and heavy bleeding with an incomplete miscarriage or with a large haemoperitoneum due to a ruptured ectopic pregnancy. These women could be in shock and need urgent resuscitation, blood transfusions and intensive care besides the routine obstetric management. A retrospective review over the last decade from a teaching hospital in Kolkatta showed a small rise in the incidence of ectopic pregnancy. Laparotomy is still the most commonly used modality for the treatment of

ectopic pregnancy. Only 20% of women are treated laparoscopically and 3% by medical treatment.[24] It is also interesting to note that Indian literature abounds with unusual cases and presentations of ectopic pregnancy. It could be related to the timing of diagnosis. In situations where diagnostic facilities are widely available, the clinical picture might be interpreted as a pregnancy of unknown location. This would be treated medically and the pregnancy is likely to resolve. In low resource settings, by contrast, the diagnosis may be established later only when the clinical picture evolves completely.

Septic abortions contribute to 60% of deaths from unsafe abortions.[25] Where access to safe abortion is difficult, septic abortions are seen. These women have a tortuous path to a tertiary health care facility and are at a high risk for mortality. Women seen at one tertiary care hospital in North India were predominantly parous, married and in a stable relationship. Their use of contraception was low and knowledge about access and availability of safe abortion care was limited. There was also a sense of inhibition in accessing care at public hospitals.[26] There is a need for sensitization, education and disseminating information about the availability and safety of abortion care facilities.

Women with GTD need a prolonged follow-up and this may be difficult in some situations. There are no registries nationally or regionally. It is up to the practising physicians to organize such follow-up clinics in regional tertiary care centers and start a trophoblastic disease registry for scientific analysis. Sekharan et al from Calicut in the northern region of Kerala in South India, have started such a centre 15 years ago and so far have followed up more than 1500 cases with excellent results.[27]

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Chapter 7

Identification and Antepartum Surveillance of High Risk Pregnancy

Amol P. Pawar and Kaizad R. Damania

Chapter Outline

Evaluating a high risk pregnancy has significant problems. Any pregnancy can turn into a high risk one any time during its course. A pregnancy at risk needs to be identified at an earlier state, often in the prenatal period in order to have an effective intervention strategy to deal with its complications. High risk pregnancy requires sophisticated maternal and fetal surveillance to help in its management decisions so as to ensure an optimal outcome for both mother and her newborn. Perinatal morbidity and even perinatal mortality, which includes still birth, is often a neglected aspect in resource sparse settings. Still births contribute nearly half of the burden of neonatal demises. This chapter provides for an overview of the methods used for fetal surveillance in high risk pregnancies, their benefits and drawbacks including their usefulness in different setting and their impact on maternal and fetal outcome.

In all the communities, worldwide, mother and children constitute a priority group; this is particularly so in developing countries. In developing countries, like India, women of the child bearing age (15–44 years) constitute 19% of the population.[1] Mothers and children not only constitute a very large group together but they are also a 'vulnerable' or special risk group. This risk is often connected with child bearing in the case of women. In case of infant and children the risk is, namely, growth, development and survival. Today, pregnancy care cannot be restricted to the care that obstetricians give periconceptionally, during pregnancy, delivery and postnatally but it needs to be holistic since the problems identified or occurring during pregnancy often affect and extend throughout the womens' lifetime. Also, today antepartum care should be aimed not only to improve the pregnant women's outcome but should encompass her complete family. A good example of preventive medicine for women, newborns, infants and children has been antepartum care and surveillance.

MATERNAL MORTALITY AND PERINATAL MORTALITY

Maternal Mortality

The International Classification of Diseases (ICD) defines maternal death as the death of a woman while pregnant or within 42 days of the end of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes (ICD 9th revision).[2] The pregnancy can be of any gestation and includes spontaneous or induced abortion and ectopic pregnancies.

The 9th ICD revision further divided maternal deaths into a number of subgroups defined as follows:

1. **Direct maternal deaths** are those deaths attributed to obstetric complications of pregnancy, childbirth or the puerperium.

2. **Indirect maternal deaths** are those deaths resulting from previous existing disease or condition that developed during pregnancy and which was not due to direct obstetric causes but which was aggravated by the physiologic effects of pregnancy.
3. **Fortuitous or coincidental maternal deaths** are those deaths from unrelated causes which happen in pregnancy or the puerperium.

   The 10th revision of the ICD introduced the term of 'late maternal deaths.'[3]
4. **Late maternal death** is one which has occurred between 42 days and 1 year after abortion, miscarriage or delivery that is due to direct or indirect maternal causes.
5. **Pregnancy-related deaths** are those deaths occurring in women while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death.

Overall worldwide figures still remain high and have high variability. These figures depend not only on the development status of the country, available medical infrastructure but even on the basis of certain legislations and accepted social and cultural customs. The major cause of maternal demise has always been related to abortion-related complications, more so in countries like Ethiopia, where abortion remains illegal. The frequency of maternal deaths in that country has been calculated at 1528 for 100,000 birth.[4]

The women in developing countries have on an average many more pregnancies than women in developed countries, and their lifetime risk of death due to pregnancy is higher. The maternal mortality in developing countries is 240 per 100,000 births versus 16 per 100,000 births in developed countries. There are also large disparities within the same country between rural and urban areas.[5]

The causes of maternal demise vary from industrial developed countries and other developing countries, too. Nearly all maternal deaths (99%) occur in developing countries. More than half of these deaths occur in South Asia. Women die as a result of complications during and following pregnancy and child birth. Most of these complications develop during pregnancy. The major complications that account for nearly 80% of all maternal deaths are:

- Haemorrhage
- Sepsis/infection
- Preeclampsia/eclampsia
- Unsafe abortion

Identifying high risk factors in pregnant women is one of the important aspects of antenatal surveillance. Identifying high risk factors helps in segregating patients who require extra care and referral to expert consultancy, especially in developing low-resource countries. Identifying high risk pregnant women also helps in effectively implementing certain preventive strategies which may alter the adverse outcome. An example is preventing thromboembolic episodes, especially in pregnant women with high risk of prolonged bed rest like preterm labor, preeclampsia and premature rupture of membranes, can be done with compression stocking or heparin therapy.

Maternal death is an unacceptable public health problem. Most of the demises are directly or indirectly attributed to pregnancy and are preventable in low-income countries, just over one-third of the pregnant women have the recommended four antenatal visits. In order to improve maternal health, barriers that limit access to quality maternal health services like poverty, cultural practices must be identified and addressed at all levels of the health system.

Perinatal Mortality

The National Centre for Health Statistics (NCHS) defines perinatal mortality rate (PMR) as the number of late fetal deaths (fetal deaths of 28 weeks gestation or more) plus early neonatal deaths (deaths of infants 0–6 days of age) per 1000 live birth plus fetal deaths (Centre for Disease Control, USA).[6] The definition of PMR provided by the World Health Organization (WHO) is somewhat different, including the number of fetuses and live births weighting at least 500 gms; or when birth weight is unavailable, the corresponding gestational age (22 weeks) or body length (25 cms crown-heel) dying before day 7 of life per 1000 such fetuses and infants.[3] For international data comparisons, only deaths of fetuses and infants weighting 1000 gms or more at delivery are included, bearing in mind that in developing countries, antepartum fetal deaths and preterm deliveries are significantly under reported.[7]

Declining infant mortality rate has shifted the focus on perinatal mortality rate, which has assumed greater significance as a yard stick of obstetric and paediatric care around birth. The idea of combining still births and deaths under first weeks of life was due to the fact that factors responsible for these two types of deaths are often similar. It gives a good indication of the extent of pregnancy wastage as well as the quality and quantity of health care provided to the mother and newborn.

Perinatal mortality is assuming serious dimensions in all countries, as infant mortality rate is at a decline. In developed countries, it now accounts for nearly 90% of all fetal and infant mortalities. In developing countries, still births are usually not registered. Nearly 3 million newborn babies die every year, and an additional 2.6 million babies are born still born each year.[8] There has been a vigorous endeavour to include these mortalities, for international comparison, in a special certificate, as recommended by the 10th (2004) Revision of International Classification of Disease (ICD-10).

Causes of Perinatal Mortality

Fetal deaths may be divided into those that occur during the antenatal period and those that occur during labour, intrapartum still births. Nearly 70–90% of all fetal deaths occurred before the onset of labor. About two-thirds of all perinatal deaths occur among infants with less than 2500 gms birth weight.

Perinatal demises may be broadly attributed to the following causes:

1. Chronic asphyxia of different underlying causes;
2. Congenital malformation;
3. Pregnancy complications affecting fetuses; and
4. Deaths due to unexplained causes.

Based on various data available, approximately 30% of antepartum fetal deaths may be attributed to asphyxia (like IUGR, placental hypermaturity, prolonged gestation), 30% to maternal complications (preeclamsia, aburtio-placentae, diabetes mellitus), 15% to congenital malformations and chromosomal abnormalities, and 5% to infection. At least 20% of still births have no obvious fetal, placental, maternal, or obstetric etiology. It is more likely that late gestational perinatal mortalities have no obvious identifiable causes.[9]

The main aim of antepartum surveillance, particularly in high risk pregnancies is to succeed in identifying malformed fetuses and recognize those fetuses which are at risk for asphyxia. Extrinsic perinatal hypoxia accounts for nearly half the number of deaths in term infants and nearly three-quarters in postterm infants. In case of still births, the study conducted by Stubblefield and Berek,[10] concluded that nearly two-thirds of the deaths were attributed to chronic process such as uteroplacental insufficiency, which could have been detected during antepartum fetal surveillance, if it had been used.

The initial clinical experience in antepartum fetal assessment has clearly indicated its usefulness. A decade of experience from 1974 through 1983, primarily with contraction stress test (CST) followed later by nonstress test (NST), was evaluated. Overall the perinatal mortality was found to be 24.4 per 1000 in nontested population versus 11.8 per 1000 in the tested population of high risk pregnant patients, a very significant difference. The still birth rate in nontested population, 11.1 per 1000 was twice that of patient who had antepartum surveillance. On correcting for congenital anomalies, the still birth rate was just 2.2 per 1000 in the tested high risk population.[11]

Antepartum surveillance for high risk pregnancies employ tests which have, unfortunately, been not commonly subjected to randomized and prospective evaluation. In most of the cases, on the basis of good observational outcomes, tests have been propagated. It requires a large number of patients to be studied in order that the results of the test may be validated; adverse events like perinatal mortality are very uncommon even in high risk population. Most of the studies, especially for nonstress testing, have not included more than 300–350 participants, in a randomized double blind prospective trials. Thus, using the outcome of such tests leads to intervention by delivering the fetus which always may not be indicated and could lead to potentially avoidable complications of prematurity.

ANTENATAL EVALUATION

Pregnancy in developing countries is often the first time a woman is medically evaluated. The objective of routine antenatal examination and laboratory tests is to search and identify any known and unknown condition which may affect the maternal and fetal outcome. Any high risk pregnancy can only be identified if the pregnant woman has access to good health care delivery system, with its constraints of trained health care personnel and appropriate infrastructure. For a pregnant woman, such an adequate prenatal care should start right before conception.

Preconception Counselling

Preconception counselling hopes to identify the potential impact of pregnancy on any pre-existing or now identified medical or obstetric disorder, and at the same time assess how pregnancy would get affected by the same. This stage would greatly benefit the woman in identifying her high risk factors and the life style modifications which may be required in order to have a maximal good outcome of pregnancy. Some of the salient features in preconceptional counselling are listed in Table 7.1.

TABLE 7.1 Salient Features of Preconception Counselling

Identifying medical and surgical high risk.
Identifying how each risk factor would alter pregnancy outcomes.
Identifying how pregnancy would alter the course of each medical/surgical disorder.
Short-term as well as long-term disability that is likely to occur both in the newborn and the mother.
Tests required for monitoring the outcome of maternal and fetal well-being in pregnancy.
Costs involved in monitoring and treating existing and potential problems in the long term.
Life style modifications and preventive treatment to be availed before conception.

IDENTIFYING HIGH RISK FACTORS

Monitoring is necessary for most pregnancies; however, the nature and frequency of tests used depends upon whether the pregnancy is low or high risks. Any problems which arise during pregnancy whether common problems like emesis gravidarum or more hazardous complications like preeclampsia, convey some added risk to the ongoing pregnancy. By reassessing these risk factors before pregnancy, during pregnancy and during parturation, it is possible to identify that segment of the high risk group which is bound to have morbidity and mortality.

To facilitate the identification of high risk pregnancies, prenatal records usually incorporate a list of details (cited in Table 7.2) to be checked at the first visit and systematically recorded. The aim of such prenatal records is to identify such high risk factors which may benefit from active intervention or referral to specialist of maternal fetal unit.

High Risk Factors

High risk factors are poor predictors, individually, of adverse outcome. Each factor has its own likelihood ratio; the higher its value, the stronger its association with an adverse outcome. However, if the adverse outcome is itself rare, then it further jeopardizes the value of the risk factor in predicting an adverse outcome. A case in point is that of the cervical length in pregnancy. A cervical length of less than 1.5 cms is associated with preterm delivery in less than 7 days with a likelihood ratio of 8.7. However, the predictive value in an unselected population (no history of preterm births) is as less as 11% as compared to the frequency of preterm delivery in a high risk population (previous history of preterm births) where the frequency of preterm labor reaches 35%.[12]

Medical High Risk

Table 7.3 tabulates the numerous medical diseases complicating pregnancy. These disorders individually or in combination complicate the outcome of pregnancy from maternal and fetal viewpoint. An increased surveillance for fetal and maternal well-being is mandated whenever such complicating factors are present. Each individual disorder may require a different set of surveillance protocol for a favourable outcome.

Obstetric High Risk

The major objective of obstetric practice has been the prevention of obstetric-maternal mortality. With advancements in managing the primary problems of maternal mortality like anaesthesia, blood transfusion, improved surgical techniques, the focus has now shifted to obtaining best possible fetal outcome. This has shifted the focus for the obstetrician from being a care provider not only for the mother but for the fetus, as a patient, too.

TABLE 7.2 Recommendations for Prenatal Care

	Recommended Timeframe
History	
Detailed medial history	Preconception or first visit
Detailed genetic family history	Preconception or first visit
Detailed surgical history	Preconception or first visit
Psychosocial and medical complaints	On every subsequent visit
Physical Examination	
General systemic examination	Preconception or first visit
Blood pressure	Every visit
Height	Every visit
Weight	Every visit
Pelvic examination	Preconception or fist visit. Especially in first trimester
Pelvimetry	At term, if necessary
Breast examination	Preconception and near term
Fundal height	At each visit after 14–16 weeks
Fetal position and heart rate	At each visit after 14–16 weeks
Cervical examination	As and when necessary
Laboratory Tests	
Haemoglobin, hematocrit	First visit and each trimester
Rh type with blood group	First visit
Antibody titre (Rh negative)	First visit and between 24 and 28 weeks
Syphilis test	First visit
HIV testing	First visit
Hepatitis B	First visit
Rubella titre (IgG)	Periconceptionally or first visit
Diabetic screen	First visit and between 24 and 28 weeks
Urine by dipstick for sugar and albumin	First visit and subsequent every visits
Urine culture	First visit
PAP smear	First visit
Thyroid screening	Periconceptionally or first visit

The identification of obstetrical high risk (Table 7.4) primarily focuses on the complications of previous and current pregnancies which are likely to affect fetal outcome and occasionally maternal outcome.

TABLE 7.3 Medical Conditions that can Cause Poor Outcomes, Classifying the Pregnant Mothers as High Risk Group

- Anaemia
- Chronic hypertension
- Diabetes Type I or II
- Chronic obstructive pulmonary disease
- Cardiac disorder, congenital or acquired
- Convulsion disorder
- Renal disorder
- Hepatic disorder
- Psychiatric illness
- Obesity and malnourishment
- Smoking, drugs and alcohol abuse
- Rh Alloimmunization
- Hepatitis B infection, Human immunodeficiency virus infection
- Syphilis, gonorrhea and chlamydia infection
- Connective tissue disorders, autoimmune disorder; thrombophilia
- Asymptomatic bacteriuria

TABLE 7.4 Obstetric High Risk Factors

- Extremes of maternal age of conception
- High parity status
- History of recurrent abortions
- History of previous preterm deliveries
- History of postpartum haemorrhage/obstetric shock
- History of frequent conceptions (less time gap)
- History of previous pelvic operative surgery (like myomectomy surgery)
- Prior cesarean delivery
- Prior history of uterine rupture/perforation
- History of instrumental deliver/difficult labour/obstructed labour
- History of cervical trauma/tear/avulsion
- History of fistula repair or IV degree perineal tear
- Congenital anomaly in uterus/cervix (including incompetent cervical os)
- History of previous pregnancy with preeclampsia or gestational diabetes mellitus
- History of prior still birth
- History of prior neonatal demise
- Prior fetus with chromosomal disorder or congenital anatomic abnormalities
- Prior birth of fetus with birth asphyxia/cerebral palsy/birth injuries
- History of puerperal sepsis

Identifying high risk factors during antenatal period leads to a unique opportunity to integrate new methods for their surveillance. These methods of surveillance, are, unfortunately, characterized by low positive and high negative predictive values. There are certain rarer associations in which detecting rarer pathological conditions (Table 7.5) affecting pregnancy and identifying them and subsequently implementing interventions to have a positive effect on maternal and neonatal outcome.

FETAL HIGH RISK EVALUATION

A variety of antenatal fetal tests are available, the use of many of them is controversial and their ability to detect fetal compromise is suspicious. As mentioned earlier, many tests have low sensitivity and poor predictive values for detecting fetal compromise.

When to start fetal surveillance? Most studies show efficiency of antepartum fetal surveillance techniques around near term or term pregnancies. Very few techniques have shown, in studies, to be effective before 32 weeks of gestation. Most of the tests evaluate or depend upon the maturity of the fetal CNS and its synchronicity with other systems, which would not have developed before 32 weeks. It is necessary to understand that testing an extremely preterm fetus can give rise to possible false-positive result. Results often require intervention in the form of terminating an intrauterine pregnancy. It is always difficult to balance between early delivery for fetal survival and the institutions capability to care for very preterm neonate.

Diagnosis specific/condition specific surveillance: It is essential to understand the underlying pathophysiology of a disease process. A knowledge of the underlying pathology of fetal compromise helps in choosing the most appropriate method of fetal surveillance technique.

Kontopoulos and Vintzileos[16] classified the pathophysiologic process (Table 7.6) that can cause fetal death or damage into following categories: decreased uteroplacental blood flow, decreased gas exchange at the trophoblastic membrane level, metabolic processes, fetal anaemia, fetal sepsis, fetal heart failure and umbilical cord accidents, and recommended the most useful tests in each situation. However, Ghidini and Poggi[17] have argued that several maternal and fetal conditions such as obesity, advanced maternal age, still birth, multiple gestation, cholestasis of pregnancy and discordant growth in twins do not fit in the set pathophysiologic process categories and hence questioning the condition-specific testing of all pregnancy complaints.

Clinical Assessment of Fetal Well-being

Correct assessment of duration of pregnancy is paramount in the assessment of fetal well-being. Human pregnancy has duration of 280 days, measured from the *last menstrual period* (LMP) till delivery. Gestational age is one of the most important criteria used for decision making in obstetrics. It is essential not only to know the exact gestational age but also the estimated fetal weight in order to take critical decisions, even in normal pregnancies. In high risk pregnancies, it makes a critical difference in the decision for intervention, especially in preterm conditions, when fetal maturity is not assured.

TABLE 7.5 Tests Done in Certain High Risk Pregnancies to Detect Rare Conditions

Screening/Diagnostic	Comment
Toxoplasmosis	Feline pets, unexplained fetal growth restriction prior to present pregnancy
Cytomegalovirus	Prior child with sensorineural hearing loss or mental retardation or chorioretinitis or microcephaly
Haemoglobin electrophoresis	Patients at risk for sickle cell trait, thalassemia or haemeglobinopathis (Sindhis, Kutchis, Parsis, etc.)
Tay–Sachs screening	Patients with Jewish ancestry
Cystic fibrosis	Recommended by ACOG
Thrombophilia screening	Patient with prior history of pulmonary embolism, history of thrombosis in a family member[13]
Culture for gonorrhea	For at-risk patients on initial visit and at 36 weeks of gestation
Culture for herpes	When woman has active herpetic like lesion, to confirm diagnosis
Culture for group B streptococci	Vaginal and rectal Group B streptococci (GBS) screening. Culture is recommended by CDC guidelines[14]
Bacterial vaginosis	Wet mount or pH at 12–14 weeks and again at 20–24 weeks; of value in certain high risk population
Integrated sonography (fetal nuchal translucency with nasal bone) and biochemical marker (beta-hCG and PAAP-A)	Performed between 11w and 13w 6d to detect trisomy 21, 13 and 18. In addition, positive test in absence of trisomies indicate risk for obstetric complications like preeclampsia, abruption, preterm labour and intrauterine growth retardation[15]

TABLE 7.6 Maternal/Fetal Conditions and their Underlying Pathophysiologic Conditions

Pathophysiologic Process	Maternal/Fetal Condition
Decreased uteroplacental flow	• Chronic hypertension • Preeclampsia • Collagen/renal/vascular disease • Most cases of fetal growth restriction (i.e. <32–34 weeks)
Decreased gas exchange	• Postdated pregnancy • Some fetal growth restriction (i.e. >32–34 weeks)
Metabolic aberrations	• Fetal hyperglycaemia • Fetal hyperinsulinemia
Fetal infection	• PROM • Intra amniotic infection • Maternal fever • Primary subclinical intra amniotic infection
Fetal anaemia	• Fetomaternal haemorrhage • Erythroblastosis fetalis • Parvovirus B19 infection
Fetal heart failure	• Cardiac arrhythmia • Nonimmune hydrops • Placental chorioangioma • Aneurysm of vein of Galen
Umbilical cord accidents	• Umbilical cord entanglement (monoamniotic twins) • Velamenatous cord insertion/Funic presentation • Noncoiled umbilical cord • Oligohydraminos

The single-most reliable clinical estimator of gestational age is an accurate LMP. By using reliable clinical information like regularity of cycle frequency, clinical information from early pregnancy like emesis, quickening one can come close to determining the gestational age. However, Naegeles' rule is dependant heavily on regularity of cycle with reliable dates.

The uterine size can be clinical estimated by *bimanual pelvic examination* during early pregnancy. The uterine size can also be measured by direct measurement over the abdomen from the pubic symphysis to the top of the uterine fundus. The fundal height measurement in centimeters using the over the curve technique can approximate the gestational age from 16–38 weeks within 3 cms. The zero mark of a nonelastic metric tape is placed at the uppermost border of the symphysis pubis of a patient in semi-recumbent position with a corrected longitudinally placed uterus. The tape is run over the woman's abdomen in the midline to the uppermost border of the uterine fundus. Clinical evaluation of uterine fundal height has its own pitfalls. The uterus may be elevated in early pregnancy in patient with a previous cesarean delivery, the height of the mother, due to the relative displacement of umbilicus, presence of multiple gestation or myomas.

Quickening, the first perceptible fetal movement felt by the mother usually occurs at a predictable time period. In primigravidae, it occurs around 19 weeks while in case of repeat pregnancies it tends to occur about 2 weeks earlier, probably due to more maternal experience.

Fetal heart sounds are heard with an unamplified fetoscope between 19 and 20 weeks. This requires observer experience, acuity and cannot be adopted universally. With the availability of electronic Doppler device, fetal heart sounds are audible as early as 11–12 weeks. Standards differ with each equipment used. However, when fetal heart tones are not heard at expected time it is necessary to look for wrong dates, fetal viability, multiple gestation or polyhydroamnios.

All clinical methods have inherent biological variability. It requires observers experience and acuity in order to arrive at a reliable date of confinement. None of the clinical surveillance method can predict the estimated confinement date beyond 90% certainty only with +/− 3 weeks.[18]

Maternal evaluation of fetal activity is a safe and reliable method in fetal surveillance. Most mothers, when taught properly, understand and follow methods to count and appreciate fetal movement. This is obviously inexpensive and has a more active participation from the pregnant female. Several methods have been used to monitor fetal activity in clinical practice. Sadovsky et al[19] have recommended that fetal movement chart be maintained by pregnant mothers for one hour for three times a day. A movement chart of less than three movements in that 1 hour, or if she appreciates no movements for 12 hours warrants further evaluation of fetal well-being. Person and Weaver[20] have advocated the Cardiff Count-to-Ten chart. They advocated that the presence of at least 10 movements in a 12-hours period is reliable indicator of fetal well-being. The pregnant mother is asked to start counting the movements in the morning and note the time taken for her to appreciate 10 fetal movements. If 10 movements are not completed by 12 hours or she takes longer time to appreciate 10 fetal movements, then she needs to contact her obstetrician.

A mother is able to appreciate 70–80% of all fetal activity. By the third trimester, the human fetus spends 10% of its time making gross fetal body movements and approximately 30 such movements are made each hour.[21] Whichever technique is used, the same must be explained to the patient carefully. Some patients are prone to get apprehensive in maintaining fetal activity chart. Various factors like anterior placentallocation, hydroamnios reduces the maternal appreciation of fetal activity. Anomalies of CNS, maternal obesity and barbiturates given to the mother may depress fetal movements. Fetal activity does not increase after meals or after maternal glucose administration.[22,23] In fact, hypoglycemia was associated with increased fetal movements.[24]

A review of current literature on maternal perception of fetal movement suggests that it is a good method of antepartum testing.[25] However, for fetal movement counting to reduce the rate of still births, diligence from the patient to accurately report diminished fetal movements and timely evaluation by the obstetrician is necessary. It would seem prudent to request that all pregnant patients, regardless of their risk status, monitor fetal activity starting at 28 weeks gestation.

Cardiotocography (CTG)

Cardiotocography is the continuous electronic record of fetal heart rate and uterine activity, which is obtained by two transducers placed on the abdomen of the mother, and having a simultaneous graphic representation of both on paper. Cardiotocography is the most widely used fetal surveillance technique utilized for assessing fetal well-being during the antenatal period.

In 1969, Hammacher[26] noted that "the fetus can be regarded as safe, especially if reflex movements are accompanied by an obvious increase in the amplitude of oscillations in the basal fetal heart rate." This forms the practical basis for the cardiotocography. Reflex movements would include spontaneous fetal activity, or activity induced from any stimulation. The hypothesis behind the use of CTG is that the integrity of the autonomic central nervous system (CNS) is a prerequisite for a healthy fetus, the CNS being responsible for controlling the fetal heart rate. The exact mechanism is unknown, but it is proposed that hypoxemia and acidemia induce an alteration of the brainstem centers, which are regulating the activity of the pacemaker cells of the heart, thereby altering the CTG trace.[27]

There are various factors which affect a CTG tracing. One needs to understand that while interpreting characteristics of fetal biophysical characters there is marked variance in the fetal neurological state. Four fetal states have been identified.[28,29] In the third trimester, the fetus spends approximately 20% of its time in quite sleep (state 1F) and 60–80% in an active sleep state (state 2F). Active sleep state is synonymous to rapid eye movement (REM). During the quite or non-REM sleep, the fetal heart rate slows and variability is reduced. There are no regular breathing movements and startled movements. This pattern of sleep may last for 20 minutes in a term fetus. The REM sleep, on the other hand, is associated with regular breathing movements and intermittent abrupt movements of head, limbs and trunks. The fetal heart shows increased variability and frequent accelerations with movements. This pattern lasts for about 40 minutes in a term fetus. These behavioral states are still not very well understood and changes upon a number of extrinsic factors like maternal activity, ingestion of drugs and nutrition. When evaluating the cardiotocography especially the nonstress test (NST) it is essential to ask oneself whether the fetus that is not making any movements or whose variability pattern is decreased is doing so due to neurological compromise or quite sleep state. In such situations, prolonging the period of evaluation usually allows the fetal sleep state to be converted and normal parameters to be visualized.

Types of cardiotocography examination:

- Nonstress test (NST)
- Contraction stress test (CST)
- Computerized CTG (cCTG)

Nonstress Test (NST)

The nonstress test is the most widely used and accepted method of antenatal fetal surveillance. It is usually performed on outpatient basis and is readily interpreted.

The nonstress test works on the hypothesis of intact neurologic coupling between the fetal CNS and fetal heart.[30] In late gestation, a healthy fetus usually exhibits on an average 34 accelerations above the baseline fetal heart rate, every hour. These accelerations average 20–25 bpm in amplitude and approximately 40 seconds in duration.[30] The presence of fetal hypoxia disrupts this pattern.

The absence of fetal heart rate acceleration is attributable often to quite fetal sleep state. A term fetus, usually has successive accelerations of heart rate every 40 minutes,[30] however, fetus may exhibit heart rate accelerations for up to 80 minutes and still be normal. CNS depressants such as narcotics and phenobarbital, as well as the B-blockers like propranolol can reduce heart activity.[31] In chronic smokers, due to increase in fetal carboxyhaemoglobin and a decrease in uterine blood flow, there is decreased fetal heart accelerations.[32]

Table 7.7 describes the procedure for performing a nonstress test.

The NST is to analysed taking into consideration the following variables:

- Baseline fetal heart rate (FHR)
- Variability of the FHR
- Presence or absence of accelerations
- Presence or absence of decelerations

The normal baseline FHR frequency is between 110 and 160 bpm. There may be tachycardia (more than 160 BPM)

TABLE 7.7 How to Perform the NST

Usually done as an outpatient care.
Time taken 20 minutes, rarely 40 minutes, in extended case.
No contraindication.
Patient may be seated in semi-Fowler's position or in a reclining chair.
Care taken to avoid supine hypotension syndrome, due to pressure on inferior vena cava by producing a left lateral tilt by placing a pillow /wedge below the right hip of the patient.
Patient's blood pressure is to be recorded before starting the test and every 10 minutes subsequently.
Place the Doppler ultrasound transducer to the maternal abdomen for measuring fetal heart rate. The tocodynamometer is also applied to detect uterine contractions.
Fetal activity may be recorded by the patient using on event marker switch or noted by the assistant performing the test.
A reactive test is considered when there are at least two accelerations of the fetal heart rate of 15 bpm amplitude and of 15 seconds duration observed over 20 minutes of monitoring.[33]
If no spontaneous fetal movement occurs in the initial 20 minutes of observation, the test is continued for another 20 minutes period of extended test. Manual stimulation of the fetus or increasing maternal glucose level has no evidentiary increase in fetal activity.[34,35,36]
If there is no acceleration, during a 40-minutes period, the test is considered nonreactive.

or bradycardia (less than 110 BPM) in this variable. Both tachycardia and bradycardia may occur due to changes in maternal heart rate or body temperature and even in fetal hypoxia. The fetal variability depends upon the fetal sympathetic and parasympathetic nervous system and is influenced by the gestational age, maternal medication fetal congenital anomalies, fetal acidosis and fetal tachycardia. The variability pattern is a very sensitive parameter; a nonreactive NST associated with decreased or absent variability is mostly due to fetal hypoxia. The absence of acceleration may be indicative of fetal sleep. The absence of deceleration in the NST is reassuring. The presence of spontaneous severe variable or late decelerations is problematic and may indicate fetal compromise. Variable decelerations may be seen often. If these are mild and nonrepetitive, then they do not suggest fetal compromise. However, repetitive variable decelerations, especially in the absence of fetal movements or uterine activity, suggest fetal compromise even if the FHR pattern is reactive.

The NST is most predictive when reactive. This predictive value is prevalent over a week. Overall a reactive NST is associated with a perinatal mortality of approximately 5 per 1000.[33,37] The perinatal mortality rate with a nonreactive NST is 30–40 per 1000, which is significantly higher, as this group includes those fetuses that are truly compromised. But the end point if considered to be perinatal asphyxia and death, a nonreactive NST has a considerable false-positive rate. Overall false-positive rate associated with nonreactive NST is approximately 75–90%,[33] and may be simply because of the fact that the fetal heart rate may not display reactivity over the 40-minute period.

Despite wide spread use, there is poor evidence that antenatal nonstress testing can reduce perinatal mortality.[38] Four blind randomized control trials (RCTs) evaluating nonstress test, although small, showed no difference in the primary outcome of perinatal mortality.[38] There is no evidence either, in the RCTs, that NST increases the number of Cesarean section. None of the studies included those from poor resource setting, hence making their conclusions inapplicable to those places. Despite the evidence of these RCTs, NSTs remain embedded in clinical practice. Its use is justified in women, with risk factors of adverse perinatal outcome. In most cases, a normal NST is predictive of good perinatal outcome for one week (providing maternal-fetal condition remains stable), except in women with insulin-dependent diabetes or with postdated pregnancy, in which case NSTs are recommended at least twice weekly.[39-41]

A vibrioacoustic stimulation (VAS) may be used in order to decrease the testing time taken for performing NST and reduce false-positive rate. A VAS changes the fetal behaviour state to a more active form. VAS usually is elicitated by an artificial larynx which produces sound at 82dB in air with a frequency of 80Hz.[42] A term fetus, when subjected to VAS test, changes its state and is associated with an immediate and sustained increase in long-term fetal heart rate variability, heart rate accelerations and gross fetal movements.[43] For performing VAS, the baseline fetal heart rate is observed for 5 minutes. If the pattern appears nonreactive, a stimulus of 3seconds is applied on the maternal abdomen near the fetal head. If the NST remains nonreactive, the stimulus may be repeated at 1 minute intervals up to three times. If there is no response to the stimulus then other methods of fetal surveillance like BPP or CST may be attempted. Using a VAS, studies have shown, there is a decrease in the incidence of nonreactive NST from 14% to 9%.[44,45] A reactive NST after VAS is as reliable as spontaneous reactivity in assessing fetal well-being. A VAS, in fact, decreases the incidence of nonreactive NST in particularly fetuses between the 26 and 28 weeks gestation, as the auditory brainstem response, on which VAS is based, is functional by that time.[46,47] There has been no long-term evidence of any neurological deficit in infants who had undergone VAS testing in utero.[48-50]

Contraction Stress Test (CST)

The contraction stress test (steps described in Table 7.8), also known as the oxytocin challenge test (OCT), is yet another test available for fetal surveillance in antenatal period, particularly testing for uteroplacental sufficiency. The basic hypothesis behind the use of this test is that the increased myometrial pressures following uterine contraction causes a decreased blood flow and oxygen exchange in the intervillous spaces of the placental circulation. Fetuses with inadequate placental reserve would demonstrate late decelerations in response to hypoxia. It helps to mimic the stress of labour.

Contraindication to CST:

- Premature rupture of membranes
- Cervical incompetence
- Multiple gestations
- Polyhydroamnios
- Placenta praevia
- Previous uterine surgeries like myomectomy or classical cesarean section

Martin and Schifrin[52] introduced the interpretation of CST in a 'ten minute window' period. A positive test would be the one in which any segment of 10 minute duration tracing shows three contractions, all showing late decelerations. A negative test would be the one in which no positive window is seen but there is at least one negative window, three contractions with no decelerations. Occasional late deceleration with at least one negative window is also a negative test. An equivocal CST is termed when there is occasional late deceleration with no negative window. A CST with both positive and negative windows is still termed as a positive CST.

TABLE 7.8 How to Perform the CST

CST has to be conducted in a labour or delivery suite.
The patient is placed in semi-Fowler's position at a 30–45° angle with a slight left tilt to avoid the supine hypotension syndrome.
The fetal heart rate is recorded by using Doppler ultrasound transducer, while the uterine contractions are monitored with the tocodynamometer.
Maternal blood pressure is recorded every 5–10 minutes.
Baseline fetal heart rate and uterine tone is to be recorded for a period of approximately 10–20 minutes.
Oxytocin is administered by an infusion pump at 0.5 mU/min. For an adequate CST, uterine contractions of moderate intensity lasting approximately 40–60 seconds with a frequency of three in 10 minutes, is required. This criterion is selected to approximate the stress experienced by the fetus during the first stage of labour.
Infusion rate may be doubled every 20 minutes until adequate uterine contractions have been achieved.[51] (Not more than 10 mU/ min is usually required.)
The time taken for the whole CST is around 1 ½–2 hours. At the completion of the test, the patient is observed till the uterine activity returns to baseline level. If activity persists then tocolysis may be given.

A negative CST is persistently associated with a good fetal outcome, enabling prolongation of a high risk pregnancy. If the CST is negative, a repeat study is usually scheduled in 1 week. Most studies have shown that the incidence of perinatal death within 1 week of negative CST is less than 1 per 1000.[53-55] Many of these deaths are attributed to acute fetal compromise like cord accidents, placental abruption and acute deterioration of glucose control in patients with diabetes, for which the CST is a poor predictor. A positive CST is associated with increased incidence of intra-uterine death, late decelerations in labour, low 5 minute apgarscores, IUGR and meconium-stained amniotic fluid.[55] Overall, the likelihood of perinatal death after a positive CST has ranged from 7 to 15%.[56]

The limitation of this test is the incidence of false positivity leading to unnecessary premature deliveries. The incidence of false-positive rate averages approximately 30%, especially before 33 weeks of gestation.[57] False-positive rates are unusually high due to misinterpretation of tracing, supine hypotension, uterine hyperstimulation or even an improvement in fetal condition postperforming a CST test. A suspicious or equivocal CST needs to be repeated after 24 hours as most will become negative. Today with the biophysical profile (BPP) giving as good or better accuracy, BPP has taken precedence.

A viable and faster alternative to the CST to produce uterine contractions is to use breast stimulation. Several methods[58,59] have been described to induce adequate uterine activity. The patient may first apply a warm moist towel to each breast for 5 minutes or gently stroke the nipple of one breast with the palmar surface of her fingers through her clothes for 2 minutes and then stops for 5 minutes. Intermittent rather than continuous nipple stimulation is the key to prevent hyperstimulation. The test averagely requires less time and makes do without oxytocin infusion. Interpretation of the results is like a routine contraction stress test. Breast stimulation has also been used for induction of labour. However, in a study where breast stimulation was used in high risk patients, there were fetal demises.[60] Hence when CST is performed, it needs to be done with continuous CTG monitoring right from the beginning of the test.

Computerized CTG (cCTG)

The CTG has shown a lot of variability in both inter- and intraobserver studies with suboptimal reliability. This leads to either unnecessary or to lack of intervention. In order to overcome this problem, the CTG information is analysed by a computer to satisfy the criteria of normality over a period of 60 minutes. These are called the Dawes–Redman Criteria.[61] Certain softwares like Sonicaid fetal care monitor, Sis porto software programme have been developed using these criteria.

The use of this is as yet not wide spread. More randomized control trials are needed to clarify its role.

Biophysical Profile (BPP)

Fetal assessment underwent a radical change with the introduction of real-time ultrasound. This modality enabled the physician to see in real time the dynamic fetal biophysical activities. The electronic monitoring of the fetal heart rate and the fetal biophysical activities are dependent upon the level of compromise in the fetus. A combination of both these tests provides a better predictive result than a single test. Further studies also revealed that a combination of tests for fetal breathing, movement, tone and quantity of amniotic fluid further enhanced the reliability of the prediction of fetal well-being.

Physiology

The fetal tone, movement, breathing and cardiac activity are regulated by the CNS which is very sensitive to hypoxia. These four variables are termed as the acute well-being variables. It is postulated that the biophysical activity appears earliest in fetal life is the last to disappear with the onset of fetal asphyxia. In early intrauterine life, the fetal tone centre appears in the cortex, beginning to function by 7–8 weeks of life. This is followed by fetal movements by 9 weeks of gestation. Fetal breathing movements become regular by 20–21 weeks, while fetal heart rate reactivity, controlled by hypothalamus and medulla, appears in the late second trimester. In presence of progressive hypoxemia, reactivity in the nonstress test and fetal breathing movements are the first biophysical profile to disappears, follows by cessation of fetal movements and finally fetal tone.[62,63] The amniotic fluid is predominantly sourced from fetal urine which is dependent upon renal perfusion. On prolonged hypoxemia, there is chemoreceptor-mediated centralization of fetal blood flow by differential channeling of blood to vital organs in the fetus (brain, heart, adrenals) at the expense of nonessential organs (lung, kidney). On prolonged or repeated hypoxemic episodes, there is persistently decreased blood flow to kidneys resulting to oligohydroamnios. Hence, decreased amniotic fluid volume is a consequence of fluid volume depletion of the fetus.[64]

Using this principle, Manning[65] developed the concept of BPP score (as in Table 7.9). The presence of a normal parameter was awarded 2 points; whereas the absence of that parameter was scored as 0. The highest score the fetus can receive is 10, the lowest is 0. The BPP can be used as early as 26–28 weeks gestation. The BPP may take as fast as 5 minutes if the fetus is in REM sleep (2F) state but can be as long as 25–30 minutes, if it is in quiet sleep (1F) stage.[66] The NST is done before the real-time ultrasound taking around 20 minutes for the same. Twice weekly testing is recommended in pregnancies complicated by FGR, diabetes mellitus, prolonged pregnancy, and hypertensive disorders of pregnancy.

A composite score of 8–10 is considered normal and correlates with the absence of fetal acidemia. A score of 6 is equivocal, and the test should be repeated after 24 hrs. However, an equivocal score with the amniotic fluid parameter being zero warrants delivery or a close fetal surveillance. A BPP score of 4 or less warrants delivery, depending upon the gestational age.

A normal BPP score is highly reassuring with a still birth rate of 0.8 per 1000 within one weeks of the test.[68] The positive predictive value for BPP for evidence of fetal compromise is approx. 50%, and a negative predictive value is of 99.9%. The fetal death rates are increased 14 fold in the absence of fetal movements, and 18 fold if fetal breathing movements are absent.[69] The BPP score correlates directly with the fetal acid-base balance; it has been shown in studies to correlate with the fetal blood pH obtained with cordocentesis.[70] Vibrioacoustic stimulation (VAS) utilized during BPP testing has been shown to improve an abnormal or equivocal BPP score in 82% cases without increasing false-negative testing.[71]

Modified Biophysical Profile

A more practical testing scheme is using the non stress test (NST) and the amniotic fluid index (AFI). The use of NST, an indicator of present fetal condition and, AFI, a marker of long-term fetal status; cuts down the time required to do a complete BPP. In this profile, an AFI greater than 5 cm is usually considered as normal, even though different criterias have been applied.[72] The assessment of NST and amniotic fluid volume appears to be as reliable as the BPP in predicting long-term fetal well-being. Overall the modified BPP had a false positive rate comparable to the NST but higher than CST and a full BPP. The low false-negative rate and ease of performance of modified BPP make it an excellent approach for evaluation of large number of high risk patients especially since CST is time consuming and has its own contraindications to perform in routine clinical practice.[73,74]

Ultrasonographic Evaluation

Over the past three decades, ultrasound has become a routine part of obstetric care. Its significance in particular for a high risk pregnancy is of paramount importance.

TABLE 7.9 Biophysical Profile[67]

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

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

Determination of Gestation Age by Ultrasonography

Determination of correct gestational age is essential in making correct management decisions especially in case of preterm labour, postdated pregnancy and preeclampsia. Without the knowledge of expected due date, it would be very difficult to diagnose growth restriction. Hence, it has become a norm to perform at least one ultrasonography in early gestation, preferably in first trimester in order to get an accurate gestational age.

The measurement of the gestational sac have been used but there is no assurance that a viable pregnancy is present. The most accurate ultrasound dating method available today is the crown-rump length. It can be best obtained trasvaginally, identifying the longest axis of the fetus. Roughly adding 6.5 to the centimeter measurement will give the gestational age in weeks. This will predict the expected delivery date to within 5-6 days over 90% of the times. The biparietal diameter (BPD) is the oldest and most widely used for assessing fetal gestational age starting from the 12 weeks gestation. Other parameters which are routinely used in measurement include the abdominal circumference, head circumference and fetal femur length measurement. The mean ultrasound ageing of the fetus includes all the above parameters. As the pregnancy progresses, the variability in fetal size grows, and ultrasound prediction of gestational age becomes progressively less accurate.[75] The composite gestational age assessment had a variability of 1.5 weeks at 24–30 weeks and 2–3 weeks beyond 30 weeks.[75]

In pregnancies, in which menstrual dates are unsure or unreliable as in recent use of hormonal contraception, scanty bleeding at time of LMP or lactation alamenorrhoeic conception, dates derived from ultrasound biometry are always preferred. There is growing evidence that ultrasound performed before 22 weeks could be used in preference to even "certain" menstrual dates.[76] Delayed ovulation or incorrect LMP is more common than an early onset severe growth disorder, hence, its reliability when done early. However, in third trimester, growth restriction being more common, reliability of ultrasound fetal biometry is poor.

Ultrasound in Detecting Chromosomal and Other Targeted Anomalies

Chromosomal anomalies are one of the common causes of perinatal morbidity and mortality, occurring in 0.1–0.2% of all live births.[77] The definitive tools for diagnosing chromosomal anomalies are chorionic villus sampling and amniocentesis; however, due to the inherent invasive nature of the procedure and the possibility of fetal loss, ultrasound and biochemical markers are used commonly in clinical practice to identify fetuses at such risk.

The most commonly encountered chromosomal anomalies are Trisomy 21, Trisomy 18, Trisomy 13 and Turners' syndrome. The ultrasonographic examination is essential to identify series of specific abnormalities which are associated with these chromosomal anomalies. Trisomy 21 is associated with brachycephaly, mild ventriculomegaly, flattening of face, nuchal edema, atrioventricular septal defect, duodenal atresia and echogenic bowel, mild phalanx hypoplasia of the fifth finger. The Trisomy 18 defect is associated with strawberry shaped head, choroid plexus cyst, absent corpus callosum, enlarged cisterna magna, facial cleft, micrognathia, nuchal oedema, heart defects, diaphragmatic hernia, esophageal hernia, exomphalos, myelomeningocele and others.

The presence of increasing number of defects increases the risk of chromosomal defects.[78,79] The ultrasonographic evaluation of mid trimester pregnancy requires a thorough check in the presence of a defect marker. Fetal karyotyping is an invasive and risky procedure. If the defect is lethal or associated with severe handicap then it is justified to search for a possible cause and its possibility of recurrence especially by fetal karyotyping. So also, the potentially correctable anomalies by surgery like cleft lip, cardiac defects, diaphragmatic hernia and others is logical to exclude chromosomal anomalies.

Minor defects or soft markers are not actual markers but are sonography findings that are associated with chromosomal abnormalities frequently. Soft markers can be either minimally increased measurement of fetal organs (i.e. increased nuchal translucency, ventriculomegaly pyelectasis) or can be normal variants without much pathological significance (e.g. choroid plexus cyst, echogenic foci of heart, echogenic bowel); routine fetal karyotyping is unjustified in all cases. Each individual case risk may be determined by assessing the background risks like maternal age, gestational age, previously affected pregnancies and in certain cases previous screening of nuchal translucency and/or biochemistry in the current pregnancy.

Benaceraf et al.[80] have developed a method of calculation of risk based on the scoring index. The major defect and markers like nuchal translucency, nuchal oedema carry a score of two (2), while other markers like mild pylectasis, echogenic cardiac focus and others would carry a score of one (1). In any women, with score of two or more (>2) would be a candidate for definitive diagnosis by fetal tissue sampling.[80]

Assessing Fetal Growth

Determining fetal growth over time is an important aspect of fetal monitoring performed by ultrasonography. Intrauterine growth restriction (IUGR) affects nearly 5–10% of pregnancies and is associated with adverse fetal outcome including prenatal mortality. An IUGR is recognized as an estimated fetal weight that is below the 10th percentile for the corrected sex and ethnicity of the fetus. However, poor perinatal outcomes are usually seen in fetuses below the 5th or 3rd percentile. A constitutionally small for gestation age

(SGA) fetus needs to be differentiated from a pathologically growth restricted fetus. The challenge lies in identifying these fetuses which are pathologically small, either of early onset (symmetrical IUGR) or of late onset (asymmetrical IUGR). Ultrasonographic examination helps to do that. This is further explained and discussed in the chapter on intrauterine growth restriction.

Fetal Echocardiography

Nearly 8 of 1000 live births have some form of congenital heart disease. Nearly half are not identifiable antenatally as they are insignificant and do not cause any haemodynamic instability. The remainder, however, are significant defects wherein prenatal diagnosis and monitoring can help to have better parental counseling, planned delivery and early neonatal care.

Nearly one-third of the cases of major heart disease can be picked up by a screening antenatal ultrasound in the second trimester.[81] These then can be referred for full fetal echocardiography. A full fetal cardiograph is a time consuming and expensive diagnostic test which can be justified in patients with prior affected children, who have a recurrence risk of 2–3%. Some of the indications for fetal echocardiography are mentioned in Table 7.10.

Full fetal echocardiography includes all the views in the fetal heart as obtained in a postnatal echocardiography and can be done by a specialist trained for the same. Additionally spectral, colour Doppler and M-mode data can be obtained, as indicated. The fetus needs to be closely monitored by ultrasound till delivery. Both structural and function relation of the fetal heart may evolve throughout the pregnancy. It is particularly important to evaluate the areas of potential obstructions and the relationship of the great arteries to the ventricles.

TABLE 7.10 Indications of Fetal Echocardiography

Familial risk
Previously affected sibling
Paternal
Fetal risk factors
Chromosomal anomalies
Nonimmune hydrops
Fetal cardiac arrhythmia
Cardiac lesions suspected on routine ultrasound scan
Maternal factors
Congenital heart disease
Exposure to teratogens like lithium, alcohol, phenytoin sodium, carbamazepine
Pregestational diabetes mellitus
Phenylketonuria

Doppler Velocimetry

The Doppler ultrasound is based on the Doppler effect, a physical phenomenon which is valid for various types of wave energies. When applied the ultrasonic waves are transmitted by a piezoelectric crystal (the transducer) into the tissue at a given frequency, when it is reflected by the moving blood cells within a vessel; the returning ultrasound is received with different frequency. This change in the ultrasound frequency is called the Doppler shift. The blood velocity can be calculated from the Doppler shift if the angle between the ultrasound beam and the blood flow within the vessels in known. The pulsed wave Doppler velocimetry provides information about three aspects of blood flow—(*i*) velocity, (*ii*) resistance to blood flow through a particular vessel and (*iii*) volume of blood flow.

The Doppler velocimetry measurements are taken of specific blood vessels. The interpretation of the same differs with the fetal haemodynamics. The uterine artery (UA) Doppler provides the index of resistance to flow in the fetal side of the placenta. An elevated UA systolic/diastolic (S/D) ratio initiates a compensatory haemodynamic response, known as centralization of the flow, which is assessed by the Doppler assessment of the middle cerebral artery (MCA). The pulsatility index or PI (systolic-diastolic/mean) and resistance index or RI (systolic-diastolic/systolic) are other indices which are used to measure the resistance to the blood flow in the vessel to be examined. Ratios are independent to the angle of insonation. The progressive fetal compromise secondary to placental insufficiency is as follows:

1. Increased UA resistance without centralization of blood flow.
2. Increased UA resistance with centralization of blood flow (Brain sparing effect).
3. Absent umbilical artery diastolic flow.
4. Reversed umbilical artery diastolic flow.
5. Alteration in the venous circulation.

The Doppler velocimetry is essential in obstetrics for the following conditions.

1. Intrauterine growth restriction (IUGR)
2. Rhesus alloimmunization
3. Monitoring fetuses on indomethacin therapy for tocolysis or polyhydramnios
4. Cardiac abnormalities

Intrauterine Growth Restriction

Doppler velocimetry makes it possible to follow haemodynamics both in the uteroplacental circulation and the fetal umbilical circulation. In most of the cases of growth restriction, the cause is placental. There is some kind of defective placentation with inadequate invasion of trophoblasts in spiral arteries. Fetuses in hypoxic situation adapt their

circulation in an attempt to utilize the available oxygen to preferential organs like brain, myocardium and adrenals. The auto-regulation of cerebral circulation leads to vasodilatation and increased cerebral flow, also called 'brain sparing' effect.

The most important use of the Doppler velocimetry is differentiating between genetically small but essentially normal healthy fetus and the one which is growth restricted usually due to some placental pathology. Doppler examination of the umbilical and maternal uterine vessels, especially repeatedly, guides the clinician in deciding further management. The timing for delivery at an appropriate time is often the only available therapy for pathological growth restriction, which may be facilitated by Doppler examination.

The Doppler evaluation in obstetrics involves assessment of various vessels of the fetus. Each has its own significance and varies in different high risk situations. In case of preeclampsia, the uterine artery velocimetry had a better predictive value than the umbilical artery, with the exception of cases which had growth restricted fetuses.[82] It is recommended to incorporate uterine artery and umbilical artery surveillance of pregnant women with diabetes with complications of vascular disease, IUGR or hypertension.[83]

Rhesus Alloimmunization

In rhesus alloimmunization, sensitization of mother's immune system to fetal RBC antigen leads to an amnestic response in subsequent pregnancies if the same antigen is present on the fetal RBC. This leads to a series of events including fetal anaemia and immune hydrops. The degree of fetal anaemia and the need for fetal transfusion, involved either amniocentesis for determining amniotic fluid OD450 for assessing degree of haemolysis or direct umbilical fetal blood haemoglobin estimation.

However, the pathophysiological reduction in the viscosity of the fetal blood resulted in an increase in the velocity of the blood flow which can be detected by the pulsed wave Doppler velocimetry. The middle cerebral artery (MCA) waveform is useful in this determination. When the MCA peak systolic velocity rises, there is a high risk of moderate to severe anaemia in the fetus. The cut-off of 1.55 MoM has a very high sensitivity for moderate to severe anaemia.[84] The charts for assessing peak systolic velocity in the MCA across gestation to detect fetal anaemia are available.

Monitoring Fetuses on Indomethacin Therapy for Tocolysis or Polyhydramnios

The use of prostaglandin synthetase inhibitors like indomenthacin for tocolysis or polyhydramnios is done in certain situations. This can result in the premature closure of ductus arteriosus and oligohydramnios. A ductus arteriosus effect is not typically seen within the first 48 hrs of treatment. Assessment of the velocity within the ductus arteriosus should be performed beyond that time, it the prostaglandin synthetase inhibitor needs to be continued. Constriction in the blood flow across the ductus arteriosus should warrant immediate stoppage of the drug.

Fetal Cardiac Abnormalities

Fetuses with cardiac abnormalities including structural or congenital heart disease, arrhythmias and congestive cardiac failures may have abnormalities that can be detected with Doppler. The blood flow velocity values and patterns have been described for different systemic vessels. Any fetal structural cardiac abnormality or precordial or postcordial vascular abnormality can affect the blood flow velocity and waveform of the vessels and valves. The Doppler waveform thus helps in diagnosing, monitoring this progression and helps in deciding postnatal management strategies antenatally.

Chorionic Villus Sampling and Amniocentesis

Although they are described in detail elsewhere in the book, a short description is presented here. The indications for invasive testing include the following:

- Advanced maternal age (more than 35 years)
- Positive serum screening testing
- Birth of previous child with chromosomal anomalies
- Pregnancy at risk for Mendelian disorder
- A parent with a balanced chromosome rearrangement

Chorionic Villus Sampling (CVS)

Either by transcervical or transabdominal approach, under ultrasound guidance, the first trimesters' developing chorionfrondosum is aspirated and the retrieved chorionic villus are either cultured or directly analyzed to identify fetal cytogenetic, biochemical or molecular disorders. The procedure is done between 10 weeks and 13 weeks 6 days gestation.

Technique: The transabdominal method, is more common, uses a 20 gauge spinal needle inserted directly in the chorionic frondosum. Once in place, a 20 ml syringe containing 5 ml of media is attached 'to and fro' aspirations from the chorionic frondosum are necessary.

In the transcervical approach, patient is in lithotomy position and vagina is prepped with a povidone-iodine solution. Bladder is partially filled for adequate visualization of uterus and cervix. A specially designed polyethylene catheter with a malleable stainless steel stylet having a blunt rounded tip is used for sampling. It is usually 27 cms long. Under ultrasound guidance the catheter is passed along the internal os in the chorion frondosum parallel to the chorionic membrane taking care to avoid piercing the membrane or going deep in the decidua basalis, which would cause bleeding. The catheter goes smoothly when in the right plane through a sufficient length of chorionic frondosum. The stylet is removed, a 20 ml syringe containing 5 ml

tissue culture media is attached and suction applied as catheter is withdrawn.

The patient is made aware of postprocedure bleeding or spotting. Rhesus negative women are given Rh immunoglobulin. Patient is asked to report if there is any leakage of amniotic fluid, fever, chills or foul discharge per vaginum within 2 weeks.

The most common complication is spotting or a small amount of vaginal bleeding occurring more frequently with transcervical approach than transabdominal approach. Other serious complications include acute rupture of membranes and chorioamnionitis. These complications are rare and adequate care may be taken by having continuous ultrasound guidance during procedure and giving prophylactic antibiotic.

The risk of miscarriage between transcervical approach and transabdominal approach is nearly the same in experienced hands. The risk of miscarriage is around 1 in 200 to 1 in 300 at good centers. For fetal safety, procedure of CVS is delayed until 70 or more days post-LMP. Oromandibular and limb hypogenesis is uniquely associated with performing CVS before this period.

CVS results reflect those of the fetus in approximately 98% of cases. Discrepancy may rarely occur with contamination of the sample with maternal decidual tissue. Rarely, discrepancy is caused due to confined placental mosaicism.

Amniocentesis

The genetic amniocentesis is ideally done between 17 and 20 weeks gestation. Performing the procedure before 18 weeks usually leaves enough time to complete cell cultures and evaluate laboratory tests, as in some countries the legal gestational age for termination of pregnancy is below 20 weeks.

Technique: Performed using a 22 gauge spinal needle, under ultrasound guidance. The needle is inserted over the prepped abdomen. Care is taken to avoid the placenta and fetal parts. Stylet is removed and amniotic fluid is aspirated. Initial some ml may be discarded as it may contain maternal cells. Approximately 20 ml is aspirated. In case of twins' gestation, indigo carmine solution is injected into the sac after the fluid specimen to act as a marker. The fluid is stored into sterile tubes and stored at room temperature. Demonstration of fetal heart post procedure is reassuring for the mother. In Rh negative women, Rh immunoglobulin is given. The risk of miscarriage is nearly the same as in CVS; however, in the hand of experienced clinician, the loss rate is closer to 1 in 1000.

Amniocentesis may be indicated in the third trimester. The technique for aspiration does not differ but certain other risks increase during the procedure. Certain indications for third trimester amniocentesis in high risk pregnancies are as follows.

1. To confirm fetal pulmonary maturity by doing lecithin: sphingomyelin ratio or phosphotidylglycerol presence in amniotic fluid, surfactant:albumin ratio, foam stability index (shake bubble test), lamellar body counts and amniotic fluid density.
2. Evaluation of fetal infection which may be the cause for growth restriction.
3. Bilirubin levels in amniotic fluid for Rh isoimmunized pregnancy.
4. Genetic karyotyping for evaluating the fetus which may have a detected anatomical anomaly in the third trimester or unexplained growth restriction or fetal amniotic fluid volume abnormalities.

The third trimester amniocentesis presents its own set of problems. Braxton Hicks contractions or premature labour pains may cause displacement of the initially placed needle. There is a theoretical risk, if any, of premature rupture of membranes and infection. It is relatively contraindicated to perform the procedure especially in the setting of maternal HIV infection and other infections like hepatitis B, hepatitis C and cytomegalovirus (CMV), wherein the risk of fetal transmission exists. Care has to be taken to prevent transplacental passage of the needle because of the increased risk of fetomaternal haemorrhage.

Fetal Blood Sampling (FBS)

Traditionally, fetal blood sampling is indicative for rapid karyotyping of the fetus. It is necessary when the results are required within a few days, such as when the time limit for legal termination is near (20 weeks in India) or when delivery is imminent. There are certain situations wherein fetal blood sampling is desirable as in multiple anatomical anomalies, wherein chromosomal anomalies may be detected in as high as 29% of cases or in true mosaicism at amniocentesis, for confirmation of fetal involvement.

Fetal blood sampling has a limited role to play in diagnosing congenital fetal infections as amniocentesis has primary superseded, its use following technological advances like polymerase chain reaction (PCR) for isolation of the infectious agent in the amniotic fluid itself. Prenatal diagnosis of rarer conditions like factors V, VII and XIII may still need FBS.

Fetal blood sampling technique has a very specific role in fetal therapy for condition like fetal platelet transfusion in maternal conditions of alloimmune thrombocytopenia or idiopathic thrombocytopenic purpura. A more conventional therapy practiced frequently is fetal blood transfusion in isoimmunized pregnancy with fetal anaemia.

The procedure for fetal blood sampling or cordocentesis is usually performed after 20 weeks of gestation. A fixed segment of the cord is preferred near the insertion of the umbilical cord at the placenta. The umbilical vein is accessed using a 20-22-gauge spinal needle with a little

longer length needle (approx. 15.0 cms). Prophylactic antibiotics and antenatal corticosteroids may be used in relevant situations. A real-time ultrasound machine with possible template software to guide the needle tract is helpful. The needle is withdrawn after sampling and the punctured site is observed for bleeding. In case of fetal therapy like transfusion, the fetal heart rate is monitored intermittently.

Maternal complications related to the procedure are unusual. Bleeding from puncture site is common, in up to 50% of cases.[85] Cord hematoma, fetal bradycardia and fetal demise may ensure. The overall pregnancy loss rate is 1.4% before 28 weeks and another 1.4% after 28 weeks.[86] The most important factor being operator experience and indication for procedure.

RECENT ADVANCES IN FETAL SURVEILLANCE

Genetic screening of the fetus can now be done by using cell free fetal DNA (cfDNA) and can be performed as early as 9 weeks of gestation. This can be used for performing screening test for trisomies 21, 18 and 13 in high risk population. The test requires only maternal blood, carries no risk of miscarriage and permits earlier detection. It has a sensitivity exceeding 98%, specifically of 99.5%.[87] The tests still need standardizing, and its positive predictive value is yet to be evaluated. The test may stand to provide information regarding disorders involving chromosomal abnormalities other than trisomies. It would also have potential to be misused for determining the sex of the fetus at a very early stage.

The fetal heart is being monitored by yet another non-invasive method. It provides the fetal electrocardiography (f ECG) of good quality. It is called as the fetal magneto-cardiography (f MCG) which allows instantaneous fetal heart rate monitoring and also analysis of fetal ECG morphology. The fetal magnetoencephalogram (f MEG) is also a promising technique for assessing fetal brain functions such as response to fetal sound and light stimulation. Tissue oxygenation can be monitored based on the haemoglobin and oxyhaemoglobin contents measured by near infrared spectroscopy.

Recent advances in f ECG have made it possible to reject confounding maternal signals. The recent devices use complex algorithms to correctly identify signals related to fetal heart rate using sensitive ECG-style electrodes. The newer device is belt-less and no wires to connect to display or printer. Some technologically advanced versions are studying the use of wireless technologies for transfer of data. There is no need for constant repositioning of transducers and the mother is free to walk around. These at present are not widely accepted.

INDIAN PERSPECTIVE

Most perinatal deaths occur in low-income and middle-income countries. India accounts for nearly one million of early neonatal demises, about one-fourth of the total global burden.[88]

There has been a steady decline in the neonatal morality rate in India. The latest infant mortality rate as per the sample registration survey of 2011 is 44 per 1000 live births. The same was 50 in 2009 and 47 in 2010. Policy makers have always stressed on safe motherhood and child survival, but have so far ignored the concept of perinatal demise, especially still births account for nearly half of all the perinatal demises.[89] Situationally, the Indian scenario is dismal.[90]

- Nearly 45% of all neonatal demises occur within first 7 days of life.
- Total neonatal deaths (0–28 days of life) account for nearly half (52%) of all under 5 deaths.
- Nearly 30% of all live births have birth weight less than 2.5 kg, that is nearly 8.1 million newborns have higher risk of mortality due to low births weight.
- The states of Uttar Pradesh, Madhya Pradesh, Bihar and Rajasthan have higher newborn deaths.
- Neonatal deaths are nearly 122% higher in the poorest population and 49% higher in rural population than the urban areas.

Major factors responsible for high perinatal demises in India are:

- Poor nutrition and anaemia among adolescent girls and women.
- Low coverage and quality of antenatal and postnatal care.
- Young age of mother at pregnancy (<20 years).
- Close spacing of births.
- High proportion of unsupervised home deliveries and poor quality of institutional deliveries.
- High proportion of low birth weight of newborns.
- Delay in seeking health care for newborns.

The Government of India has undertaken through the National Rural Health Mission (NRHM), 2005, certain concrete steps in order to improve the maternal and perinatal survival. Some of the highlights under this programme are:

- Promotion of institutional deliveries through a case-based incentive programme called the *Janani Suraksha Yojana* (maternity security scheme).
- Capacity building of health care providers in basic and comprehensive obstetric care, integrated management of neonatal and childhood illnesses and *Navjaat Shishu Suraksha Karyakram* (newborn protection programme).

- Operationalization of subcentres, primary health centers, community health centers and district hospitals for providing 24×7 basic and comprehensive obstetric care and child care services.
- Special emphasis on newborn care by setting up newborn care corners in all health facilities, special newborn care units at district hospital and newborn stabilization units at the first referral units.
- Iron and folic acid supplementation daily for pregnant and lactating women, and weekly for adolescent girls.
- Village health and nutrition days in rural areas as an outreach activity, for provision of maternal and child health services.
- Home-based newborn care through accredited social health activists (ASHAs) to improve newborn care practices at the community level and for early detection and referral of sick newborn babies.
- Name-based web-enabled tracking of pregnant women and children has been introduced to ensure antenatal, intranatal and postnatal care of pregnant women and care to newborns, infants and children.
- Introduction of mother and child protection card in collaboration with Ministry of Women and Child Development to monitor service delivery of mothers and children.

The rural and urban divide is very evident in India. Antenatal surveillance and early neonatal care is by far very sophisticated and at par with developing countries in urban India. The same is not true for rural area. There is a need to develop awareness in the general public about the importance of maternal and fetal health. At the same time, appropriate resource allocation, utilization and accountability needs to be enhanced so that the culmination of healthy parturient with a healthy child becomes a reality for rural India.

Important Points

- Declining infant mortality rate has shifted the focus on perinatal outcome as a yardstick for good obstetric and neonatal care.
- Detailed preconception evaluation with general and systemic examination is essential in identifying potential risk factors which are likely to have an adverse outcome on pregnancy. It also helps in identifying corrective measures which can be undertaken in order to prevent or minimize the possible complication factors.
- All pregnancies require some amount of surveillance; a high risk pregnancy may require a frequent, detailed or a special surveillance.
- The underlying disease physiopathology should form the basis for studying and monitoring a particular risk factor for the fetus.
- The tests employed for surveillance have often not been subjected to randomized and prospective evaluation. In most cases, these tests are used as a result of good observational outcome.
- Clinically, assessment of fetal well-being is done with confirmation of gestational age with help of menstrual period, pelvic examination, assessing fetal heart sounds and maternal appreciation of fetal activity.
- The continuous electronic fetal heart rate monitoring, cardiotocography forms the very basis of all the fetal surveillance available. Various forms like nonstress test, contraction stress test and vibrioacoustic test have their own merits and demerits.
- The biophysical profile provides for an alternative, short time evaluation of fetal cardiac and neurological well-being without the problems related to the contraction stress test.
- The ultrasonographic evaluation of the fetus is essential in today obstetrics not only for accurate dating of fetus, identifying anatomical defects but also studying fetal physiology including uteroplacental circulation by using Doppler velocimetry.
- Invasive procedures like chorionic villus sampling, amniocentesis and fetal blood sampling have specific use in already diagnosed problematic situations like chromosomal anomalies or anatomical fetal defects.

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Chapter 8

Preterm Birth

Lilian Alabi-Isama and Austin Ugwumadu

Chapter Outline

INTRODUCTION

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide. A better understanding of the pathophysiology of preterm prelabour rupture of membranes and spontaneous preterm birth has improved our ability to identify those women at increased risk. There is increasing evidence that cervical insufficiency and infections may play a major role in the pathogenesis of spontaneous preterm birth. Predictors of preterm birth including patient demographics, cervical length measurements, fetal fibronectin test and microbiological screening improve diagnosis, allows early intervention and hence, a reduction in its health and economic burden. In this chapter, the authors will describe the implication and aetiology of preterm birth, the role of cervical insufficiency, pPROM and infection in its aetiology, its prediction with ultrasound scan and other adjunct tests, and available interventions to reduce preterm birth.

Preterm birth (PTB) may be defined as birth between the age of viability and 37 completed weeks of gestation.[1] In the United Kingdom, PTB includes deliveries between 24^{+0} and 36^{+6} weeks gestation, and many developed and developing countries officially records all births with birth weight above 500 g. The incidence of preterm birth range from 5% to 8% in most developed and developing countries, but it is still increasing worldwide[2] attributed to the rise in multiple gestations from assisted reproductive techniques, better dating scans and iatrogenic deliveries. Preterm birth may follow preterm labour with intact membranes, 40% of cases, or preterm prelabour rupture of membranes, 30% and iatrogenic, 30%.

IMPLICATIONS OF PRETERM BIRTH

Preterm birth is the leading cause of neonatal morbidity and mortality worldwide and accounts for 75% of neonatal deaths and 50% of long-term morbidity, including respiratory disease and neurodevelopmental impairment.[3] The risk of morbidity and mortality are inversely related to the gestational age at birth. The EPICure study in the United Kingdom and Ireland[4] assessed survival trends and health outcomes in infants born $\leq$26 completed weeks ($20–25^{+6}$) over a period of 10 months in 1995. The study showed increased survival and reduced rate of severe disability with each additional week of intrauterine gestation. It also reported that 50% of survivors at 23–25 weeks gestation were impaired, half with severe disability. The Epipage study also recruited babies born in nine French regions during 1997 and the Trent health region study also produced similar results on rates of survival and discharge.[5,6] The EPICure 2 study collected data on all babies born in England in 2006 between 22 and 26^{+6} weeks gestation.[7] They found improved survival of these babies by 13% (40–53%) and more so at 24 and 25 weeks. They also found the care provided to these mothers and babies have improved but unfortunately,

despite these new advances, the number of babies discharged from hospital with disabilities such as abnormal brain scans, lung, bowel and eye problems are very similar to the findings of EPICure in 1995. Preterm birth carries significant social and economic burden which is estimated to cost the public sector £2.9 billion a year.[8] The cost of preterm birth estimated by Khan and coworkers was £15,688 for up to 34 weeks and £12,104 for up to 37 weeks.[9] It is therefore important that asymptomatic high-risk women and symptomatic women in threatened preterm labour are identified early to allow preventive interventions and management strategies, to reduce the incidence of perinatal morbidity and mortality.

AETIOLOGY OF PRETERM BIRTH

Cervical Insufficiency

The cervix is a unique and complex structure with a central role in maintaining the growing and developing embryo in the uterus until term. It achieves this objective by remaining closed and non-compliant until the onset of labour at term. The cervix is therefore likely to play a significant role in the aetiology, prevention and treatment of preterm labour (PTL). In the non-pregnant state, the cervix consists of an extracellular connective tissue matrix made up of collagen, elastin, proteoglycans, a thin layer of smooth muscle and fibroblasts, which penetrate the connective tissue matrix. During pregnancy, the cervix increases in mass, water content and vascularity with a progressive reduction in collagen content as pregnancy advances leading to cervical softening. If these changes occurred in early pregnancy, an 'insufficient cervix' would result. *Cervical insufficiency* is defined as painless cervical effacement and dilation resulting in second trimester pregnancy loss or preterm delivery.[10] This occurs in up to 2% of all pregnancies, but responsible for only 8–9% of all preterm births compared to 40–50% from spontaneous preterm labour and 20–30% from preterm prelabour rupture of membranes (PPROM).[11,12] It has many causes which include:

- **Previous history:** Several studies have investigated the relationship between a history of prior preterm labour and short cervical length**.** Iams and coworkers reported a strong correlation between cervical length in the index pregnancy and previous obstetrics history in a study including women with a history of cervical insufficiency (32 women), previous preterm delivery <26 weeks (98 women), 27–32 weeks (98 women), 33–35 weeks (127 women) and a control group of women with previous term delivery (106 women).[13] The gestational age at the first preterm delivery was significantly correlated with cervical length in the index pregnancy at each gestational interval between 20 and 30 weeks in a continuous manner.[13] Guzman and coworkers also found a strong relationship between previous obstetric history and cervical length in the subsequent pregnancy.[14] Similarly, Andrews and coworkers found that women with a history of spontaneous second-trimester miscarriage and preterm delivery due to cervical insufficiency had an increased risk of recurrence in a subsequent pregnancy.[15-17]
- **Congenital abnormalities:** Female offspring's of women who took diethylstilboestrol (DES) until the early 1970s were at increased risk of uterine anomalies with approximately 30% of these affecting the cervix.[18]
- **Cervical surgery:** Pregnant women with a history of cone biopsy, large loop excision of transformation zone (LLETZ), or laser ablation of the cervix are at increased risk of preterm birth. A recent meta-analysis showed that cone biopsy and LLETZ increased the risk of preterm delivery.[19] The risk was greater if the depth of excision was >10 mm compared to excision depths of <10 mm.[20] Laser vaporization, cryotherapy and punch biopsy have not been shown to be associated with preterm birth.[21] Trachelectomy for early cervical cancer is a major risk factor for preterm birth and a prophylactic cerclage at the time of the initial cancer surgery or in early pregnancy is recommended.
- **Obstetric trauma:** Cervical laceration or injury may occur during labour or delivery, including spontaneous labour, forceps and vacuum delivery, or caesarean section.[22] At least theoretically, the cervix may be disrupted during manual removal of the placenta. These may weaken the cervix and contribute to cervical insufficiency.
- **Uterine over-distension:** Multiple pregnancies and polyhyramious also carry an increased risk of preterm labour. Nearly 40% of twin pregnancies will have spontaneous preterm labour or pPROM. Women with multiple gestations were shown to be more likely to have a short cervix at 24 weeks, which is probably due to a rapidly expanding uterus putting extra pressure on the cervix.[23] It is difficult to ascertain whether short cervix is inherent in women with multiple gestations after a certain gestation and what this gestational age might be.
- **Multiple dilatation and evacuation:** Forced and aggressive dilatation of the cervix during surgical termination of pregnancy may in some women lead to cervical damage. Two or more prior dilatation and evacuation especially for late termination of pregnancy is associated with increased risk of cervical insufficiency and preterm labour.[24] The RCOG recommends the use of cervical ripening agents such as vaginal misoprostol prior to the procedure.[25]
- **Infection:** Infection may have a causal or effect relationship with cervical insufficiency. A proportion of women

with cervical insufficiency in the second trimester have microbial invasion of amniotic cavity (MIAC).[26,27] This may be caused by premature cervical dilatation with the exposure of the chorioamniotic membranes to the microbial flora of the lower genital tract. Alternatively, intrauterine infection either through the ascending or haematogeneous route in the second trimester of pregnancy may produce cervical ripening and dilatation, and uterine contractions.[28] These contractions are usually silent in the mid-trimester and the clinical scenario may be indistinguishable from that of an incompetent cervix.[26] The detection of abnormal vaginal flora such as bacterial vaginosis (BV) or intermediate flora is associated with an increased risk of late miscarriages and early preterm delivery and in women with a short cervix.[29,30] Other genital tract infections have also been implicated in preterm births including chlamydia, Group B streptococcus (GBS), mycoplasma and gonorrhea, but there are as yet no studies linking them with a short cervix other than as a final common pathway.

- **Connective tissue disorders:** Connective tissue disorders such as Ehlers-Danlos and Marfans syndrome have been implicated in the aetiology of preterm birth.[31] It is characterized by disorganization of collagen fibrils in the cervix leading to cervical incompetence and preterm labour.[21]
- **Preterm prelabour rupture of membranes:** Preterm prelabour rupture of membranes (pPROM) is defined as the spontaneous rupture of fetal membranes prior to the onset of labour and before 37 weeks' of gestation. It complicates 2% of pregnancies and occurs in 14,000 pregnancies in the UK and 150,000 pregnancies in the USA and accounts for 30% of preterm deliveries.[32] It is associated with significant maternal risks including chorioamnionitis with serious systemic infection and neonatal morbidity and mortality including prematurity, sepsis and pulmonary hypoplasia.[33,34] Subclinical intrauterine infection has been implicated as an aetiological factor in the pathogenesis of pPROM and its associated maternal and neonatal sequelae. In women with pPROM, studies have shown the presence of positive amniotic fluid cultures in a third of pregnancies following amniocentesis.[35,36] Women with intrauterine infection have a shorter latency period than non-infected women and babies born with sepsis have a four-fold mortality rate compared with babies without sepsis.[37] These findings have fuelled interest in the use of antibiotics to prevent pPROM in high-risk women, reduce chorioamnionitis, improve latency following pPROM, completion of corticosteroids, and as prophylaxis and treatment against neonatal respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, neonatal sepsis and mortality.

MANAGEMENT OF ASYMPTOMATIC HIGH-RISK WOMEN

Patient Selection

Of all the predictors of preterm birth, past obstetric history is the strongest predictor of recurrent preterm birth. Ideally, women with prior preterm birth should be seen postnatally and the events leading to their preterm birth including autopsy reports and medical records reviewed. Following this, a plan of care for subsequent pregnancies highlighted. All modifiable risk factors should be discussed (Table 8.1). Finally, these women should be seen early in their subsequent pregnancies preferably in a preterm surveillance clinic.

Microbiological Screening

Screening and treating lower genital tract and sexually transmitted infection is recommended prior to and in the first trimester of pregnancy. For bacterial vaginosis, a vaginal swab of vaginal secretions is rolled onto a glass slide; gram stained and looked at under the microscope using the Nugent scoring system. At present, there is no consensus on the antibiotic choice of treatment, or the best route of administration and the optimal timing for initiating therapy. Randomized controlled trials have demonstrated that oral metronidazole or clindamycin significantly reduces the risk of preterm birth in high-risk women with bacterial vaginosis.[38,39] Asymptomatic bacteriuria has been linked to preterm birth. Screening for and treatment of asymptomatic bacteriuria in pregnancy have become standard practice in obstetric care and most antenatal guidelines include routine screening for asymptomatic bacteriuria. Group B streptococcal (GBS) colonization has been linked with preterm births. Additionally, preterm infants are more susceptible to early onset GBS infection through the birth canal if mother is heavily colonized. In women at risk of preterm delivery, it is appropriate to screen for GBS antenatally which allows

TABLE 8.1 Preventive Strategies

Avoid smoking and use of illicit drugs
Weight loss and exercise
Avoid multiple pregnancies (ART)
Appropriate inter-pregnancy interval
Vaccinations (varicella, rubella)
Folic acid supplementation
Balanced diet
Screen for and treat asymptomatic bacteriuria
Screen and treat BV
Screen and treat sexually transmitted infection
Avoid vaginal douching

intrapartum intravenous antibiotics to be given at the time of labour. Screening for GBS involves the use of a combined lower vaginal and rectal swab. Antibiotics prophylaxis during pregnancy in unselected women is not associated with prevention of preterm birth but can lead to neonatal infections with penicillin-resistant organisms such as *Escherichia coli*.

Cervical Length Scan

Cervical length is a good predictor of PTB in high-risk women in particular, those who have had a prior PTB.[40] A positive predictive value of 70% and a sensitivity of 60–80% is observed with a transcervical ultrasound cervical length (TVS CL) of less than 25 mm between 14 and 18 weeks gestation.[20] It was interesting to note only a 4% risk of delivering preterm was observed in high-risk women with normal cervical measurement between 14 and 18 weeks.[41] TVS CL has been studied and found to be predictive of PTB in other high-risk women including women with prior cone biopsy, prior multiple dilation and evacuations (D&Es) and mullerian anomalies.[42-44] Women with uterine abnormalities and a short cervix on TVS have a 13-fold increase in spontaneous PTB, with those having a unicornuate uterus having the highest rate of PTB. One of the major significant contributors to perinatal morbidity and mortality in multiple gestations is spontaneous PTB. Several studies have looked at the use of cervical length as a predictor of PTL in twin gestations. Its predictive accuracy varies between studies. Skentou and coworkers found a TVS CL less than 20 mm to have a 100% predictive value for PTB before 28 weeks gestation.[45] Similarly, Goldenberg and coworkers found a cervical length of less than 25 mm at 24 weeks gestation to be a strong predictor of PTB.[23] Guzman and his team also found TVS CL to be predictive of PTB in women with triplet pregnancies.[46] There is conflicting information regarding the relevance of a short cervical length in the prediction of PTB in multiple gestations. Women with multiple gestations were shown to be more likely to have a short cervix at 24 weeks which may be due to a rapidly expanding uterus exerting extra pressure on the cervix and not particularly due to an incompetent cervix, it is therefore difficult to determine if the short cervix is inherent to women with multiple gestations after a certain gestation and at what gestational age this cervical changes occur.

Fetal Fibronectin

Fetal fibronectin (fFN) is a glycoprotein that is secreted by the fetal membranes and helps attach the chorion to the decidua. It acts like 'glue' binding the choriodecidual membranes. It is rarely present in vaginal secretions between 23 and 34 weeks gestation. Any disruption in the choriodecidual interface results in fFN release into the cervico-vaginal secretions. It is performed by the bed side and its technique is important in ensuring a correct result. Digital examination of the cervix should not be performed prior to fFN testing and no lubricating gel is used. A positive fetal fibrnectin test is considered to be greater than 50 ng/ml.[47] Many studies have evaluated the role of fetal fibronectin test both in asymptomatic high-risk women and women in preterm labour. A positive fFN test is associated with an increased likelihood of birth before 34 weeks' gestation with 14 days of the test with a positive predictive value of only 16%.[48,49] However, if the test is negative, the risk of preterm delivery is <1% within 14 days of the test.[50,51] In most obstetric units, the test is useful to aid the diagnosis of preterm labour and avoid unnecessary admission and treatment.

PREVENTION OF PRETERM LABOUR

Progesterone

Progesterone is an important hormone for the continuation and maintenance of pregnancy and a decline in its action has been implicated in cervical ripening and dilatation and in preterm labour.[52-57] The progesterone receptor antagonist (mifepristone) has been used to ripen the cervix during the mid-trimester and at term confirming its action on the cervix during pregnancy.[54,58,59] Several randomized trials have shown efficacy of progesterone supplementation in women with cervical insufficiency or a short cervix.[25,60-64] A recent meta-analysis on the use of vaginal progesterone in asymptomatic women with a short cervix (≤25 mm) in the mid-trimester showed a significant reduction in the rate of preterm labour and neonatal morbidity and mortality.[65] The authors concluded that in women with a sonographic short cervix in the mid-trimester, singleton gestation and previous spontaneous preterm birth, vaginal progesterone administration was associated with a 53% significant reduction in the risk of preterm birth at <32 weeks. Placement of a cervical cerclage showed a 34% significant reduction in the risk of preterm birth at <32 weeks with no differences in efficacy between vaginal progesterone and cerclage in the prevention of preterm birth or other adverse perinatal outcomes.

Cervical Cerclage

Women with suspected cervical insufficiency may be managed with elective cervical cerclage or by serial ultrasound cervical assessment in doubtful cases with a view to insertion of cerclage if the length of the cervix was found to be absolutely short or progressively shortening**.** This approach is better described as '*therapeutic cerclage*'. A rescue cerclage is performed as a salvage procedure in the case of premature cervical dilatation with exposed fetal membranes in the vagina. In general, cervical cerclage is believed to provide physical support for a structurally weak cervix and might also improve the cervical immunological barrier by improving retention of the mucous plug.[66] An occlusion

stitch is sometimes used to allow retention of the mucus plug and reduce the risk of ascending infection by placing a continuous non-absorbable suture around the external os. Transabdominal cerclage is usually considered in women with very small volume cervix or previous failed transvaginal cerclage. It can be performed as an open or laparoscopic procedure and once in place requires hysterotomy or caesarean section for delivery. It is associated with increased maternal morbidity. Prior to the insertion of cerclage, ultrasound fetal assessment for viability and anomalies should be done, and contraindications for the procedure such as vaginal bleeding, clinical chorioamnionitis, rupture of membranes, fetal compromise and fetal death should be excluded. At present, there is insufficient data to support routine microbiological screening before cerclage; however, we recommend preoperative genital tract screening in women with prior pregnancy loss or preterm delivery driven by chorioamnionitis, those with a history of bacterial vaginosis or other genital tract pathogens. Intraoperative tocolysis, antibiotics, choice of anaesthesia and technique of cerclage insertion is at the discretion of the managing obstetrician. Postoperative best rest, progesterone and abstinence from sexual intercourse are not routinely recommended. Complications such as rupture of membranes, suture displacement and chorioamnionitis may occur.

MANAGEMENT OF PRETERM LABOUR

A number of strategies involving the use of prophylactic tocolysis, antibiotics, corticosteroids administration have been used in the management of preterm labour.

Tocolytics

The use of tocolysis in women in preterm labour aims to inhibit uterine contractions and reduce perinatal morbidity and mortality associated with early delivery. Unfortunately, several trials have not found tocolysis to reduce the incidence of preterm birth, improve perinatal or neonatal morbidity and therefore, it is reasonable not to use them. However, they may be used to allow completion of antenatal corticosteroids or to facilitate in-utero transfer to a specialist neonatal facility. A variety of agents are currently in use including ritodrine, nifedipine, atosiban, indomethacin, nitric oxide donors and magnesium sulphate. Ritodrine is the most widely used tocolytic and has been shown to be effective in prolonging pregnancy at 24 h, 48 h and 7 days.[67] However, these trials have not shown any improvement in perinatal outcome or births before 37 weeks. Ritodrine and other betamimetics are known to cause serious maternal side effects including nausea, tachycardia, tremor, headache, chest pain and pulmonary oedema.[68] Indomethacin has been found to significantly increase the risk of intraventricular haemorrhage, necrotizing enterocolitis, acute renal failure, oligohydramious due to reduced renal blood flow if used for more than 48 h and premature closure of the ductus arteriosus if used after 32 weeks gestation. Therefore, the current RCOG guidelines suggest atosiban and nifedipine as they appear to have comparable effectiveness in delaying delivery, with fewer maternal side effects than alternatives such as ritodrine or indomethacin. Although the use of nifedipine for preterm labour is unlicensed, it has the advantages of less frequent side effects, oral administration and a low purchase price.

Antenatal Corticosteroids Administration

Current evidence supports the administration of a single course of antenatal corticosteroids between 24^{+0} and 34^{+6} weeks of gestation to enhance fetal lung maturation. A Cochrane review of 21 studies (3885 women and 4269 infants) showed that the administration of a single course of antenatal corticosteroids reduced the risk of neonatal death by 31% (95% CI 19–42%), respiratory distress syndrome by 44% (95% CI 31–57%) and intraventricular haemorrhage by 46% (95% CI 31–67%).[69] The use of corticosteroids compared with placebo or no treatment reduced the need for admission to special care baby units, assisted ventilation, incidence of necrotizing enterocolitis or systemic infections in the first 48 h.[69] This is most effective in reducing respiratory distress syndrome in women who deliver 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids. Weekly repeated courses of antenatal corticosteroids reduces the occurrence and severity of neonatal lung disease (RR 0.60, 95% CI 0.48–0.75) and the risk of serious health problems in the first few weeks of life (RR 0.79, 95% CI 0.67–0.93),[70] these short-term benefits are associated with a non-significant higher risk of cerebral palsy among children who had been exposed to repeat doses of corticosteroids (RR 5.7, 95% CI 0.7–46.7, $P=0.12$).[71] The most extensively studied regimens of corticosteroid treatment for the prevention of RDS are two doses of betamethasone 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart with betamethasone treatment causes a larger reduction in RDS than dexamethasone.

Antibiotics

Following the publication of the ORACLE II trial, the routine administration of antibiotics for the treatment of preterm labour with intact membranes is not recommended.[72] Also, they found a greater proportion of children whose mothers had been prescribed erythromycin and/or co-amoxiclav developed cerebral palsy than those whose mothers had received no erythromycin (OR 1.18, 95% CI 1.02—1.37).[73] Several trials including a meta-analysis have found antibiotics use delayed preterm delivery within 48 h (RR 0.71; 95% CI 0.58–0.87) and 7 days (RR 0.80; 95% CI 0.71–0.90), reduced

chorioamnionitis (RR 0.57; 95% CI 0.37–0.86), neonatal infection (RR 0.68; 95% CI 0.53–0.87), and maternal and neonatal mortality following a diagnosis of pPROM.[74] Therefore, routine antibiotics use is recommended in the context of pPROM. The Royal College of Obstetricians and Gynaecologist currently recommend treating women with pPROM with 250 mg of erythromycin 6 hourly for 10 days. Co-amoxiclav was associated with an increase in the numbers of babies born with necrotizing enterocolitis and is best avoided.

Magnesium Sulphate for Neuroprotection

Doyle and coworkers in the Cochrane review concluded that antenatal magnesium sulphate therapy given to women at risk of preterm birth substantially reduced the risk of neonatal cerebral palsy (RR 0.68; 95% CI 0.54–0.87).[75] There was also a significant reduction in the rate of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44–0.85).[75] There is no consensus on the dose, if maintenance dose or repeat dose needs to be given, duration and timing of treatment. The current recommendation is a 4 g IV loading dose followed by a maintenance dose of 1 g per hour for 24 h unless preceded by birth.[76] The RCOG has concluded that magnesium sulphate given to mothers shortly before delivery reduces the risk of cerebral palsy and protects gross motor function in those infants born preterm.[77] The effect may be greatest at early gestations and is not associated withadverse long-term fetal or maternal outcome.

MODE OF DELIVERY

There is insufficient evidence to suggest the most appropriate mode of delivery for preterm infants. Vaginal delivery is associated with lower maternal morbidity and mortality and should be the preferred option unless there are indications for caesarean section. In gestations less than 26 weeks of gestation, vaginal delivery will be favoured given the poor outcome for the fetus. A caesarean section in gestation less than 28 weeks of gestation are more likely to be classical caesarean section, in absence of a well-formed lower segment and can have greater risks for the mother and has implications for future pregnancy and risks of adherent placenta.

Important Points

- Preterm birth is the main cause of perinatal and neonatal morbidity and mortality and the rate appears to be rising.
- Treatment strategies including antenatal corticosteroid administration, tocolysis and antibiotics have been studied, but antenatal corticosteroid is the only intervention that has been shown to significantly improve perinatal outcome.
- Further research is required to improve the prediction and prevention of preterm labour in high-risk women and develop better management strategies.

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Chapter 9

Post Term and Prolonged Pregnancy

Avinash Bhatt and Kaizad R. Damania

Chapter Outline

INTRODUCTION

A pregnancy is said to be term when it is between 37 weeks and 42 weeks of gestation. As the weeks progress in this period, so does the incidence of perinatal morbidity and mortality. In clinical practice, it is difficult to decide at what gestational age, in this period, should the patient be best delivered. Recent studies have shown that the risk to the fetus and to the mother, in continuing the pregnancy beyond the estimated date of delivery, is higher than what was estimated earlier.[1-6] Some observational studies that have evaluated the risk of perinatal mortality at each gestational week show an increased risk as gestational age advances beyond the expected date of delivery.[7-9] A study by Caughey and Musci, found an increase in the rate of meconium and intrauterine death for every week after 37 weeks gestation, and a large increase beyond 41 weeks.[5] Smith et al, have shown that there is a rise in the contingent and accumulative risk of fetal death with increase in gestational age after 37 weeks.[9] Managing pregnancies continuing beyond their due date remains to be a tricky situation for the obstetrician.

The American College of Obstetricians and Gynaecologists (ACOG) and the World Health organization (WHO) had defined post-term pregnancy as that lasts 42 weeks (294 days) or more from the first day of the last menstrual period.[10,11] However, it was noted that from gestation of 37 weeks to 42 weeks, the timing of delivery during this 5-week gestational period often determines the neonatal outcomes, especially respiratory morbidity. It was observed that uncomplicated deliveries taking place between 39-0/7 weeks of gestation and 40-6/7 weeks of gestation had the lowest neonatal morbidity.[12,13] To address this lack of uniformity, recently the ACOG has endorsed a recommendation that the label "term" be replaced with the designations *early term* (37-0/7 weeks of gestation through 38-6/7 weeks of gestation), *full term* (39-0/7 weeks of gestation through 40-6/7 weeks of gestation), *late term* (41-0/7 weeks of gestation through 41-6/7 weeks of gestation), and *post term* (42-0/7 weeks of gestation and beyond) to more accurately describe deliveries occurring at or beyond 37-0/7 weeks of gestation.[14]

In view of the earlier mentioned perinatal morbidity and mortality data, it would be reasonable to conclude that any pregnancy beyond 41 weeks warrants clinical concern. In this chapter, a pregnancy between 41 and 42 weeks will be referred to as prolonged pregnancy, while those beyond 42 weeks will be referred to as post term pregnancy.

The duration of pregnancy does show variation due to ethnicity of the mother. Balchin et al found that for nulliparous women delivering single infants after spontaneous onset of labour, the median gestational age at delivery was 39 completed weeks in the black and Asian ethnic groups.[15] In another study, Caughey et al again noted that ethnic groups like the African American and the Asian population were much less likely to reach 41 and 42 weeks gestation.[16] Also, the rate of antepartum stillbirths in South Asianbabies born in North West London was statistically significantly higher than in white babies, with a rate of 1.91 at 40 weeks as compared to 3.21 at 41 weeks gestation.[15] Therefore, the duration of pregnancy and the subsequent management would need to be different for these groups of population.

INCIDENCE

About 4 to 15% of pregnancies result in being prolonged pregnancies, depending on the method used to calculate the gestational age. Boyd et al found an incidence of post term pregnancy of 7.5% when the diagnosis was based on menstrual history, 2.6% when diagnosis by early ultrasound examination, and 1.1% when the diagnosis was based on concurrent menstrual history and ultrasound examination.[17]

AETIOLOGY

The most common cause for prolonged pregnancy is an error of last menstrual period. Therefore, accurate dating of the pregnancy plays a very important role in the management of these patients. Prolonged pregnancy is seen more in primigravidas than in multiparous women, and women with previous history of prolonged pregnancy have a higher chance of recurrence. Maternal obesity is also an independent predictor of post-term pregnancy. It is well established that women with low prepregnancy body mass index (BMI), less than 18.5 kg/m^2, have a higher risk of preterm birth. In contrast, women with prepregnancy BMI greater than 25 kg/m^2 had a higher risk of post-term pregnancy.[18] Rare causes include placental sulfatase deficiency (an X-linked recessive disorder) which results in reduced placental estrogen synthesis. This leads to poor expression of oxytocin and prostaglandin receptors in myometrium. Fetal adrenal hypoplasia and anencephaly can also result in prolonged pregnancy, since in these fetuses, the hypothalamic–pituitary–adrenal axis is dysfunctional leading to lower corticotrophin releasing hormone (CRH) levels. The CRH through complex pathways increases prostaglandin and estrogen and decreases progesterone, which is necessary for labour initiation.

DIAGNOSIS

The diagnosis of a true prolonged or post-term pregnancy is by accurate dating of gestation. Dating a pregnancy by last menstrual period (LMP) alone is associated with more error. Therefore, an early pregnancy ultrasound (in the first trimester) measuring the crown-rump length (CRL) of the fetus to date the pregnancy should be done. If this is within 5 days of the dates as per the LMP, then the dues dates are not revised. A Cochrane database systemic review has shown that early sonographies lead to a reduction in need of induction of labour for post-term pregnancy.[19]

Accurate methods used for dating of pregnancy include correct knowledge of LMP, early scan (first trimester) and a combination of both. In cases of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), the dates for procedures like pick up and transfer of embryo are used for calculating the duration of pregnancy. Other less reliable methods include uterine size, fundal height measurement, quickening and detection of fetal heart tones on Doppler.

PATHOPHYSIOLOGICAL CHANGES SEEN IN PROLONGED GESTATION

A number of changes take place in the amniotic fluid and placenta in prolonged pregnancy and these changes play an important role in the management and outcome of these cases.

Amniotic Fluid Changes

The amniotic fluid volume reaches its peak at around 38 weeks of gestation after which there is a gentle decline. The fluid then reduces every week and has a massive reduction by 33% per week after 42 weeks of gestation.[20,21] The drop in amniotic fluid is attributed to a reduced urine output by the fetus, which in turn is caused by the redistribution of fetal circulation and reduction in renal perfusion. The fluid becomes thick due to an increased amount of vernix caseosa. So not only is the volume reduced but also there is added density to it. Addition of meconium in such amniotic fluid often leads to respiratory complications for the newborn baby. After 38 weeks, fluid volume declines by approximately 125 mL/week, to an average volume of 800 ml at 40 weeks and this decline can be picked up sonography.[20,21]

Although clinical estimation of liquor adequacy was traditionally done by abdominal examination, today assessment of the amniotic fluid volume is done with ultrasonography by estimating the Amniotic fluid index (AFI)—four-quadrant

measurement or the single deepest pocket (SDP). The AFI is the score (expressed in centimeter) given to the amount of amniotic fluid seen on ultrasonography of a pregnant uterus. To determine the AFI, doctors may use a four-quadrant technique,[22] when the deepest, unobstructed, vertical length of each pocket of fluid is measured in each quadrant and then added up to the others. An AFI between 8 and 20 cm is considered normal. An AFI < or = 5 cm. is considered as oligohydramnios. The AFI identifies a significantly greater number of women as having oligohydramnios compared to SDP, leading to more interventions without improving perinatal outcome.[23] The SDP (< 2cm), however, has been found to be least likely to lead to a false-positive diagnosis of oligohydramnios.[24] Thus, in clinical practice, it may be prudent to screen for reduced amniotic fluid volume by utilizing AFI (< 8 cm), and to use SDP (< 2 cm) as a marker for intervention. The sonologist may thus be requested to assess liquor quantum by estimating both AFI and SDP in the patient.

Placental Changes

As the pregnancy goes into 38 weeks and beyond, the placenta starts showing infarcts and calcifications. These changes increase with weeks of gestation. Along with this, there is development of fibrinoid necrosis and atherosclerosis in the decidual and chorionic blood vessels. The incidence of placental infarcts significantly increases after 42 weeks of gestation. Morphologic changes that occur with placental senescence can be observed by ultrasound. During early pregnancy, the ultrasound 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 dispensed 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 placenta). 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 an increase in the confluence of the comma-like densities that become inter-cotyledon septations. Also, characteristically, the central portion of the cotyledons becomes echo-free (fallout areas), and large irregular densities in the form of acoustic shadows appear in the substance of the placenta (grade III placenta). The correlation between Grade III placenta and fetal pulmonary maturity is excellent in pregnancies near term. Although grade 0 or grade I placenta are not found with prolonged or post-term pregnancies, grade II or grade III placenta are found with similar frequencies in this group. Thus, placental grading by itself is a poor predictor of post-term pregnancy or postmaturity.[25]

FETAL, NEONATAL AND MATERNAL COMPLICATIONS

Fetal and Neonatal

Perinatal Death

The incidence of perinatal mortality rates (still birth plus neonatal mortality) at 42 weeks is twice as much as that at 40 weeks and is fourfold at 43 weeks increasing to fivefold at 44 weeks.[26-28] Uteroplacental insufficiency, meconium aspiration, and oligohydramnios are known factors to increase the perinatal mortality rate.

Fetal Asphyxia

Intrauterine asphyxia results from a deficit in the required amount of oxygen being delivered to the fetus. Prolonged pregnancy is often associated with oligohydramnios. This with acute intermittent cord compression or even uteroplacental insufficiency could be causative factors for asphyxia in these cases. High-risk pregnancies like those with chronic hypertension or diabetes mellitus, often have a poor placental function before term. The risk of perinatal morbidity and mortality is significantly increased in these pregnancies when they continue past their delivery date.[29] Asphyxia could present in a benign form as warnings (variable decelerations) in the cardiotocography during labour or could manifest into more serious conditions like permanent neurological damage with its sequel in the newborn.

Meconium Aspiration

Passage of meconium in a mature fetus is physiological. However, in prolonged pregnancies, the fluid becomes scanty and more viscous and the presence of meconium can lead to severe complication of meconium aspiration syndrome (MAS). Meconium aspiration is eight times more common in prolonged pregnancy, and its complications include pneumonia, pneumothorax, a requirement for assisted ventilation, and the development of pulmonary hypertension.

Fetal Trauma

The incidence of fetal macrosomia, fetal weight beyond 4000 g is higher in prolonged pregnancies. Pre-gestational diabetes and gestational diabetes are also associated with fetal macrosomia. The diagnosis of fetal macrosomia is far from being accurate. In those cases where the clinician suspects fetal macrosomia, the diagnosis of a large baby by clinical examination and palpation (Leopold's maneuvers)

would be as inaccurate or accurate as the estimation of fetal weight by sonography. If the thickness of the anterior abdominal wall of the fetus on ultrasound is more than 10 mm, it is often associated with macrosomia.

Large babies are often associated with difficult vaginal deliveries and these have a higher incidence of shoulder dystocia, which in turn increases the risk of birth asphyxia, clavicle or humerus fracture, and brachial plexus injury. There is a higher incidence of operative vaginal deliveries. Apart from the complications mentioned above, there is also an increase in injuries due to instrumentation like cephalohaematomas and facial nerve palsy.

Postmaturity Syndrome

The hallmarks of the postmature infant as described by Clifford include meconium staining, loss of subcutaneous fat reserves, and skin peeling.[30] The infant's appearance is like that of a wizened old man—long, thin, and wrinkled with reduced muscle mass and long nails at the extremities. These infants are predisposed to metabolic disturbances like hypoglycemia, hypothermia, and polycythemia due to low stores of fat and glucose.

Maternal Complications

As shown in Table 9.1, there is an increase in maternal morbidity with higher rates of intervention, postpartum bleeding, and infection.

MANAGEMENT

Antepartum Management

The first step of management is an accurate diagnosis, which has been discussed earlier. Prolonged pregnancy is associated with increase in operative interventions and maternal and neonatal complications. Antenatal care includes an accurate dating of the pregnancy, fetal surveillance, and the option of induction of labour or expectant management, which should be discussed with the patient with prolonged pregnancy.

TABLE 9.1 Risks Associated with Prolonged Pregnancy

Maternal	Neonatal
Perineal trauma	Asphyxia
Operative intervention	Perinatal death
Cervical tear	Meconium aspiration
Postpartum haemorrhage	Pneumonia
Postpartum infection	Birth injuries

Fetal Surveillance for Prolonged Pregnancy

Induction of labour can be offered to patients with prolonged pregnancy. If after counselling, the patient still chooses to decline the option of induction, then this pregnancy needs to be monitored till the time of spontaneous onset of labour. However, no test till date has completely eliminated the risk of stillbirth and on the other hand, false-positive tests lead to an increase in un-indicated interventions.

The gestation at which this surveillance should start is debatable. Data have shown a significant percentage of perinatal asphyxia in the range of 40–42 weeks of gestation. The Royal College of Obstetricians and Gynaecologists (RCOG) recommends offering induction of labour between 41 and 42 weeks of gestation and increased fetal surveillance from 42 weeks in women who decline induction of labour,[31] while the American College (ACOG) has a level C recommendation to initiate fetal surveillance between 41 and 42 weeks.[32] Many obstetricians, however, would choose to start surveillance after 40 weeks of gestation.

Antenatal surveillance is in the form of Non-stress Tests (NST), sonography for the AFI and SDP assessment. Both the RCOG and ACOG recommend twice weekly NST and sonography for assessment of depth of amniotic fluid.[31,32] Surveillance by Biophysical profile (BPP) though sensitive has its restrictions. The score assigns equal numerical values to its parameters and even a drastic reduction in amniotic fluid would reduce the score by just 2. Since oligohydramnios is a very important factor in prolonged pregnancy, it would be advisable to deliver women with oligohydramnios in prolonged pregnancy. Umbilical Doppler studies are often used to identify fetal compromise due to altered fetal circulation. Studies in prolonged pregnancy to show the use of Doppler to predict adverse fetal outcomes like abnormal fetal heart rate tracing, meconium aspiration, need for operative delivery, neonatal encephalopathy, have had contrasting outcomes.[33-37]

Induction of Labour

The Cochrane database systemic review of 22 RCTs showed that a policy of labour induction compared with expectant management is associated with fewer perinatal deaths and fewer caesarean sections. Majority of the trials adopted a policy of induction at 41 completed weeks (287 days) or more.[38] Fewer babies in the labour induction group had MAS compared with a policy of expectant management. The Canadian multicentric post-term pregnancy trial (CMPPTT) compared induction at 41 weeks versus expectant management till 44 weeks. The expectant group had a higher rate of caesarean section for fetal distress.[39]

There are certain indications, however, where the obstetrician would recommend delivery of the baby and not

waiting for spontaneous labour. These can be identified by clinical examination, NST and ultrasonography.

- In pregnancies associated with maternal complications like hypertension and diabetes, delivery is indicated due to the medical complications. Prolonging the pregnancy would increase the risk for the mother and the fetus.
- Pregnancies with oligohydramnios need delivery. There is evidence to show that reduced amniotic fluid is associated with increase in perinatal morbidity and mortality.
- Fetal growth restriction in prolonged pregnancy is often associated with oligohydramnios and meconium aspiration. The cardiotochography (CTG) in labour will often show abnormal patterns. These babies show wasting of subcutaneous fat. Such pregnancies need delivery rather than expectant management.
- Advance maternal age is a risk factor for antepartum stillbirths. A population base study from New South Wales, Australia, quantified the risk of advanced maternal age by gestation and concluded that women who were greater than 40 years and in their first pregnancy be offered induction of labour by 40 weeks rather than waiting until 41 weeks or beyond.[40]
- In cases of suspected fetal compromise as seen on fetal surveillance, delivery is indicated. As mentioned earlier, fetal surveillance is done by NST and AFI scan two times a week.

Methods of Induction

Once a decision for induction of labour is made, the obstetrician needs to do an assessment of the cervix for Bishop scoring. The Bishop score is determined by doing a vaginal examination, and is based on the dilation, station, effacement (or length), position and consistency of the cervix. A score of eight or more generally indicates that the cervix is ripe, or 'favourable' – when there is a likelihood of spontaneous labour, or a positive response to interventions made to induce labour.

If the score is low or unfavourable, then modes of ripening of the cervix are used to increase the chances of a vaginal delivery. Ripening of the cervix can be done by membrane stripping, Foley catheter, oxytocin and most effectively by prostaglandins. Other methods that have been tried include enemas and castor oil but there have been no trials that have shown their clinical benefits for cervical ripening and induction of labour.

An inflated Foley catheter acts as a gradual mechanical dilator of the cervix. Also, the inflated Foley catheter may cause release of prostaglandin F2-alpha from the decidua or prostaglandin E2 from the cervix. Traction is added by strapping the catheter under tension to the patient's inner thigh. The concern with them is the chance of infection and their use has to be individualized as per the patient.

Prostaglandins

Prostaglandin (PG) E2 derivatives are used intravaginally as well as intracervically. In those women with an unfavourable cervix, PGE2 is associated with an increase in successful vaginal delivery in 24 hours, decrease in caesarean section rates and a decrease in the rates of cervices remaining unchanged or unfavourable after 24 hours.

The National Institute for Health and Care Excellence (NICE) guidelines recommend the vaginal PGE2 preparation as the preferred method for induction of labour. Intracervical PGE2 is less effective than vaginal PGE2 in achieving vaginal birth within 24 hours. However, in women with a favourable cervix, maternal and fetal outcomes are comparable between intracervical and vaginal PGE2.[31]

PGE2 derivative dinoprostone is available as a gel for intracervical application in a dose of 0.5 mg. If there is inadequate cervical change with minimal uterine activity after one dose of intracervical dinoprostone, a second dose may be given 6–12 hours later. The recommended maximum cumulative dose is 1.5 mg of dinoprostone (three doses of the gel).

Misoprostol, the PGE1 derivative is the newer prostaglandin that is used for induction of labour. It is safe, effective and therefore may be seen as the first-line option for cervical ripening and induction of labor. The ACOG recommends 25 mcg as the initial dose for cervical ripening and induction of labour, which can be repeated in every 3–6 hours.[32] A Cochrane database systemic review reports that vaginal misoprostol in doses more than 25 mcg four-hourly was more effective than conventional methods of labour induction, but with more uterine hyperstimulation (tachysystole). Lower doses were similar to conventional methods in effectiveness and risks.[41] Studies have shown that the vaginal route acts faster but has a higher incidence of hyperstimulation compared to the oral route.[31,32,42] The outcomes for both remain similar.

According to the NICE guidelines, oxytocin alone should not be preferred for induction and the combination of amniotomy and induction should be used for inducing those in whom there are specific contraindications to the use of vaginal PGE2, in particular, the risk of uterine hyperstimulation.[31]

The ACOG in their practice bulletin on "Induction of Labour" regarding the use of oxytocin recommend the following.[32] The regime used for oxytocin can be a low dose regime or a high dose regime. The low dose regime is started at 0.5–2 mU and increased 1–2 mU/min every 15–40 minutes. This is associated with decrease in uterine tachysystole and associated fetal heart rate changes. The high dose is started at 6 mU, increased by 3–6 mU/min every 15–40 minutes. The high dose regime is associated with a shorter duration of labour and lesser chorioamnionitis and caesarean section for cervical dystocia, but an increased incidence of uterine tachysystole.

The ACOG recommends that a guideline should be made and followed for preparation and administration of oxytocin. They suggest that synthetic oxytocin is generally diluted 10 units in 1000 mL of isotonic solution for an oxytocin concentration of 10 mU/mL. They recommend that oxytocin be administered by infusion using a pump that allows precise control of flow rate and permits accurate minute by minute control. Bolus administration of oxytocin can be avoided by piggybacking the infusion into the main intravenous line near the venipuncture site.[32] It is important to maintain strict control on the rate and monitor the uterine contractions. The fetal heart rate should also be closely monitored.

Intrapartum Care

The intrapartum care of the patients with prolonged pregnancy have to be carefully monitored. They are more likely to present with abnormality in fetal heart rate monitoring, shoulder dystocia, meconium aspiration, fetal trauma and maternal perineal injuries.

Abnormal Cardiotocography (CTG)

Prolonged pregnancies often have reduction in amniotic fluid volume. The CTG can often show reduced variability and variable decelerations. If causes like uterine tachysystole are ruled out and the abnormality persists, these babies need to be delivered by caesarean section.

Meconium Aspiration

There is a higher incidence of meconium stained amniotic fluid in prolonged pregnancies. This is often accompanied with oligohydramnios, which increases the incidence of meconium aspiration. In cases of abnormal CTG, the passage of meconium is more common. Meconium aspiration is a serious complication in the newborn and very often these babies require being on a ventilator. The obstetrician should be prepared for this complication. The presence of trained staff for neonatal resuscitation or a neonatologist is required. Recent evidence suggests that both oropharyngeal suctioning on perineum after delivery of the head followed by airway visualization and suctioning does not reduce the incidence of meconium aspiration syndrome. Hence, nowadays both of the above are not recommended when the baby has cried and is active, even in the presence of meconium. In cases with significant meconium and where the baby is not active (poor Apgar), the larynx needs to be visualized with a laryngoscope and suctioning needs to be done under direct vision. In some cases, the baby may need endotracheal intubation.

Shoulder Dystocia

Prolonged pregnancy is one of the known risk factors for shoulder dystocia. Preparation and anticipation are keys in the management of these cases. When anticipated, the obstetrician should get a team ready, which should include an assistant, an anesthetist and a neonatologist.

The obstetrician should not rush with the delivery of the head. The episiotomy can be enlarged if required. If the posterior shoulder is felt in the hollow of the sacrum, one should proceed with the McRobert's maneuver. This includes abducting the mother's legs and sharply flexing them against the abdomen. This would create a cephalad rotation of the pubic symphysis. The assistant needs to give a firm suprapubic pressure to deliver the anterior shoulder under the pubic arch. Constant, moderate traction on the fetal head should be applied at the time of suprapubic pressure.

If the above fails, rotation maneuvers are attempted next. Rotation maneuvers to move the shoulder into an oblique diameter of the maternal pelvis, which include the Rubins and the Woods maneuver, are tried. If the above steps have failed, then an attempt to deliver the posterior shoulder is made.

If the posterior shoulder cannot be delivered, the all fours position can be tried. The mother is assisted on her hands and knees and a downward pressure is applied on the fetal head to deliver the shoulder. If this fails too, the head needs to be restituted by Zavanelli maneuver and the baby needs to be delivered by caesarean section.

The obstetricians and their team need to be well trained in the drill and maneuvers for shoulder dystocia. The process should not take more than 5 minutes and the team and equipment should be ready for neonatal resuscitation.

Fetal Trauma

Prolonged pregnancy is often associated with fetal macrosomia. Cases with shoulder dystocia have a higher incidence of fetal injury like brachial plexus injury, clavicle or humerus fracture. Instrumental deliveries can cause cephalic haematomas and skull fractures. All large babies should be carefully evaluated post deliveries for any trauma. However, there is no evidence to support that labour induction should be used as a preventive measure in fetal macrosomia. With an estimated fetal weight more than 4500 g, a prolonged second stage of labor or arrest of descent in the second stage is an indication for caesarean delivery.

Maternal Perineal Injuries

Third and fourth degree perineal tears, deep vaginal lacerations and cervical tears are seen with difficult instrumental deliveries or while deliveries of large babies. An adequate sized, well-timed episiotomy is important in deliveries of large babies.

INDIAN PERSPECTIVE

Perinatal morbidity and mortality increases with increase in gestational age, more so after 40 weeks.[26] It has been widely accepted that factors like race, ethnicity affect the duration of pregnancy with Asians and African Americans

having a shorter duration.[15] A study of Indian women by Mathai M. et al found that the median gestation at delivery following spontaneous labour was 39 weeks.[43]

A study on duration of pregnancy and outcomes on a population in Southern India also showed that pregnancy beyond 40 weeks have a higher rate of meconium stained amniotic fluid and meconium aspiration. The study had found that between 40 and 41weeks and then beyond 41 weeks, meconium aspiration was two and two and half times respectively, compared to 39 completed weeks.[44] In view of the above, the definition for prolonged and post-term pregnancy needs revision in women of certain ethnic origin, especially Indians. Certain ethnic groups such as Indians also have a predisposition towards a constitutionally small baby with a tendency towards early maturity. This may predispose them to an early postmature state. It would be prudent in such cases to offer labour induction at the completion of 40 weeks of gestation (beyond due date) to reduce perinatal morbidity.

In a retrospective analysis of pregnancies continuing beyond their due date, Aseeja V. et al found the incidence to be 8.13%. The incidence of meconium-stained liquor and cesarean sections were higher in women after 41 weeks than those who delivered between 40 and 41 weeks.[45] In a study by Chhabria et al on 2010 women whose pregnancies carried beyond 40 weeks, intrapartum fetal complications were meconium-stained liquor in 18.6%, adverse fetal heart rate patterns in 8.4% and shoulder dystocia in 2%. The study found that a policy of induction of labour reduced risk of perinatal mortality and reduced caesarean sections for fetal distress.[46]

However, a study from Pakistan has suggested that more women delivered vaginally when labour was induced beyond 41 weeks as compared to induction performed at 40 weeks. This finding was independent of association between the induction agent, parity and the mode of delivery. The better result in the 41 weeks group was as a result of better Bishop score in that gestation group.[47]

Thus, clinicians should be well aware of this trade-off between induction failure and perinatal morbidity.

Important Points

- Though the definition of prolonged pregnancy is one beyond 42 weeks gestation, there is enough clinical data that warrants the pregnancy to be closely monitored after 41 weeks.
- The incidence drops from 7.5% to 2.6% when gestation age is calculated by early ultrasound rather than menstrual dates. Therefore, an early ultrasound is important in the accurate diagnosis of prolonged pregnancy.
- The pathophysiological changes include reduction in amniotic fluid volume and enhanced maturity changes in placental structure leading to increased infarcts and calcifications.
- Complications like meconium aspirations, macrosomia and fetal trauma, increased perinatal morbidity/mortality and post maturity syndrome are associated with prolonged pregnancy. Also, for the mother, there is an increase in operative interventions, perineal injuries and prolonged recovery.
- Fetal antepartum surveillance is done by twice weekly NST and AFI/SDP scans.
- Induction is recommended after 41 weeks gestation. Prostaglandins (PGE1 and PGE 2) are the preferred drugs used for induction of labour. Amniotomy along with oxytocin can also be used.
- The obstetricians and their team should anticipate and be prepared for complications like shoulder dystocia and meconium aspiration.
- Studies have found that in certain races (like Asians), the duration of pregnancy is shorter and have increased fetal and neonatal risks.

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Chapter 10

Antepartum Haemorrhage

Vedrana Caric and Amarnath Bhide

Chapter Outline

ANTEPARTUM HAEMORRHAGE

Antepartum haemorrhage (APH) is defined as bleeding from the genital tract in the second half of pregnancy. Despite the decline in the number of deaths from haemorrhage, in The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom (2011), obstetric haemorrhage remains an important cause of maternal death.[1]

Haemorrhage is the major cause of severe maternal morbidity in almost all 'near miss' audits in both developed and developing countries. It complicates 2–5% of all pregnancies.

Conditions responsible for APH are shown in Table 10.1.

Management of Antepartum Haemorrhage

All women over 20 weeks with significant vaginal bleeding or a suspicion of concealed bleeding should be admitted to hospital and assessed clinically. Haemorrhage involving an estimated blood loss of 500–1000 ml (and in the absence of clinical signs of shock) should prompt basic measures, which involve the immediate assessment and management of the airway, breathing and circulation. Once the mother is stabilized, a speculum examination and an ultrasound scan are useful to ascertain a diagnosis. If bleeding continues after an estimated blood loss of 1000 ml (or there are clinical signs of shock or tachycardia associated with a smaller estimated blood loss), every hospital should have an established obstetric haemorrhage protocol and it should be activated at this stage.[2] All steps of such protocol should be undertaken simultaneously and include communication, documentation, resuscitation, monitoring, investigation, fluid replacement, arresting the bleeding, obstetric intervention and anaesthetic management (Diagram 10.1).

Resuscitation starts with (Diagram 10.2):

- ***Airway:*** 10–15 l/min of oxygen via face mask
- ***Breathing***
- ***Circulation:*** Two 14-gauge intravenous lines and 20 ml blood for diagnostic tests (FBC, coagulation screen, cross match 6 units, Urea and electrolytes, Kleihauer) and commence crystalloids

Monitoring includes:

- BP, pulse, oxygen saturation, capillary refill, respiratory rate, urine output.

Investigations:

- Digital examination of the cervix is contraindicated. There is a serious risk of causing major haemorrhage if the underlying cause is placenta praevia.
- Fetal monitoring (CTG).
- Ultrasound for placental localization, estimated fetal weight, presentation (only if maternal and fetal condition are stable).

TABLE 10.1 Causes of Antepartum Haemorrhage

Placenta praevia (4–5/1000 of all pregnancies)
Placental abruption (1% of all pregnancies)
Other causes APH of indeterminate origin (1–1.5% of all pregnancies) Vasa praevia Pathology of the cervix – erosion, polyp, tumour Bleeding from the lower genital tract Blood-stained cervical mucus (Show)

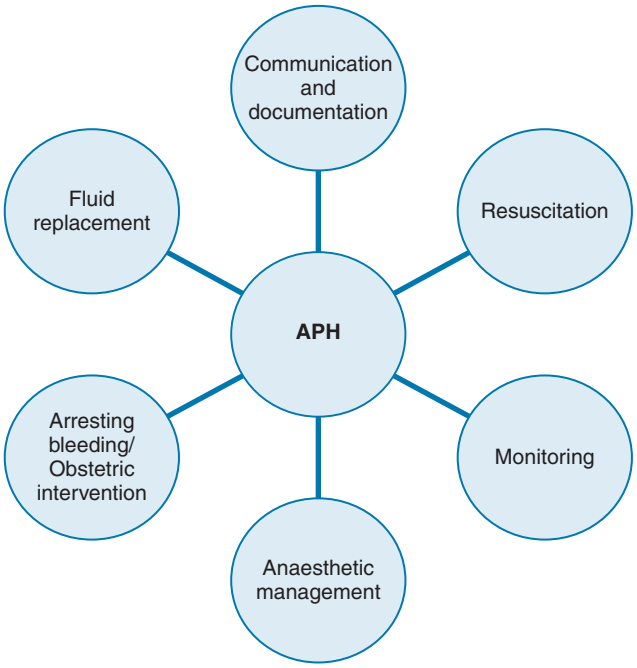

DIAGRAM 10.1 Pathway for antepartum haemorrhage.

Obstetric intervention (also see Chapter 23 on postpartum haemorrhage)

- ***Delivery*** of the baby.
- ***Medication*** (Syntocinon 10 iu iv, Ergometrin 500 mcg im – twice, if no history of high blood pressure; Syntocinon infusion 40 iu in 500 ml of Hartmann's – 125 ml/h rate, Prostaglandin F2α [Carboprost] 250 mcg i.m.,15 min apart, up to 8 doses and Misoprostol 800 mcg to 1000 mcg rectally).
- ***Bimanual compression***
- ***Surgical*** options: Uterine tamponade, B-Lynch suture, hysterectomy.
- ***Radiological*** option: Selective uterine artery embolization.

Visual blood loss estimation often underestimates blood loss. Visible blood loss should be measured as soon as it is practical to do so. It is important to be aware that minor haemorrhage can easily progress to major haemorrhage and is sometimes unrecognized.

PLACENTA PRAEVIA

Placenta praevia is defined as a placenta that lies wholly or partly within the lower uterine segment. The prevalence of clinically significant placenta praevia is estimated to be approximately 4 or 5 per 1000 pregnancies at term.[3]

With the rising incidence of caesarean sections combined with increasing maternal age, the number of cases of placenta praevia and its complications, including placenta accrete is likely to continue to increase.

Classification

Historically, placenta praevia is divided into four types or grades (Fig.10.1).

- **Type 1** – Low-lying placenta: Where the lower placental edge in the lower uterine segment, but does not reach the internal os.

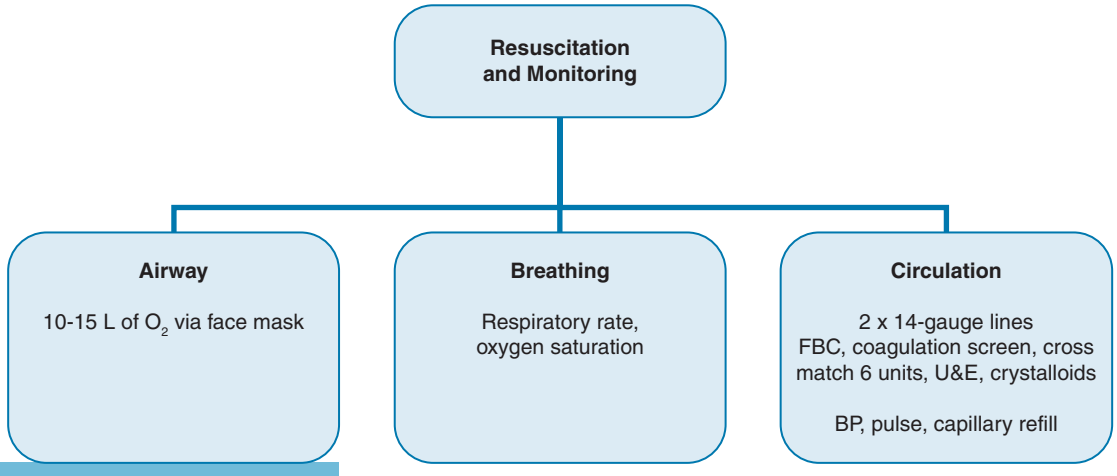

DIAGRAM 10.2 Resuscitation pathway.

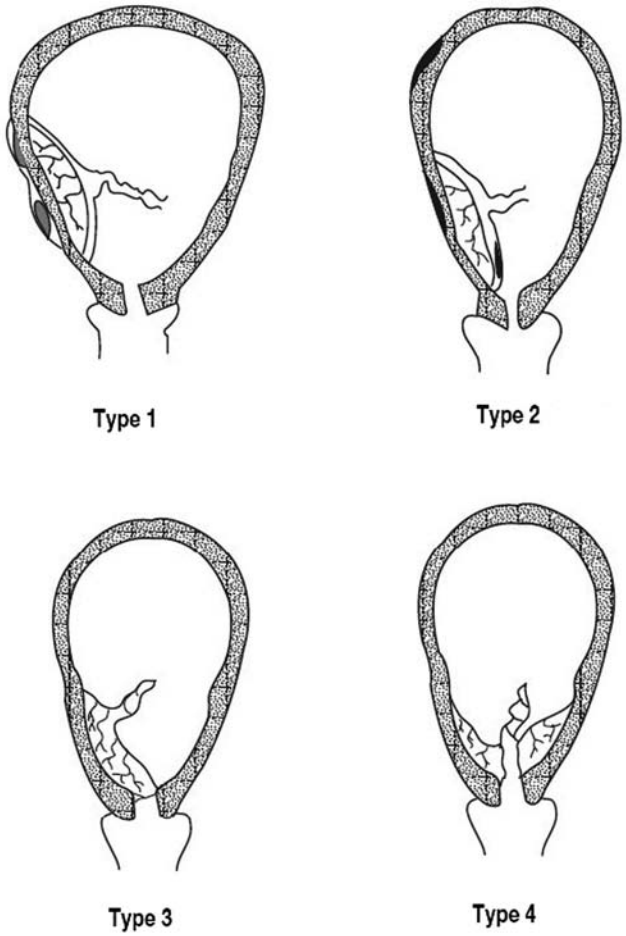

FIGURE 10.1 Types of placenta praevia.

- **Type 2** – Marginal praevia: Where the lower placental edge reaches the internal os.
- **Type 3** – Incomplete central praevia: Where the placental edge overlaps the internal os, but the placental attachment is asymmetric across the internal os.
- **Type 4** – Complete central praevia: Where the placental edge symmetrically overlaps the internal os.

In the modern world, the diagnosis requires localization of the placental site by ultrasound. Placenta with the edge reaching or overlapping the internal cervical os is considered a major praevia. If the placental edge is not covering the internal os but is within 2 cm, it is considered minor or partial praevia. At term, both these varieties are termed *placenta praevia*, and vaginal birth is considerably risky.

The distance of the placental edge from the internal os can change with advancing pregnancy. Typically, the distance from the lower placental edge and internal os increases with growth of the lower uterine segment in late pregnancy (often referred to as 'formation of the lower uterine segment and 'placental migration').

Aetiology and Associated Factors

Placenta praevia occurs when the blastocyst is implanted low in the uterine cavity. Factors associated with the development of placenta praevia are shown in Table 10.2. It is associated with previous placenta praevia, advancing maternal age, increasing maternal parity, large placental size (multiple pregnancy), endometrial damage (previous dilatation and curettage), uterine scars like previous caesarean section or myomectomy, pathology-like endometritis, placental pathology such as marginal cord insertions and succenturiate lobes. Previous history of placental praevia and, curiously, cigarette smoking increases the chance of placenta praevia.

Clinical Presentation and Diagnosis

Most women in the UK will have a routine scan at 21–23 weeks (anomaly scan), which would include placental localization. The placenta will be low-lying in some, necessitating a repeat scan later in pregnancy (Fig. 10.2).

Placenta praevia shoud be suspected in all women with vaginal bleeding after 20 weeks of gestation. A high presenting part, an abnormal lie and painless or unprovoked bleeding are more suggestive of a low-lying placenta, irrespective of previous imaging results. The definitive diagnosis is achieved by ultrasound. Every woman with a suspected diagnosis of placenta praevia at anomaly scan should have diagnosis confirmed by transvaginal scan, to reduce the number of those for whom follow-up will be needed. A further follow up imaging is required for all women where the lower edge of the placenta reaches or overlaps the cervical os at their anomaly scan as follows (Diagram 10.3)[4]:

- Women with vaginal bleed should be managed individually according to their needs.
- In cases of asymptomatic suspected minor praevia, follow-up imaging can be delayed until 36 weeks.

TABLE 10.2 Risk Factors for Placenta Praevia

Risk Factor	Odds Ratio
Advanced maternal age	
Multiparity	
Previous caesarean delivery x 1	2.2
Previous caesarean delivery x 2	4.1
Previous caesarean delivery x 3 or more	22.4
Past history of placenta praevia	9.7
Multiple pregnancy	

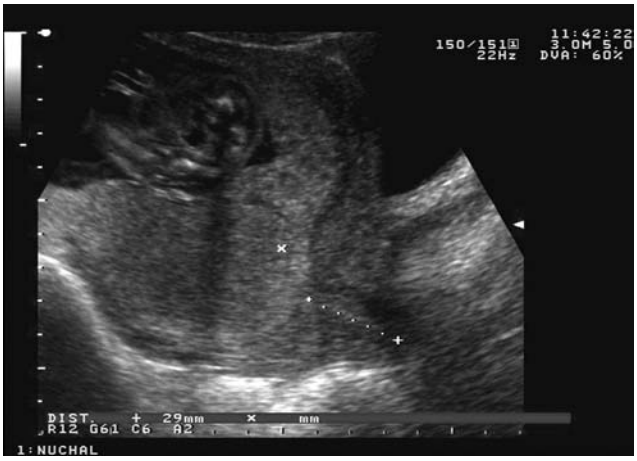

FIGURE 10.2 Abdominal ultrasound scan showing posterior placenta covering the internal os. The cervical canal is marked by callipers.

- In cases with asymptomatic major placenta praevia, a transvaginal ultrasound scan should be performed at 32 weeks to confirm the diagnosis and to allow planning for third-trimester management and delivery.

Approximately 1.5–4.2% of placentas are found to be low lying on ultrasound examination at anomaly scan.[5,6] Several studies have demonstrated that placenta praevia at term will not be encountered unless the placental edge is at least reaching the internal cervical os at mid-pregnancy. Transvaginal ultrasound is safe in the presence of placenta praevia, and is more accurate than transabdominal ultrasound in localization of the placental edge. Ultrasound is useful to observe and document the phenomenon of placental migration from the lower uterine segment. It is widely believed that this process is not a true migration of placental tissue. It is thought to occur due to degeneration of the peripheral placental tissue and slow placental growth as a result of suboptimal vascular supply as compared to better perfused uterine areas, (placental trophotropism). None of the cases presented with confirmed placenta praevia at term, unless the placental edge overlapped the internal os at least by 1.0 cm at the mid-trimester scan. The average rate of placental migration was 0.1 mm/week in the group with overlap of 1.0 cm or more. In contrast, cases where the placenta eventually migrated away from the internal os, the observed mean rate of migration was 4.1 mm/week. Placental edge overlapping the internal os at the mid-trimester scan, and a thick placental edge (where the angle between the placental edge and the uterine wall is less than 135°) are known to be associated with reduced likelihood of placental migration.[5,7]

Placental migration is less likely with posterior placentae and with previous caesarean section. If the placental edge is overlapping, the internal os or is within 2 cm on transvaginal scan at 38 weeks, elective caesarean section is reasonable (Fig. 10.3).

Increased rates of interventions such as caesarean delivery, manual placental removal and a higher prevalence of placenta accreta were encountered in women where the placenta failed to migrate.

Women classically present with painless vaginal bleeding. The bleeds are thought to occur due to the formation of the lower uterine segment. Fetal malpresentation or unstable lie is found in at least a third of cases. Many women with major placenta praevia do not bleed until the onset of labour.

Management

The management of placenta praevia depends upon clinical presentation, gestational age, severity of bleeding and the

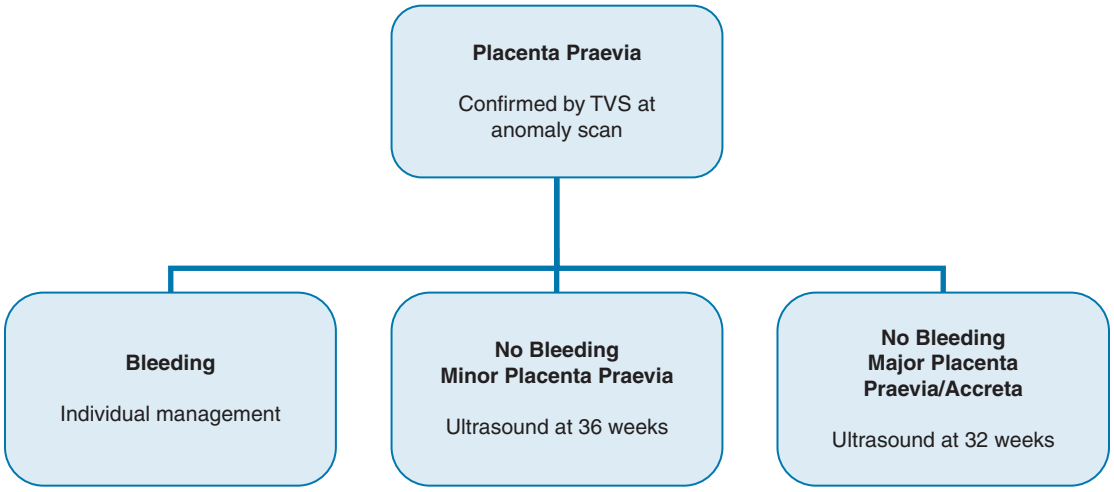

DIAGRAM 10.3 Management of placenta praevia diagnosed at anomaly scan.

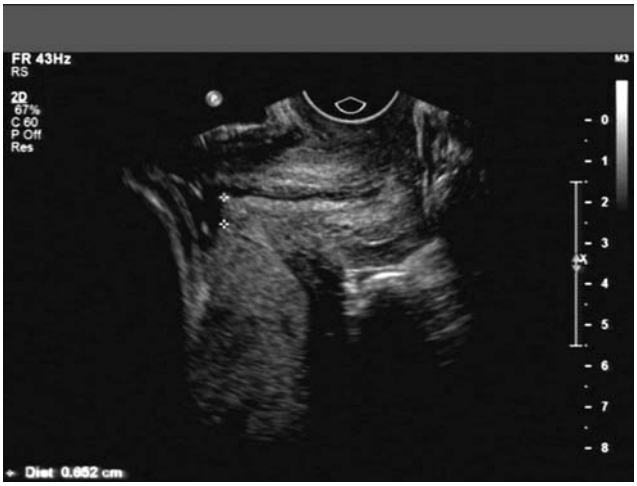

FIGURE 10.3 Transvaginal ultrasound scan showing a posterior low placenta. The distance of the placental edge from the internal os is 6.5 mm.

degree of praevia. Most cases presenting with APH would already be known to have a low-lying placenta. Initial haemorrhages called *warning haemorrhages* are often small and tend to stop spontaneously. Delivery may be needed for severe, intractable or recurrent bleeding. Fetal morbidity is because of iatrogenic prematurity.[8,9]

Women who have had a previous caesarean section and also have either placenta praevia or an anterior placenta underlying the scar of the previous caesarean section are at increased risk of placenta accreta and should be managed as if they have placenta accreta, with appropriate preparations for surgery.[10]

Antenatal imaging by colour flow Doppler ultrasonography should be performed in these women. Where this is not possible locally, such women should be managed as if they have placenta accreta until proven otherwise. Women with major placenta praevia, who have previously bled historically, are admitted and managed as in-patients from 34 weeks of gestation. There is current international opinion, which recommends that all women at risk of major antepartum haemorrhage should be advised to remain close to the hospital of intended birth, for the duration of the third trimester of pregnancy. Constant company of an adult and full-informed consent of the pregnant woman are required for home-based care of women with major placenta praevia. They should be advised to contact the hospital early in the event of abdominal pain or vaginal bleeding. Prior to the delivery a discussion about the delivery plan, risks of severe haemorrhage, need for blood transfusion and the possibility of surgical intervention including removal of the uterus should take place.

The risk of thromboembolism associated with prolonged hospitalization should be kept in mind. Gentle mobility and the use of elastic compression stockings should be encouraged. Anticoagulation to reduce the risk of clots should be reserved for those women at a particularly high risk of thrombosis, and regular unfractionated heparin should be preferred due to its short duration of action.

Traditionally, caesarean section has been the recommended mode of delivery for major placenta praevia, whereas for minor praevia an attempt at vaginal delivery was considered appropriate. Until recently, no evidence-based protocol was available for management of delivery guided by the findings of the ultrasound scan. We reported that in cases where the placental edge was within 1 cm of the internal cervical os within 2 weeks of delivery, all women required a caesarean delivery due to bleeding. It was proposed that cases with placental edge to internal os distance of less than 2 cm be referred to as major placenta praevia and an elective caesarean section should be recommended.[11] In contrast, the likelihood of achieving a vaginal delivery was at least 60% if the placental edge to internal cervical os distance was 2–3.5 cm at the last ultrasound scan within 2 weeks of delivery. However, the risk of postpartum haemorrhage remains high in this group. Therefore, it is recommended that these cases be still referred to as low-lying placenta. An attempt at vaginal delivery is considered appropriate. Vergani and colleagues reported that more than two-thirds of women with a placental edge to cervical os distance of >1.0 cm deliver vaginally without increased risk of haemorrhage.[12] Bronsteen and coworkers also reported that 26/34 (76.5%) of women with placental edge-internal os distance of 1.0–2.0 cm within 4 weeks of delivery and were allowed to labour, achieved a successful vaginal birth.[13] Both these studies were retrospective, and not all eligible women were offered an attempt at vaginal birth. Placenta edge-internal os distance was measured up to 4 weeks before delivery in both the studies.

The above two studies show that safe vaginal birth may be possible even for those women with placental edge to internal os distance of 1.0–2.0 cm. Prospective studies in which the distance was measured closer to the time of birth are needed to confirm these findings. Current guidelines from the Royal College of Obstetricians and Gynecologists (RCOG) recommend caesarean delivery for women with placental edge – internal os distance of less than 2.0 cm. The guidelines also recommend that any women going to the operation theatre with known major placenta praevia should be attended by an experienced obstetrician and anaesthetist. This is especially true if these women also have previous uterine scars, an anterior placenta or are suspected to be associated with placenta accreta. Four units of cross-matched blood should be kept ready, even if the mother has never reported vaginal bleeding. Delivery of women with placenta praevia should not be planned in units where out-of-hour blood transfusion facilities are not available. The choice of anaesthetic technique for caesarean sections is usually made jointly by the anaesthetist, the obstetrician

and the pregnant women. The timing of surgery should be deferred till 38 weeks if possible in order to reduce neonatal morbidity.

PLACENTAL ABRUPTION

Placental abruption is the premature separation of a normally situated placenta from the uterine wall, resulting in haemorrhage before the delivery of the fetus. It occurs in approximately one in 80 deliveries and remains a significant cause of perinatal mortality and morbidity.

Pathology and Aetiology

The precise cause of abruption is unknown. Abruption arises from haemorrhage into the decidua basalis of the placenta. This results in the formation of haematoma and an increase in hydrostatic pressure leading to separation of the adjacent placenta. The resultant haematoma may be small and self-limited or may continue to dissect through the decidual layer. That releases thromboplastins and bleeding into myometrial layers (Couvelarie uterus). This damage interferes with uterine contractility, causing atony predisposing postpartum haemorrhage. However, the bleeding may be in completely or partially concealed, if the haematoma does not reach the margin of the placenta and cervix, the blood loss may not be revealed. Therefore the correlation between the amount of revealed haemorrhage and the degree of actual blood loss is poor. The list of conditions associated with placental abruption can be seen in Table 10.3.

TABLE 10.3 Associated Conditions with Placental Abruption

Gestational hypertensive disease
Advanced maternal age
Increasing parity
Presence of multiple gestations
Polyhydramnios
Chorioamnionitis
Prolonged rupture of membranes
Trauma
Possibly thrombophilias
Maternal use of recreational drugs such as cocaine
Maternal smoking
Unexplained elevation of maternal serum alpha-fetoprotein (MSAFP) levels in the second trimester

A causal relationship between hypertension and abruption is not completely proven. Hypertension may be associated with vascular or placental abnormalities, increased fragility of vessels, vascular malformations, or abnormalities in placentation. Decreased placental blood flow and abnormal endothelial responses to vasoactive substances may be due to the absence of transformation from high-resistance muscular arterioles to low-resistance dilated vessels as in normal pregnancy, and the lack of trophoblastic invasion of uterine vessels. These abnormal placental vessels may predispose to ischemia and rupture of involved vessels, thus leading to placental abruption.

Clinical Presentation

The diagnosis of placental abruption is clinical, based on characteristic signs and symptoms. This is then confirmed by evaluation of the placenta after delivery on gross examination of the placenta, which reveals a clot and/or depression in the maternal surface. Clinical signs of abruption are tense, tender and/or irritable uterus (this may be less obvious if posterior placenta), signs of shock which are out of proportion to estimated blood loss (concealed abruption), frequent uterine contractions on tocograph suggestive of uterine irritability with or without associated fetal heart rate abnormalities on the cardiotocography traces.

There is a serious risk of development of coagulopathy in the mother due to consumption of the clotting factors. The clinical signs of blood loss are more pronounced than the amount of visible vaginal bleeding. Ultrasound is an insensitive and unreliable tool for detecting or excluding placental abruption, as negative sonographic findings are common with clinically significant abruptions.

The diagnosis of placental abruption may not be obvious in less severe cases, particularly if the haemorrhage is largely concealed. It may be misdiagnosed as idiopathic preterm labour. The majority of fetal morbidity is due to prematurity. Low birth-weight, fetal growth restriction, neonatal anaemia and hyperbilirubinaemia are significantly more common. Premature separation of the placenta also leads to fetal hypoxia. In cases presenting with the fetus still alive, fetal heart rate abnormalities are common.

In severe abruption, complications include large haemorrhage requiring transfusion, disseminated intravascular coagulopathy (DIC), infection and rarely, maternal death. A marked elevation in stillbirth rate is observed if the separation exceeds 50% of the placental area.

Management

Action should be swift and decisive once placental abruption has been suspected, because the prognosis for mother and fetus is worsened by delay. Treatment consists of initial

TABLE 10.4 Degrees of Severity of Placental Abruption

Mild (grade 1): This is not recognized clinically before delivery and usually diagnosed by the presence of a retro-placental clot. This is a retrospective diagnosis.
Moderate (grade 2): This is an intermediate grade in which the classical clinical signs of abruption are present but the fetus is still alive. The frequency of fetal heart rate abnormalities is high.
Severe (grade 3): This is the severe grade in which the fetus is dead and coagulopathy may be present. The volume of blood loss is appreciable in this condition.

resuscitation and stabilization of the mother and recognition and management of complications, as described previously. It is individualized based on the extent of the abruption, maternal and fetal reaction to this insult, and gestational age of the fetus. For the purpose of management, Sher and Statland classified placental abruption into three degrees of severity (Table 10.4).

There are several management options for different clinical presentations (Diagram 10.4).

- Expectant: In the hope that the pregnancy will continue.[14]
- Immediate caesarean section.
- Rupture the membranes and aim at vaginal delivery.

In mild placental abruption, the bleeding may stop and the symptoms gradually resolve with satisfactory fetal monitoring and the patient can often be discharged after a few days and managed as an out-patient. The management of moderate or severe placental abruption is resuscitation and delivery of the fetus. Coagulation defects may arise and need prompt attention. This requires management in a labour ward with facilties for intensive monitoring of both mother and fetus. A trial of labour and vaginal delivery is recommended whenever tolerated by the mother as well as the fetus. Labour is usually rapid, and continuous fetal heart rate monitoring is indicated. Delivery should be expedited in the form of an emergency caesarean section if fetal distress is evident. Major abruption should be regarded as an emergency, requiring multidisciplinary input from the obstetrician, anaesthetist and haematologist. A fulminant maternal DIC can occur within hours of a complete abruption. Therefore, delivery should be arranged, as it is the only means with which to halt the DIC. Replacement of blood and its components should begin before surgery. Invasive monitoring with arterial lines and central venous access may be necessary, and women are best treated in a high-dependency unit. Particular attention should be given to maternal urine output, as renal failure is a potential complication.[15]

In the triennium 2003–2005, two maternal deaths were reported attributable to placental abruption in the UK. Multiple studies have shown expectant management to be safe and effective in a select population of patients with preterm placental abruption, provided that the fetal heart rate tracing is normal. In some observational studies, tocolysis allowed a median delay of delivery of several days without increasing neonatal or maternal morbidity, including the need for transfusion or delivery by caesarean section. However, there are no randomized controlled trials, and the benefits of tocolysis remain uncertain.[16]

The probability of a recurrence of abruption increases in future pregnancies following a history of placental abruption. There are no reliable predictors of the timing in pregnancy at which this may happen, and there are no known interventions to reduce recurrence. In the subsequent pregnancy, a practice of elective delivery after reaching fetal maturity is reasonable.

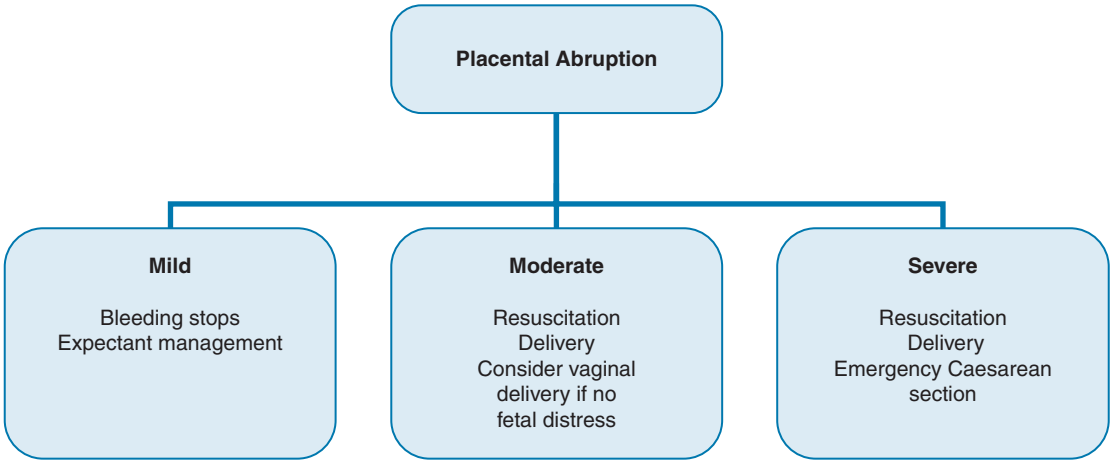

DIAGRAM 10.4 Management options for placental abruption depend on clinical signs.

PLACENTA ACCRETA

A morbidly adherent placenta includes placenta accreta, increta and percreta as it penetrates through the decidua basalis into and then through the myometrium (Fig. 10.4).

Although placenta accreta is uncommon (0.004%) in women with a normally situated placenta, it occurred in 9.3% of women with placenta praevia according to data from a study from Southern California.[17] Ultrasound features of placenta accreta in second and third trimesters include visualization of irregular vascular sinuses with turbulent flow, abnormalities of the bladder wall on ultrasound inspection and, possibly, myometrial thickness of less than 1 mm (Fig. 10.5).[18] Absence of the echo-lucent space between myometrium and the placenta is not a reliable sign (Table 10.5). Colour flow mapping is a useful test for the diagnosis (Table 10.6). Magnetic resonance imaging (MRI) recommended if ultrasound is inconclusive (Table 10.7). When a probability of placenta accreta is raised, multidisciplinary input involving the patient and her family, the anaesthetist, obstetrician and the sonographer should be arranged. The risks from placenta accreta include massive haemorrhage, risk of hysterectomy, infection and even maternal death.[19-21]

Advance planning should be made for management of delivery. Delivery of the baby by caesarean section in the presence of a suspected placenta praevia-accreta should be considered by opening the uterus at a site away from the placenta, and delivering the baby without disturbing the implantation site, in order to enable conservative management of the placenta or elective hysterectomy. Entering the uterus through the placenta in order to achieve delivery is associated with more bleeding and a high chance of hysterectomy**.** Some studies have described successful conservative management of placenta accreta that can preserve fertility. If the placenta separates, the placenta needs to be delivered if it begins to separate. Any haemorrhage that follows, needs to be managed in the normal way. If the placenta partially separates, the separated portion(s) should be delivered and any haemorrhage that occurs should be dealt with. Adherent segments can be left in place, but blood loss in such circumstances can be large and management of massive haemorrhage should follow without delay. Chandraharan E and coworkers introduced a Triple-P procedure as a conservative surgical alternative to peripartum hysterectomy for a placenta accreta that entails perioperative placental localization, pelvic devascularization, placental non-separation with myometrial excision.[22] The woman should be warned of the risks of bleeding and infection postoperatively and monitored. Prophylactic antibiotics may be useful in the immediate postpartum period to reduce this risk.

Neither methotrexate nor arterial embolization reduces these risks and neither is recommended as a routine practice. Follow-up of the woman is recommended using ultrasound and serum beta-human chorionic gonadotrophin (hCG) measurements. Following a decision of leaving, the placenta in situ, delayed haemorrhage requiring hysterectomy has also been reported.[23]

BLEEDING OF INDETERMINATE ORIGIN

The exact cause of bleeding in late pregnancy remains unknown in about 50% of cases presenting with antepartum haemorrhage. The woman typically presents with painless

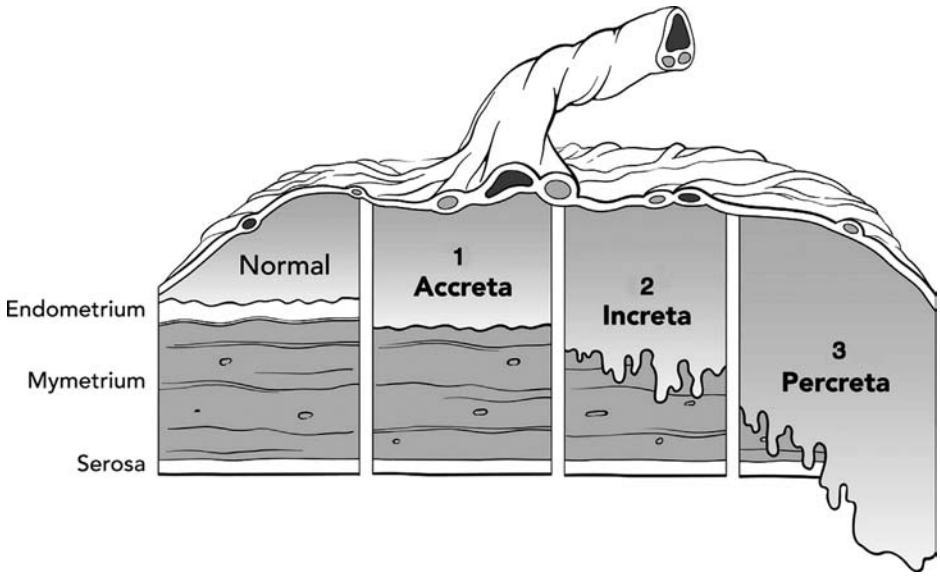

FIGURE 10.4 Types of placenta accreta.

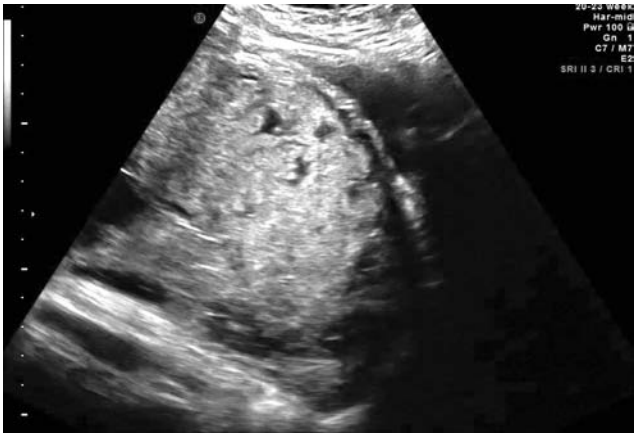

FIGURE 10.5 Ultrasound image of a case with confirmed placenta accreta. Note the echo-luscent spaces (lacunae) in the placental substance.

TABLE 10.5 Grey-scale Ultrasound Features of Placenta Accreta

Abnormal placental lacunae
Loss of the retroplacental echo-lucent zone
Irregular retroplacental echo-lucent zone
Thinning or disruption of the hyperechoic serosa–bladder interface
Presence of focal exophytic masses invading the urinary bladder

TABLE 10.6 Colour Doppler Features of Placenta Accreta

Colour Doppler:
Diffuse or focal lacunar flow
Vascular lakes with turbulent flow on colour flow mapping (peak systolic velocity over 15 cm/s)
Hypervascularity of serosa–bladder interface
Markedly dilated vessels over peripheral sub-placental zone.
Power Doppler (Including 3-D Power Doppler):
Numerous coherent vessels involving the whole junction of uterine serosa and urinary bladder (basal view)
Hypervascularity (lateral view)
Inability to distinguish between cotyledonal and intervillous circulations, chaotic branching of vessels, detour vessels (lateral view).

TABLE 10.7 The Main MRI Features of Placenta Accreta

- Uterine bulging
- Heterogeneous signal intensity within the placenta.
- Dark intraplacental bands on T2-weighted imaging.

vaginal bleeding without ultrasound evidence of placenta praevia. Exclusion of placenta praevia is easy by an ultrasound scan. The diagnosis of placental abruption is based on clinical signs and symptoms, and is difficult to confirm or exclude, particularly in mild cases. Approximately 15% of women with unexplained APH will go into spontaneous labour within 2 weeks of the initial presentation. In the majority of cases, the bleeding is mild and settles spontaneously. Further management is usually expectant, particularly if remote from term. If pregnancy is beyond 37 weeks gestation and the bleeding is recurrent or is associated with fetal growth restriction, elective delivery by labour induction is the management of choice. There may be a case for immediate delivery even if the gestation is below 37 weeks if episodes of bleeding are recurrent or the amount of bleeding is large. Fetal well-being should be monitored if a policy of expectant management is adopted. Once the bleeding has settled and the woman has been observed as an in-patient for 24–48 h, it may be considered safe to allow her to be managed as an out-patient. Antenatal steroids should be administered in view of the risk of preterm delivery, if the gestational age is below 34–36 weeks. In a small proportion of cases where placenta praevia and placental abruption have been excluded, a cause may still be found. These causes include ‘show’, cervicitis, trauma, vulval varicosities, genital tract tumours, haematuria, genital infections and vasa praevia. Many of these conditions are evident at the time of initial speculum examination.

VASA PRAEVIA

Vasa praevia is described when fetal vessels coursing through the membranes over the internal cervical os and below the fetal presenting part, unprotected by placental tissue or the umbilical cord (Fig. 10.6). This can be secondary to a velamentous cord insertion in a single or bi-lobed placenta or from fetal vessels running between lobes of a placenta with one or more accessory lobes. The incidence is approximately 1:6000 pregnancies, but the condition may be under-reported. Vasa praevia carries a significant risk to the fetus. Unprotected fetal vessels are at risk of disruption with consequent fetal haemorrhage, when the fetal membranes are ruptured either spontaneously or artificially. Therefore, vasa praevia often presents with fresh vaginal bleeding and fetal heart rate abnormalities at the time of membrane rupture. Fetal demise can occur in the

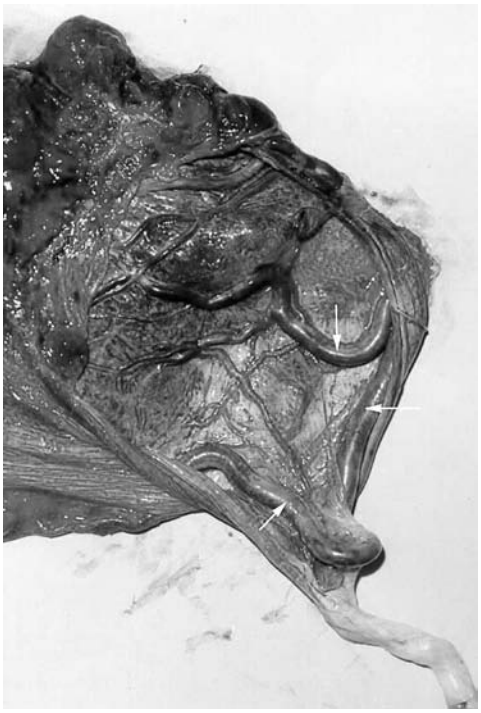

FIGURE 10.6 Velamentous insertion of the cord. Note the unsupported fetal vessels in the membranes. If present over the internal os, these constitute vasa praevia.

absence of prompt intervention and the mortality rate is around 60%. Significantly improved survival rates of up to 97% have been reported if the diagnosis is made antenatally.[24]

The diagnosis is difficult before membrane rupture, but the experienced observer may be able to feel vessels on digital examination below the presenting part. A speculum examination may also show the vessels on inspection. '*Apt test*' on vaginal blood can be performed to demonstrate the presence of fetal blood, but it is often impractical in day-to-day practice. In the presence of vaginal bleeding, especially associated with membrane rupture and fetal compromise, delivery by caesarean section should not be delayed in an attempt to diagnose vasa praevia.

The possibility of vasa praevia should be raised if echogenic parallel or circular lines near the cervix representing the umbilical cord are seen on grey-scale ultrasound. The diagnosis of vasa praevia can be confirmed by Doppler and transvaginal ultrasound studies, if this condition is suspected on grey-scale ultrasound. Several reports have linked vasa praevia to pregnancies resulting from in-vitro fertilization.

The diagnosis should be kept in mind in cases of in-vitro fertilization pregnancies with low placenta, and cases where the placenta had been low-lying at the mid-trimester scan, but has receded from the internal os on repeat assessment. Delivery by a planned caesarean section after fetal pulmonary maturity is established (and preferably at term), but prior to the onset of labour should be aimed for, unless obstetric complications supervene.

INDIAN EXPERIENCE OF THIRD TRIMESTER BLEEDING

Bleeding in late pregnancy or APH may be of placental origin (placenta praevia, abruptio placentae), due to local causes or of unclassified origin. The incidence of antepartum bleeding has been quoted to be 2.5–3.8%.[25-30] 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[31] revealed that placenta praevia 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,[28] 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 colour 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 favourably 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 praevia, abruptio placentae and unclassified causes account for APH. Their distribution as reported in Indian studies has been presented in Table 10.8.

In general, about one-third of patients presenting with antepartum bleeding have placenta praevia. 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.

TABLE 10.8 Distribution of the Causes of Antepartum Bleeding and Fetal Outcome

Authors	Year	Placenta Praevia	Abruptio Placenta	Unclassified APH
Bhatt[26]	1971–1975	36.8%	51.09%	12.04%
Daftary et al.[32]	1981	40.0%	50.0%	10.0%
Menon and Sokhi[31]	1951–1961	18.7%	66.05%	14.8%
Arora et al.[25]	2001	46.4%	25.0%	28.6%
Chauhan and Krishna[28]	2001	33.3%	45.6%	22.1%
PNMR		25.0%	53.5%	28.0%
Low Apgar (<5)		41.0%	40.0%	30.0%

PNMR = perinatal mortality rate

The risk factors in cases of APH include high maternal age, high parity, previous caesarean 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 anaemia, tumours 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 and coworkers from Pondicherry revealed the following data.[25] The incidence of APH was 2.53%. The booking status revealed that 62% of the patients were non-booked 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 praevia, 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 praevia, 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 caesarean section in placenta praevia was 65% as against 50% in accidental haemorrhage. 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, haematinics, 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 praevia (Table 10.9).

Table 10.9 shows that many babies are delivered preterm and are often born with a low Apgar score. In many centres in India, quality neonatal care is non-existent, general paediatricians continue to care for newborns; intensive care facilities are very few in number and often not available.

TABLE 10.9 Perinatal Mortality in Antepartum Bleeding and Its Causes

Authors	Year	PNMR—Contribution of Principal Causes			
		Placenta Praevia	Abruptio Placenta	Prematurity	Perinatal Asphyxia
Arora et al.[25]	2001	25.5%	53.5%	67.0%	38.0%
Bhide et al.[27]	1990	10.0%	54.0%	56.0%	35.0%
Khosla et al.[33]	1989	27.0%	51.0%	66.0%	41.0%
Pinto and Prabhu[34]	1971	32.0%	68.0%	55.0%	45.0%

Important Points

- APH cannot reliably be predicted.
- APH is associated with maternal and perinatal morbidity and mortality.
- It is a good practice to avoid vaginal examination and to advise to avoid penetrative sexual intercourse if placenta praevia is diagnosed.
- All women presenting with APH should be assessed to establish whether urgent intervention is necessary to manage maternal or fetal compromise.
- Multidisciplinary approach and senior input is necessary in making decision about timing and mode of delivery.
- Investigations should be performed to assess the extent and physiological consequences of the APH.
- Ultrasound can be used for the diagnosis of placenta praevia, but ultrasound scan does not exclude abruption. Placental abruption is a clinical diagnosis and no sensitive or reliable diagnostic tests are available.
- In women presenting with APH, an assessment of the fetal heart rate should be performed, usually with a cardiotocograph (CTG) once the mother is stable or resuscitation has commenced, in order to make a decision on the mode of delivery.
- Various tests to differentiate between fetal and maternal blood have been described if vasa praevia is suspected, but are often not applicable in clinical practice.
- All women with APH heavier than spotting and women with on-going bleeding should be recommended hospital stay at least until the bleeding has stopped.
- The pregnancy should receive consultant-led care following APH from placental abruption or unexplained APH, and serial ultrasounds for the monitoring of fetal growth are recommended.

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Chapter 11

Venous Thromboembolism in Pregnancy

Gargee Pandit and Kaizad R. Damania

Chapter Outline

INTRODUCTION

Deep venous thrombosis (DVT) and its complications are a major cause of maternal mortality. Pregnancy itself is a risk factor for DVT. Hence, identification of other problems in pregnancy which can accelerate the chances of DVT, initiation of prophylactic anticoagulation whenever required, early recognition of symptoms and signs of thromboembolism and its prompt treatment, all can help to reduce morbidity and mortality due to DVT.

Venous thrombosis was originally called 'milk leg' as it was thought to occur due to accumulation of milk in the leg veins of a nursing mother. In 1856, Rudolf Virchow, a German pathologist, postulated the Virchow's triad for thrombosis consisting of venous stasis, hypercoaguability and changes in the blood vessel wall (endothelial changes). Pregnancy being a hypercoaguable state increases the risk of venous thromboembolism four to five times more than the nonpregnant state.[1,2] The clinical presentation of VTE is acute, varied and needs a high index of suspicion to diagnose it. Hence, the diagnosis and treatment of deep venous thrombosis in pregnancy poses a challenge to obstetricians worldwide.

The absolute incidence of VTE in pregnancy varies between 0.025 and 0.1%. Around 85% of the gestational VTE are deep venous thrombosis rather than pulmonary thromboembolism. Majority of the DVT occur antenatally (around 65%). Almost half of these antenatal VTE occur prior to 15 weeks gestation. Hence, the need for early risk identification (even prepregnancy) and thromboprophylaxis. However, the rate of VTE is greatest in the puerperial period, the risk being greater than that during the antenatal period. 90% of the cases occur on the left side which may occur due to compression of the left common iliac vein by the right iliac artery (postulated May Thurner syndrome). More than half of the DVT in pregnancy occur in the ileofemoral veins which have a great tendency to embolize and also difficult to diagnose.

PATHOPHYSIOLOGY

Conditions which result in any of the three components of the Virchow's triad can predispose to DVT.

1. **Hypercoaguability:** Pregnancy is a hypercoaguable state. There is alteration in the coagulation proteins. Factors I, VII, VIII, X and plasminogen activator inhibitor increase. There occurs relative resistance to the action of natural anticoagulants protein C and S. The level of free protein S decreases. These changes are further aggravated by thrombophilias both hereditary as well as acquired.[3]
2. **Stasis:** The gravid uterus causes compression of the pelvic and lower limb veins resulting in slowing of venous flow. Similarly, prolonged bed rest and immobilization during pregnancy, labour and postpartum period especially after

caesarean delivery predispose to stagnation of blood in the veins of the lower limbs.[4,5]

3. **Endothelial injury:** This more commonly occurs at the time of delivery. This exposes the highly thrombogenic subendothelial surface and precipitates thrombus formation.

PATHOGENESIS

Various factors play a role in initiating thrombus formation at the cellular level. Deficiency of the natural anticoagulants mainly antithrombin III, protein C, protein S results in clot formation. Any stimulus activating the tissue factor causes activation of the coagulation cascade and conversion of prothrombin to thrombin. Hypoxia at the tissue level is worsened by stasis. This activates hypoxia inducible factor 1 and early growth response protein 1 which in turn stimulate the monocytes to release microvesicles filled with tissue factor. Similarly, hypoxia also stimulates the production of reactive oxygen species which damage the endothelial lining causing thrombogenesis.

RISK FACTORS

These could be pre-existing or new onset/transient.

Pre-Existing Risk Factors

These could be inherited or acquired risks.

Previous history of VTE is a major risk factor for subsequent thrombosis.[6] The risk is three to four times higher in pregnancy. Others include age more than 35 years, parity more than three, obesity (BMI > 30kg/sqm) either preconceptional or in early pregnancy, smoking, oral contraceptives, hormone replacement therapy, sickle cell anaemia, renal disease with nephrotic range proteinuria, cancers like those of the bone, ovaries, lymphomas and chemotherapy.[7] Certain infections like HIV, autoimmune diseases like SLE, etc., also increase the risk of DVT.

Thrombophilias, both inherited and acquired, can cause VTE.[8] Inherited thromobophilias include protein C deficiency, protein S deficiency, antithrombin III deficiency, factor 5 Leiden mutation and prothrombin gene mutation (G20210A). Antithrombin III deficiency is the most thrombogenic among these. It has been observed that individuals with non O blood group have higher levels of von Willebrand factor and factor VIII increasing the risk for DVT.

Transient or New Onset Factors

Majority of DVT occur in early pregnancy due to certain precipitating factors. Dehydration and haemoconcentration caused due to hyperemesis gravidarum or ovarian hyperstimulation syndrome can cause DVT. Excessive blood loss due to conditions like incomplete abortions, ruptured ectopic pregnancy, antepartum or postpartum haemorrhage (>1 litre) disturb the coagulation cascade resulting in thrombus formation. Preeclampsia itself is an independent risk factor. Caesarean section, any surgical procedure in pregnancy or puerperium like appendicectomy, tubal sterilization, systemic infection like pneumonia requiring admission, puerperal sepsis, all increase the risk of DVT. Prolonged immobilization (>3 days) due to any reason may cause DVT. Similar may occur if there is prolonged travel >4 hours with immobilization.[7]

It is necessary to elicit proper history and identify the risk factor or factors so as to grade the potential risk of DVT in the present pregnancy. This stratification also helps to decide the duration and dose of thromboprophylaxis required in the antenatal and postpartum period accordingly.

PREVENTING DVT

From an obstetrician's point of view it is necessary to know who to give thromboprophylaxis, what agent to use when it should be started and for long it should be continued. It is important to identify patients at risk for DVT antenatally or as early as possible in the antenatal period. Various guidelines including those given by RCOG[9] and ACOG[10] all recommend a documented assessment of risk factors for venous thromboembolism in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to the hospital for any reason or develops other concurrent problems. The recommendation also is to start thromboprophylaxis as early in pregnancy as possible, after documentation of fetal viability.

Traditionally, unfractionated heparin was used both for prevention and treatment of DVT. However with the introduction of newer and better agents, low molecular weight heparin has now been recommended as the drug of choice for antenatal thromboprophylaxis. However, difficulty arises in proper patient selection for antenatal heparin therapy.

The RCOG green top guidelines[9] have classified patients at risk for thromboembolism into very high risk, high risk and intermediate risk groups.

- **Very high risk group:** These include patients with either previous VTE on long-term warfarin, previous VTE with antiphospholipid antibody syndrome or antithrombin III deficiency (even if asymptomatic).
- **High risk group:** These include patients with previous recurrent or unprovoked VTE, estrogen or pill provoked VTE, known thrombophilia with a previous VTE, previous VTE with a family history of VTE or asymptomatic high risk thrombophilia (either combined defects or homozygous factor V Leiden).
- **Intermediate risk:** These include patients with previous single VTE with a transient factor which is no longer

present, no thrombophilia or family history or other risk factors. Patients with asymptomatic thrombophilia other than those in the high and very high risk group are in this category.

Another approach is to look at the number of risk factors for DVT. Presence of three or more persisting risk factors, other than previous VTE and thrombophilia, requires thromboprophylaxis antenatally. Patients who did not require thromboprophylaxis antenatally may need it in the postpartum period.

The RCOG recommends continued risk assessment for DVT even in the postpartum period.[9] Heparin therapy for a short duration (1 week postpartum) may be considered in patients with two or more persisting risk factors or those who underwent emergency caesarean or those who had an elective caesarean with one or more risk factors (recommendation level C). In case the risk factors are still persisting then the duration of therapy may be extended. Hence, each case needs to be individualized.

THROMBOPROPHYLAXIS

Noninvasive and Mechanical Methods

Early mobilization, adequate hydration, calf exercises, graduated stockings are all easy and noninvasive methods to prevent DVT and subsequent complications. Graduated compression stockings have been recommended for the following group of patients[9]:

- Hospitalized patients with contraindication to LMWH
- Post caesarean section while in the hospital (along with LMWH) in those with high risk for VTE
- Patients with previous VTE managed on outpatient basis
- Prolonged travel (>4 hours)

These stockings should preferably be thigh length, though knee length ones may also be used if the other is uncomfortable or ill fitting.

Following a symptomatic DVT, patients must continue day time use of graduated compression stockings maintaining an ankle pressure gradient of 30–40 mm of Hg. This helps prevent and reduce the occurrence of symptoms of post-thrombotic syndrome.

Drugs for Thromboprophylaxis

As mentioned previously, the recommended drug of choice is low molecular weight heparin (LMWH). As an alternative, unfractionated heparin is also used. Newer drugs include heparinoids, direct thrombin inhibitors, factor Xa inhibitors, etc. Aspirin is not recommended for thromboprophylaxis in pregnancy. It may be used to improve fetal outcome in certain cases.[9]

Unfractionated Heparin

Heparin is found to be safe in pregnancy.[11] It does not cross the placenta and hence lacks fetal toxicity. There is increased volume of distribution and lesser peak plasma concentration of heparin in pregnancy as compared to the nonpregnant state. Thus, there is need for higher dose and frequency of administration in pregnancy. For prophylaxis heparin is administered subcutaneously. The dose is dependent on the weight and the aPTT value. Standard prophylactic dose for weight between 50 and 90 kg is 5000 units 12 hourly. Some suggest the dose to be increased to 7500 units BD after 14 weeks and 10,000 units BD after 28 weeks. In case of high and very high risk group, therapeutic dose needs to be given to achieve target aPTT value which is 2-2.5 times the INR.

Unfractionated heparin is used intravenously in case of an acute episode of DVT. The loading dose of 80units/kg given bolus followed by 18 units/kg IV so as to achieve the required aPTT of 1.5 to 2.5 times the control. The aPTT must be checked 4–6 hours after loading dose, 6 hours after changing the dose and then daily once target level is achieved. Intravenous heparin is continued for 5–7 days and then converted to subcutaneous.[12] Therapeutic anticoagulation must be continued for at least 6 weeks postpartum or for a total duration of 6 months after the episode. Warfarin is safe during breast feeding but is contraindicated during pregnancy. Warfarin has a 14–50% risk of causing miscarriages, 30% chance of congenital fetal anomalies, bleeding disorder and still birth.[13,14]

However, there are complications of heparin therapy. These include bleeding, skin necrosis, thrombocytopenia and osteoporosis.[11,15]

Heparin induced thrombocytopenia (HIT) could be early or late onset. Early onset or benign or reversible thrombocytopenia occurs generally in the first 48 hours of initiation of therapy. This is self-limited and does not require treatment and resolves in around 5 days. It may be due to activation of platelets by heparin. But the late onset heparin induced thrombocytopenia (HIT) is immune mediated (IgG antibodies). Platelet count falls to <50% of baseline. It occurs due to formation of antibodies against the heparin-platelet factor 4 complex which can result in widespread platelet activation, destruction and aggregation. This can cause bleeding and also paradoxical venous and arterial thrombosis. Heparin needs to be stopped and some other appropriate anticoagulant needs to be given. Platelet transfusion is not indicated as it increases the risk of thrombosis. Late onset HIT usually manifests between 5 and 14 days of heparin therapy. Hence, platelet count should be done prior to initiation as well as after 3 days and 1 week. Thereafter, platelet count needs to be regularly monitored.

Prolonged heparin treatment also causes osteoporosis. Calcium intake should be increased and sometimes heparin therapy requires to be stopped.

The effect of heparin is reversed with protamine sulphate. 1 mg of protamine sulphate neutralizes 100 units of heparin.

Low Molecular Weight Heparin

These are lesser in molecular weight than the standard heparin. They are also safe in pregnancy and do not cross the placenta. They are administered subcutaneously.[16] Members of this group include enoxaparin, dalteparin and tinzaparin. The advantage of LMWH over unfractionated heparin is that complications like bleeding, HIT and osteoporosis are much lesser. There may be risk of osteopenia. Effectiveness of LMWH therapy can be assessed by measuring anti Xa levels. Monitoring anti Xa level is not recommended. However, a baseline platelet count and another one after starting therapy must be done as thrombocytopenia may occur. Subsequent monitoring is not required. The commonly used among these is enoxaparin given as 40 mg daily for prophylaxis. The dose needs to be modified in cases of obesity and renal failure. In the high risk group, therapeutic dose of enoxaparin which is 1 ml/kg twice daily needs to be given. Action of LMWH is not completely reversible with protamine sulphate. Other disadvantages are higher cost and longer half life making management in labour little difficult.

In case of complications (especially HIT) or intolerance to heparin therapy, alternative drugs can be used. Danaparoid is a heparinoid with anti II and anti Xa activity. It can be given subcutaneously or intravenously. No adverse fetal outcome has been noted.[9]

Direct thrombin inhibitors like lepirudin, hirudin, bivalirudin, argatroban are available. These are category B drugs and not sufficient data is available regarding the safety of these drugs in human pregnancy.

Fondaparinuax is an anti Xa inhibitor. Placental transfer of this drug is minimal and it appears to be the safest newer anticoagulant as an alternative to heparin in the absence of danaparoid.[17]

Newer oral anticoagulants have been introduced, dabigatran and rivaroxaban. These act by direct inhibition of thrombin and factor Xa, respectively. However, these have not been approved for use in pregnancy.

Contraindications to heparin therapy: Heparin should be avoided in those patients with high risk for haemorrhage.

- Active antepartum or postpartum haemorrhage
- History of stroke in the last 4 weeks
- Thrombocytopenia (75,000/cmm), haemophilia, von Willebrand disease
- Uncontrolled hypertension (>200/120 mm Hg)
- Severe renal and hepatic disease

Duration of Thromboprophylaxis

As previously mentioned, thromboprophylaxis should begin as early as possible. In the very high risk group, antenatal high dose LMWH and postpartum LMWH or warfarin at least for a period of 6 weeks has been recommended. Both heparin and warfarin are safe during breast feeding. The patients belonging to this group should be collectively managed by obstetricians in consultation with haematologists.[9]

Patients in the high risk group should also receive antenatal and postnatal (6 weeks) LMWH. In the intermediate risk group, antenatal LMWH may be considered, but is not recommended. Strict antenatal surveillance may be all that is required. However, in the course of pregnancy, if three or more risk factors develop, antenatal LMWH may be considered. In the postnatal period 6 weeks prophylactic LMWH is recommended.[9]

In those patients with asymptomatic thrombophilia (excluding homozygous factor V Leiden, antithrombin III deficiency and combined defects) postnatal prophylaxis is recommended for 7 days. This may be extended to 6 weeks if family history or other risks.[9]

Thromboprophylaxis in the Peripartum Period

Anticoagulation needs to be stopped before elective delivery and in labour. Before induction of labour or elective caesarean, UFH needs to be stopped at least 12 hours prior. This interval is 24 hours for LMWH. In case of epidural analgesia and regional anaesthesia, the last of prophylactic LMWH should not be earlier than 12 hours while in case of therapeutic dose, the last dose of LMWH should be at least 24 hours prior. A platelet count must be done if the patient was on UFH therapy previously. Postregional anaesthesia or removal of epidural catheter, LMWH should not be started earlier than 4 hours. Anticoagulation should be restarted in the postpartum period, after 4–6 hours of a normal delivery and 6–12 hours for a caesarean delivery. However, here the danger of haemorrhage is high. Hence anticoagulation must be started as soon as risk of haemorrhage is reduced, since even excessive intrapartum and postpartum haemorrhage can predispose to thrombosis. UFH has an advantage over LMWH of having a shorter half life. Hence, managing a patient on UFH in labour may be relatively easier. Regional anaesthesia and analgesia may be administered if the last dose of UFH has been taken more than 6 hours ago. Similarly, UFH can be started after just 2 hours after removal of the epidural catheter. Due to these reasons, some practitioners may prefer to stop LMWH at 36 weeks and convert to UFH of equivalent dose till labour and delivery.[18]

All women on anticoagulation should be warned regarding per vaginal bleeding. Anticoagulation must be stopped if any such episode. If such a patient goes in labour, the time of the last dose of heparin must be noted. A baseline platelet count and aPTT should be done. Protamine sulphate should be kept available. Fresh frozen plasma should also be kept ready if required. Care should be taken to prevent postpartum haemorrhage.

CLINICAL FEATURES OF VTE IN PREGNANCY

Signs and symptoms of VTE in pregnancy are nonspecific and can be neglected as common symptoms of pregnancy itself. Many women experience mild dyspnea, tachypnea, tachycardia, edema in the lower limbs and low grade ache in the extremities. Physical examination may not reveal any significant findings. Thus, a high index of suspicion is necessary for diagnosing thromboembolism in pregnancy.

The two most common symptoms of DVT are pain and swelling of the lower extremity. 80% of women with DVT have these complaints.[19] Although 70% women experience dyspnea in pregnancy, only few have pulmonary embolism. Classic symptoms of PE are dyspnea, abrupt onset chest pain and cough which are also seen commonly in pregnancy. Thus if the clinician suspects PE, anticoagulation therapy and appropriate immediate diagnostic testing should be performed unless an alternative diagnosis is made. Massive pulmonary embolism may present as syncope, hypotension, pulseless electrical activity or even death.

A severe uncommon form of DVT is phlegmasia cerulea dolens in which there is almost complete venous occlusion in the lower limb outflow including the femoral and the iliac veins. It can be life threatening. The leg appears cyanosed and edematous and may result in gangrene.

Clinical assessment for DVT is done by the Well's score (possible score −2 to 9).[20]

1. **Active cancer (treatment within last 6 months or palliation):** +1 point
2. **Calf swelling >/= 3 cm compared to asymptomatic calf (measured 10 cm below the tibial tuberosity):** +1 point
3. **Swollen unilateral superficial veins (nonvaricose in symptomatic leg):** +1 point
4. **Unilateral pitting edema in symptomatic leg:** +1 point
5. **Previous documented DVT:** +1 point
6. **Localized tenderness along the deep venous system:** +1 point
7. **Swelling of entire leg:** +1 point
8. **Paralysis or paresis or recent cast immobilization of lower extremity:** +1 point
9. **Recently bedridden for more than 3 days, or major surgery requiring regional or general anaesthesia in the past 12 weeks:** +1 point
10. **Any other alternative diagnosis at least likely:** −2 points

Clinical probability for DVT depends on the score:

<0 – low
1–2 – intermediate
>3 – high

If both the legs are symptomatic, the more symptomatic leg is chosen.

Similarly, there is a Well's prediction rule for diagnosing pulmonary embolism.[21]

1. **Previous pulmonary embolism or DVT:** 1.5 points
2. **Heart rate >100/min:** 1.5 points
3. **Recent surgery or immobilization:** 1.5 points
4. **Clinical signs of DVT:** 3 points
5. **Alternative diagnosis less likely than pulmonary embolism:** 3 points
6. **Haemoptysis:** 1 point
7. **Cancer:** 1 point

The probability for pulmonary embolism is low (score 0–1), intermediate (2–6 points) and high (>7 points).

The utility of the Wells scoring system in pregnancy is not fully certain.

The opinion of hematologist is often sought both for diagnosis and subsequent treatment of VTE in pregnancy.

DIAGNOSTIC TESTING FOR VTE

After initial clinical evaluation, applying the appropriate diagnostic test for identifying thromboembolism is necessary.

An approach suggested in a clinical guideline given by the American College of Physicians is as follows:[22]

- Clinical prediction score must be used to estimate the probability of VTE.
- In those with a low probability for DVT or PE, a d-dimer test is a good option; if negative it indicates very low likelihood for VTE.
- Ultrasound is recommended for those patients with intermediate to high probability for DVT.
- Those with intermediate or high probability for pulmonary embolism require diagnostic imaging studies.

Currently, compression duplex ultrasound is the primary diagnostic test to detect DVT. If diagnosis is confirmed on Doppler ultrasound, anticoagulation is immediately started.[9,23] If negative and there is chance of an alternative diagnosis then investigation may be stopped. However, if the suspicion is still high then an alternative diagnostic technique must be employed. These include magnetic resonance imaging (MRI) venography, computed tomography (CT scan), conventional venography or pulsed Doppler studies. Sometimes if the first ultrasound is negative but the index of suspicion is very high, anticoagulation may be continued till performance of the second test. If on repeat testing DVT is negative, the treatment may be discontinued.

For diagnosis of pulmonary embolism, basic initial testing in the form of electrocardiogram and chest X-ray may be done. This can rule out other pathologies if present. The ECG may show the S1Q3T3 pattern and focal opacities may be seen on X-ray. However for definitive testing of PE, CT pulmonary angiography or a ventilation perfusion scan should be done.

CT angiography has a better sensitivity and specificity for moderate emboli. The multidetector CT can better

detect smaller thrombi. It poses very less radiation risk to the fetus. It can also detect other pulmonary pathology if present such as pneumonia, effusion or even aortic dissection. The test is not time consuming. Hence, if chest X-ray is abnormal or if the patient is unstable or in labour, CT angiography may be preferred. However, inter observer variation is more with CT angiography.

As compared to this, V/Q scan interpretation is more standardized and causes minimal radiation exposure. It may be done if the chest X-ray is normal. The disadvantage is that it is time consuming and cannot offer alternative diagnosis.

D-dimer assay has a very high false positive rate but a good negative predictive value. A negative value may be helpful in case of low suspicion of DVT. However in case of high suspicion, d-dimer test does not avoid further testing.

Other laboratory tests that should be done prior to starting anticoagulation are platelet count, aPTT, renal and liver function test. In case of an acute episode, performing thrombophilia screen is not recommended as there would be no change in the immediate management. However, it can be considered as the duration and dose of anticoagulation may differ depending on the reports.

TREATMENT OF ACUTE VTE

The treatment of acute VTE in pregnancy is by heparin either UFH or LMWH. Doses of these have been mentioned earlier.

Supportive therapy in the form of hydration, stockings, monitoring in an intensive care unit should be done. It is also important to monitor fetal well-being.

In case of massive pulmonary embolism with haemodynamic instability, thrombolytic therapy may be considered as only anticoagulation may not reduce obstruction of pulmonary circulation. Thrombolytic agents like streptokinase, alteplase have high molecular weight and may not cross the placenta. However, this therapy is associated with increased risk of maternal bleeding. Thus if thrombolysis is done, the loading dose of heparin should be omitted.

Patients on therapeutic anticoagulation must continue it as long as possible till delivery. During labour and delivery, it should be temporarily stopped and restarted as soon as possible. In the postpartum period heparin is continued, the duration depending on each individual case. Heparin therapy can then be overlapped with oral warfarin monitoring the PT/INR such that it is maintained two to three times the control. Heparin can then be stopped and further anticoagulation can be with warfarin. The usual dose of warfarin is 5 mg daily for therapeutic anticoagulation.

In case of patients in the peripartum period with recent VTE (within 2 weeks), placement of inferior vena cava filters may be considered. This is because fresher the clot, higher is the chance of embolization. These filters are associated with own complications of bleeding, migration, thrombosis at site of placement and others. Hence, patient selection must be appropriate.

FETAL SURVEILLANCE IN PATIENTS WITH VTE

Patients with thrombophilia or other risk factors for VTE in pregnancy may also be at a risk for placental thrombosis. This can cause uteroplacental insufficiency, fetal growth restriction, sudden fetal death, abruption placentae and hence a poor perinatal fetal outcome. Patients who were receiving anticoagulation in the periconceptional period with warfarin are at risk for congenital fetal anomalies. Thus, intense fetal monitoring should be done.

In the first trimester, documentation of fetal cardiac activity should be done as early as possible for early initiation of heparin therapy. Those taking warfarin should be converted to heparin.

A detailed anomaly scan in the second trimester is recommended in all patients at 18–20 weeks. A Doppler at around 24–28 weeks should be done to look for placental insufficiency.

Regular antenatal visits, if the patient is receiving treatment on outpatient basis, are important for monitoring fetal growth clinically. Ultrasound assessment at regular intervals for fetal growth should be done in the third trimester. The importance of fetal kick count should be explained to the patient. In the patients with other obstetric complications like pre-eclampsia, fetal growth restriction, oligohydramnios, etc. further testing with antepartum Doppler, biophysical profile, cardiotocography would be necessary.

As these patients are on anticoagulation therapy, it is always better if delivery is planned rather than encountering such a patient in emergency. After confirming fetal well-being and once pregnancy reaches term, delivery should be planned and appropriate measures taken accordingly.

Thus with a thorough assessment of patients at risk for VTE in pregnancy and appropriate anticoagulation therapy, the morbidity and mortality due to VTE can be reduced.

INDIAN PERSPECTIVE

Studies have shown increasing incidence of VTE in Asian population.[24] As compared to the Western population, the incidence of postoperative DVT in the Indian population is higher. Also in those with symptomatic DVT, the rate of PE is also higher in Indian patients.[25,26] Another study showed that the prevalence of DVT in India is similar to reports published elsewhere and that both inherited and acquired thrombophilia show a strong association with pregnancy.[27]

In women with acute VTE, a study suggests either low dose LMWH throughout pregnancy or IV UFH for at least 5 days, followed by adjusted dose of UFH or LMWH for the

remainder of the pregnancy. Anticoagulation to be continued for at least 6 weeks postpartum.[28]

VTE expert group 2006 suggest a combination of clinical and ECG evaluation along with duplex scan as diagnostic requirements for DVT in pregnancy. There is emphasis on pelvic rest, hydration, early mobilization, resting of the pregnant woman in lateral position to avoid caval compression. It also suggests risk stratification of obstetric patients and depending upon the risk, treatment be given.[29]

Important Points

- Pregnancy increases the overall risk of VTE by 4-5 times.
- Various conditions developing in pregnancy such as pre-eclampsia, obstetric haemorrhage, etc. further increase the risk of venous thrombosis.
- Risk factors for VTE could be pre-existing or transient newly developing. It is important to identify and thus classify patients into risk groups depending on the type and number of risk factors.
- Heparin (preferably LMWH) is the drug of choice for thromboprophylaxis.
- Aspirin is not routinely recommended for thromboprophylaxis in pregnancy.
- Dose and duration of heparin therapy should be individualized depending on the risk group.
- Management of VTE in pregnancy needs collaborative effort of obstetrician and hematologist.
- Thus with a high index of suspicion, thorough assessment and proper anticoagulation, the morbidity and mortality due to VTE in pregnancy can be reduced significantly.

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Chapter 12

Multiple Pregnancy

Tiran Dias and Amarnath Bhide

Chapter Outline

INTRODUCTION

Early diagnosis of multiple pregnancy is important as they carry high risks of pregnancy associated complications irrespective of the period of gestation. Monochorionic multiples are at more than five times higher risk of pregnancy complications than dichorionic counterpart. First trimester scan between 11 and 14 weeks can be used reliably to assess gestational age, chorionicity, orientation and twin pregnancy complications. Serial fetal assessment between 16 and 24 weeks is needed for monochorionic twins in order to identify fetal transfusion syndromes. Fetal growth of multiple pregnancy should be monitored at least once in 4 weeks ultrasonically until delivery. In case of suspected fetal transfusion syndrome, discordant growth >25%, monochorionic monoamniotic multiples and higher order multiples should be managed in tertiary-care set-up. Uncomplicated dichorionic and monochorionic twins should be delivered after 38 and 37 weeks, respectively. Mode of delivery is decided by the presentation and the fetal well-being of the twins. Higher order twins should be delivered by plan caesarean section.

INCIDENCE AND EPIDEMIOLOGY

Ethnic Variation

The incidence of natural twin pregnancy varies with the maternal age, nutritional status of the mother, race and the season of conception. Naturally conceived twin pregnancies occur most frequently in Nigeria, where the majority of such births are fraternal due to simultaneous ovulation. This high dizygotic twinning rate among the Yoruba people in Nigeria is attributed to the high rate consumption of a specific type of yam containing a natural phytoestrogen which may stimulate superovulation. The lowest frequency of twin pregnancies has been reported in Japan, where almost two-thirds of multiple births are identical twins. The prevalence of naturally conceived MZ twins is relatively constant worldwide with a

frequency of approximately 3.5 per 1000 births, and differences in the overall incidence of twining are due to variable frequencies in the prevalence of DZ twins.[1]

Geographical Variation

In addition to the known variation of twining with ethnicity, there are documented geographical changes in the rate of twining within the same ethnic group. Multiple birth rates in the countries in the European Union were published recently and overall, multiple birth rates varied between under 15 per 1000 women with live or stillbirths in Italy, Poland and Estonia to more than 20/1000 in the Denmark and Cyprus. The reported rates for the United Kingdom are 15.0/1000 in England and Wales, 14.3 in Scotland and 15.3 in Northern Ireland.[2]

Advanced Maternal Age

The decline in the DZ twinning rate in the early twentieth century and the increase in twinning rate reported in the late 1970s has been mainly associated with lower mean maternal age with lower number of maternities and an older age at childbearing respectively.[3,4] The reason for the increased frequency of twin pregnancies among mothers with advanced age is thought to be due to dynamic hormonal changes between the pituitary gland and the ovary.[5] In younger women, there is essentially a pool of growing follicles in the ovary which responds immediately to the rise in follicular stimulating hormone (FSH) at the beginning of each menstrual cycle. These growing follicles produce oestrogens which send hormonal signals back to the brain and pituitary gland to down regulate FSH signal.[6,7] This stops the growth of other follicles and the one dominant follicle usually goes on to ovulate at mid-cycle. With age, the pool of ovarian follicles diminishes.[5] Consequently, when FSH rises at the beginning of each cycle, large follicles may not be available to secrete estrogen resulting in a further rise in FSH. When this happens, more than one follicle matures and ovulates, increasing the chance of having twins. Therefore, the increase in DZ twinning with age is thought to be due to rising FSH concentrations driving the selection of more ovarian follicles.

Assisted Reproductive Techniques

Most countries observed a stunning increase in the prevalence of multiple births since the introduction of in-vitro fertilization (IVF) along with large-scale use of ovarian hyperstimulation. In the USA, twin birth rates rose by 75% between 1980 and 2000, representing around 3% of total births.[8] Similar trends have been reported for European countries.[9] The delay in childbearing accounts for no more than 30% of the recorded overall increase in multiple pregnancies.[10] Although an association between advanced maternal age and multiple gestations is clear, it is difficult to differentiate the contribution of assisted reproductive techniques in twin pregnancy rate. The contribution of maternal age and assisted reproductive technologies to multiple births in United States was established by the Centre for Disease Control and Prevention (CDCP).[11] According to the CDCP, both maternal age and the IVF are equally responsible for higher twining rate in last decade.[12] Available data suggest that most twin births are unrelated to infertility therapies.[10,13-15] The rate of triplet and higher order multiple pregnancy has risen four-fold over the same period, which can be attributed almost entirely to infertility treatments. Overall births resulting from infertility treatments account for around 1–3% of all singleton live births, 30–50% of twin births, and for more than 75% of higher order multiple births.[16] Recently, an increase in MZ twin births has been reported after IVF and ovulation induction.[17,18]

MECHANISM OF TWINNING

Twins can be classified by their zygosity (number of originating eggs/zygotes) or by their chorionicity (number of placentas). The latter classification is of major clinical relevance. Most twins are dizygotic (DZ) and approximately 30% of twins are identical [monozygotic (MZ)]. The corresponding distribution of chorionicity is considered to be 80% for dichorionic and 20% for monochorionic twins as one-third of MZ twins result in a dichorionic placenta (Fig. 12.1).

Zygosity

MZ twinning occurs when one single fertilized egg gives rise to two separate embryos. The timing of this division is thought to be an important contributory factor in determining the post-zygotic discordance in MZ twins. It is generally agreed that monozygotic twins are genetically 'identical'. However, it is apparent that genetic differences can exist among monozygotic twins and they are rarely truly 'identical'.[19] The monozygotic twinning process is potentially susceptible to uneven separation of genetic and/or cytoplasmic material between two zygotes. This could result in two cell populations derived from the same sperm cell and ovum but with subtly different characteristics. These may occur as a result of post-zygotic mitotic crossing over, non-disjunction, imprinting differences, inactivation and expression of selected genes, differences in telomere size, X-inactivation and discordant cytoplasmic segregation.[20,21] It is also presumed that there is an equal division of the blastomere mass during the twinning process, but further differences may arise due to unequal allocation of these cells.[19]

In DZ twins, each embryo is derived from different ova. These ova are mainly arisen from the same follicle or separate follicles maturing in the same cycle. Each ovum may theoretically be fertilized by sperm from the same source or

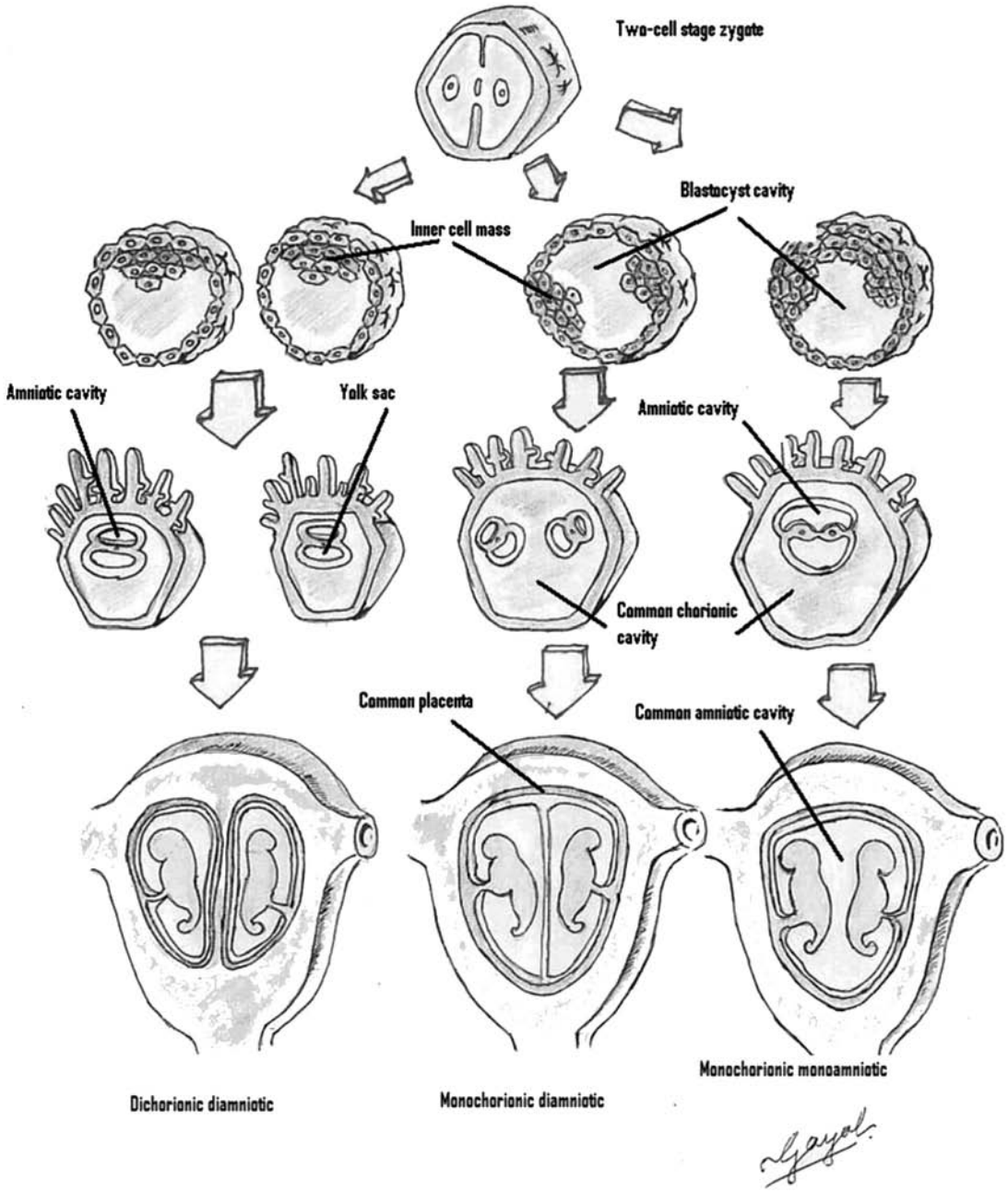

FIGURE 12.1 Mechanism of twinning.

from separate sources. However, almost all human dizygotic twins result from superovulation in the same cycle with fertilization from the same source. Dizygotic twins are different in genetic composition.

Chorionicity and Amnionicity

The timing of zygotic splitting in MZ twins will determine the differences in amniotic sac, chorionic and placental anatomical development.[1] In principle, the earlier the splitting takes place, the lesser are the twins to share common supportive structures. Two separate placentas and sets of membranes are formed if twinning takes place before 96 hours following conception. Such twins are called *dichorionic diamniotic (DCDA) twins*. Majority of monozygotic twins result from separation taking place at the early blastocyst stage and resulting two embryos have a common placenta but two separate amniotic sacs (monochorionic diamniotic, MCDA) (Fig. 12.1). Uncommonly, embryonic splitting occurs late at the stage of bilaminar germ disc and results in monoamniotic (MA) twins with a single placenta and a common amniotic cavity (Table 12.1).

TABLE 12.1 Classification/Distribution of Monozygotic Twins

Days	0–3	3–9	9–12	12–15
Placental number	2	1	1	1
Number of amnions	2	2	1	1
Number of fetuses	2	2	2	1
Classification	DCDA	MCDA	MCMA	Conjoint
Proportion	33%	65%	1%	<1%

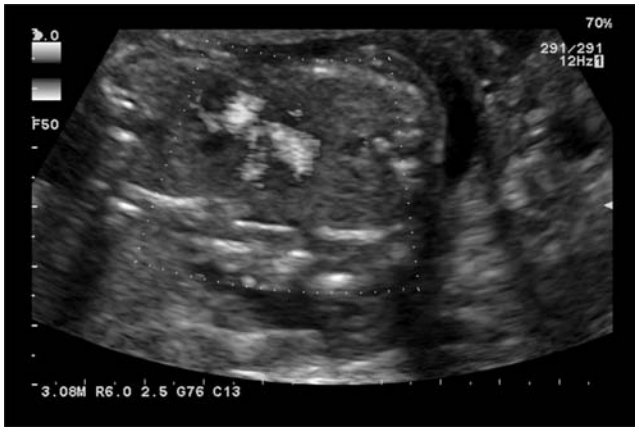

FIGURE 12.2 Thoracophagus conjoint twins sharing common heart.

Rarely, incomplete splitting of the embryo from later zygotic division results in conjoint twinning who sometimes even share somatic organs. The reported incidence of conjoint twins is 1:200 of monozygotic twins or one in 68,000 births.[22] The extent of conjunction is variable, with several recognized types of conjoint twins and combination of different types. These include omphalophagus, thoracophagus, cephalopagus, ischiopagus, craniopagus, rachipagus, pygopagus, parapagus, syncephalus and dicephalus. In all dizygotic twins, each zygote develops its own amnion, chorion and placental circulation, and hence will be dichorionic diamniotic (DCDA) (Fig. 12.2).

COMPLICATIONS OF MULTIFETAL PREGNANCY

Maternal Morbidity

Multiple gestations are likely to have increased physiological responses compared with singleton pregnancies due increased placental and fetal mass.[23,24] This leads to increase stroke volume and heart rate in multiple gestations suggesting that there is a decrease cardiac reserve. These exaggerated physiological changes in multiple pregnancies are associated with an increase in adverse maternal outcomes such as pulmonary oedema, venous thromboembolic disease and even death.[25] Walker and coworkers reported significant increases in maternal complications as such heart failure (RR 12.94, 95% CI 2.69–62.3), haematological morbidity (RR 2.65, 95% CI 2.04–3.46), pre-eclampsia (RR 2.78, 95% CI 2.61–2.88), gestational diabetes (RR 1.12, 95% 1.06–1.18), postpartum haemorrhage (RR 1.88, 95% CI 1.81–1.95), prolonged hospital stay (RR 2.45, 95% CI 2.42–2.47), the need for operative vaginal delivery (RR 1.84, 95% CI 1.81–1.88), hysterectomy (RR 2.29, 95% CI 1.66–3.16) and blood transfusion (RR 1.67, 95% CI 1.13–2.46) in multiple pregnancies than in singletons.[25]

Perinatal Mortality and Morbidity

Twins are associated with an increased risk of prematurity, cerebral palsy, learning disabilities, slow language development, behavioural difficulties, chronic lung disease, developmental delay and perinatal mortality as compared to singletons.[26] The risk of spontaneous loss of the entire pregnancy is 8% for twins.[27] The relative risk of cerebral palsy in twins and triplets compared with singletons is 4.9 and 12.7, respectively.[28] The risk of death by age 1 year is seven times higher in twins and 20 times higher in triplets, as compared with singletons.[29] All above complications are more common in monochorionic twins and accounting for five times higher perinatal morbidities and mortalities than dichorionic twin. Perinatal mortality rate at 42 weeks of a singleton pregnancy is equivalent that of twins at 38 weeks.[30]

Neonatal morbidity with advancing gestation of twins has not been studied much. In a retrospective study by Hack and coworkers, the authors noted 80% of MC twins and 66% of DC twins were admitted to the neonatal unit.[31] The proportion of twins admitted to the NICU was also higher for MC twins than for DC twins (29.4% and 19.5%, respectively). Twins are at increased risk for cerebral palsy (CP) than singleton pregnancies. Both population-based registers of CP and multiple birth registers have confirmed this finding. As multiples are more likely to be born prematurely, comparison of crude prevalence rates of CP in singletons and multiples disregards the confounding effect of prematurity.[32] Petterson and coworkers compared the birth weight specific CP prevalence of twins and singletons. Noticeably, there is no statistically significant difference in prevalence of CP between twins and singletons in low birth weight group (<2500 g). In contrast, twins compared with singletons show a significant increased prevalence of CP in birth weight group >2500 g. As the prevalence of CP is high in normally grown twins, prematurity can only be attributed partly for CP in twins.[32] Approximately 70–80% of time, the cerebral impairment is thought to occur during antenatal period.[33] Cerebral impairment occurring during labour,

usually ascribed to birth asphyxia, accounts for 10% of CP.[34] In twins, it is generally believed that CP is predominantly associated with an insult before the labour. In MC twins, co-twin death can pose a great risk to the surviving co-twin in which can either die or can have severe neuro-development damage due to acute hypoxia and this subsequently lead to CP. Topp and coworkers noted that the incidence of CP was higher in second twin than first-born twins. Intrapartam asphyxia is thought to be the reason for this in the second born twin after vaginal delivery.[35]

Preterm Birth

Unquestionably, twin pregnancies are more likely to be delivered preterm than singleton pregnancies, although the magnitude of preterm delivery may be underappreciated.[36] In 2006, of the 137,085 twins who were delivered in the United States, approximately 60% of the twins were preterm (78,824 infants) and weighed <2500 g (82,799 infants).[36] Approximately 1 in 10 twins were born at <32 weeks of gestation or weighed <1500 g.[36] Aetiology of preterm birth can be categorized into three distinct clinical subtypes based on the aetiology. These groups are preterm birth following preterm prelabour rupture of membranes (pPROM), medically indicated/iatrogenic preterm birth and preterm birth following spontaneous onset of preterm labour without pPROM.[37] Schaaf and coworkers studied a cohort of singleton and multiple pregnancies in Netherlands and their incidence of preterm births between 2000 and 2007.[38] The study showed that overall incidence of preterm deliveries is eight times higher in multiple pregnancies and commonest aetiology for preterm birth been spontaneous onset preterm labour without pPROM. It has become apparent that in singleton pregnancies, cervical length screening between 19 and 24 weeks and progesterone prophylaxis in women with a short would reduce the incidence of preterm birth before 33 weeks by 45%.[39] To and coworkers carried out a study of cervical length measurement in twins between 22 and 24 weeks' gestation and reported that the risk of delivery before 32 weeks' gestation was strongly associated with cervical length.[40] Using cut-offs of <25 mm, <20 mm and <15 mm, the respective detection rates of spontaneous preterm birth before 32 weeks' gestation were 35%, 49% and 67%.[40] There is no evidence for prophylaxis measures to prevent spontaneous preterm births in twins.[41,42] Paradoxically, cervical cerclage in those with a short cervix (less than 25 mm) increases the risk of early preterm birth.[43]

Fetal Growth Restriction and Discordant Fetal Growth

Under normal circumstances, twins grow at the same rate as singletons up to at least 32 weeks' gestation, regardless of chorionicity.[44,45] After 32 weeks' gestation, studies described slower rates of growth for twins.[44] The decreased rate may be related to reduced intrauterine physical space or to uteroplacental insufficiency. The assessment of fetal growth is an essential component of good antenatal care.[46] Symphisiofundal distance (SFD) measurement is inappropriate for growth monitoring in multiple pregnancies. Ultrasound biometry is now standard for growth assessment in multiple pregnancies. Similar to singleton pregnancies, the aetiology for fetal growth restriction (FGR) in DC twins can be diverse. The causes include uteroplacental insufficiency, infection, genetic/chromosomal problems, fetal structural anomalies, placental and cord abnormalities, maternal complications such as hypertension and pre-eclampsia. Although FGR can coexist with growth discordance, fetuses do not have to be small to be growth restricted. Growth discordance can be a marker for FGR. It is important to note that FGR can affect one as well as both twins in which case both twins are small but not discordant.

Growth discordance is a unique complication of twin gestations and can be defined in three ways. First, the '*absolute definition*' only considers the birth weight difference between the smaller and the larger twin. This definition assigns the same degree of discordance to a twin pair of 3000/2500 g and another pair of 1500/1000 g.[47] The second definition is the '*percent definition*', in which birth weight disparity is calculated as a percentage of the larger infant.[47] In the third definition birth weight differences are expressed either in terms of percentiles or in standard deviations from a pre-defined mean of twin birth weights. Fetal growth in DC twins is usually assessed every four–six weeks by ultrasound biometry. In case of severe growth discordance with extreme prematurity, delivery can be delayed till viability to give the maximum benefit to the healthy twin. The healthy twin should not be compromized in the event of a co-twin death, as they have two different placental vascular systems. In a large study including more than 2000 twin pregnancies, the authors demonstrated that perinatal loss in twins with a birth weight discordance of more than 25% was significantly greater (60.9/1000 fetuses) compared to those with a discordance less than 25% (8.6/1000 fetuses). Their analysis further demonstrated that birth weight discordance and gestational age but not chorionicity and individual fetal size percentile were the only independent predictors of perinatal mortality in twin pregnancies.[48]

Complications of Monochorionicity

In almost all MC twins, there is a shared circulation in the placenta with different anastomoses. These could be arterial to venous (A–V), venous to venous (V–V) and arterial to arterial (A–A) anastomoses. It has been increasingly known that sharing placenta between twins is not equal. Combination of placental vascular anastomoses and unequal placental sharing predispose MC twins to specific complications

such as twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR) and the consequence of co-twin death.

Twin-to-Twin Transfusion Syndrome

Twin-to-twin transfusion syndrome (TTTS) occurs if there is shift in the net blood flow between the two fetuses resulting in hypervolemia in one fetus and hypovolemia in the other fetus, this shift is caused by the architecture of the vessels on the surface of the placenta.[49-51] The donor is characterized by hypovolemia and oligo-/anhydramnios. This is often associated with an empty bladder, growth restriction and abnormal Doppler flow in the umbilical artery.[52] Not all MC twin pregnancies are affected by severe TTTS. Inter-twin transfusion through arterio-venous anastomoses is generally balanced, but only about 15% of the MC twin pregnancies are complicated by severe TTTS in case of imbalanced interfetal transfusion.[53,54] Quintero and coworkers introduced a staging system to describe the pathophysiological cascade in the development of mild to moderate and severe TTTS. Stage I represents the most benign form of TTTS with polyhydramnios of the recipient (deepest vertical pocket 8 cm) and oligohydramnios of the donor twin (deepest vertical pocket, 2 cm) with its bladder still visible. Stage V describes the fetal demise of either or both twins (Table 12.2).[55]

Selective Fetal Growth Restriction (sFGR)

Selective fetal growth restriction (sFGR) is a recognized condition associated with MC twin and it is increasingly considered to be an important complication of MC twins, and is associated with significant risks of intrauterine fetal demise or neurological adverse outcome for one or both twins.[56-58] Different fetal parameters have been proposed to define this condition. These include estimated fetal weight (EFW) less than 10th percentile fetal weight discordance and fetal abdominal circumference.[56,59-62] The reported prevalence of sFGR based on an EFW below the 10th centile ranges from 10% to 15%.[60,63,64] Severity of sFGR has been classified according to the Doppler of the umbilical artery diastolic flow. According to this classification, pregnancies are defined as type I (normal umbilical artery Doppler), type II (persistent absent or reversed end-diastolic flow, AREDF) or type III (intermittent absent or reversed end-diastolic flow iAREDF).[65] In recent years, the pathophysiological aspect of sFGR has been considerably improved. It is postulated that the main cause of sFGR is unequal placental sharing where one fetus gets blood from major placental territory than the other. Moreover, this placental territorial mismatch has been related to the subsequent birth weight discordance. Studies showed that birth weight discordance increases with increased placental territory discordance.[50,66-68]

Single Fetal Demise

Single intrauterine death of a fetus in a monochorionic multiple pregnancy has profound consequences for the surviving twin, including a 30–50% risk of death or neurological damage. A recent systematic review of monochorionic twin pregnancy with co-twin death reported an overall risk of neurological abnormality in the surviving co-twin of 18%.[69,70] Many other organ systems of the body can also be affected by co-twin death, including renal cortical necrosis, unilateral damage of a kidney, small bowel atresia, aplasia cutis and terminal limb infarction, etc.[71] In general, DC twins are not at higher risk of neurological damage in case of co-twin death. The rate of neurological abnormality in monochorionic co-twin demise is eighteen times higher than the DC co-twin demise.[69]

Monoamniotic Twins

Monoamniotic twins (MA) twinning is resulted from late embryonic splitting at the stage of bilaminar germ disc and responsible for 1–5% of all monozygotic twins.[72,73] Perinatal mortality of the MA twins has been reported as high as 30–70% in literature.[74,75] Congenital malformations, twin-to-twin transfusion syndrome (TTTS), twin reverse arterial perfusion (TRAP) thought to be responsible for the majority of such losses.[76-79] Cord entanglement is uniformly present in MCMA

TABLE 12.2 Staging of TTTS Based on Sonographic and Doppler Findings (Quintero et al.)

Stage	Poly/ Oligohydramnios	Absent Bladder in Donor	Doppler Abnormalities	Hydrops	Death
I	+	–	–	–	–
II	+	+	–	–	–
III	+	+	+	–	–
IV	+	+	+	+	–
V	+	+	+	+	+

twins and not itself is a bad prognostic sign (Fig. 12.3). There is no consensus regarding antenatal fetal surveillance of MA twins, and some studies recommend in-patient management till delivery. Furthermore, there is a paucity of data regarding optimal timing of delivery in MA twins, but regardless of this, elective delivery at 32–34 weeks is often undertaken.[80-82] Current ultrasound technology enables diagnosis of monoamniotic twinning from 8 weeks' gestation by the delineation of one placenta with two fetuses in a single amniotic cavity.[83]

Twin Reversed Arterial Perfusion (TRAP)

Approximately 1% of monozygotic twins can be complicated with TRAP.[84-86] If the heart of one MC twin stops, the body may continue to be partially perfused by the surviving twin through the large fetal arterial-to-arterial anastomoses that exist in a shared placenta. Diagnosis of TRAP can be suspected with the absence of cardiac pulsation and poor definition of fetal parts in one MC twin. Definitive diagnosis is established with colour Doppler demonstrating reversal of blood flow within the abnormal fetus. Blood flow pattern is characterized by the paradoxical direction of arterial flow towards rather than away from the TRAP twin and retrograde flow in the TRAP twin's abdominal aorta. Different treatment modalities have been described in the literature and the optimal method depends on gestational age at diagnosis and the availability of expertize.[84]

Conjoined Twins (Siamese Twins)

The reported incidence of conjoint twins is 1:200 of monozygotic twins or one in 68,000 births.[86,87] With the introduction of high-resolution transvaginal ultrasound imaging, accurate prenatal diagnosis of conjoined twins can be reliably made early in pregnancy. Standard anatomical classification of conjoint twining is based on the areas of fusion. Overall, the prognosis depends on the type of fusion and presence of associated structural defects (Fig. 12.4).

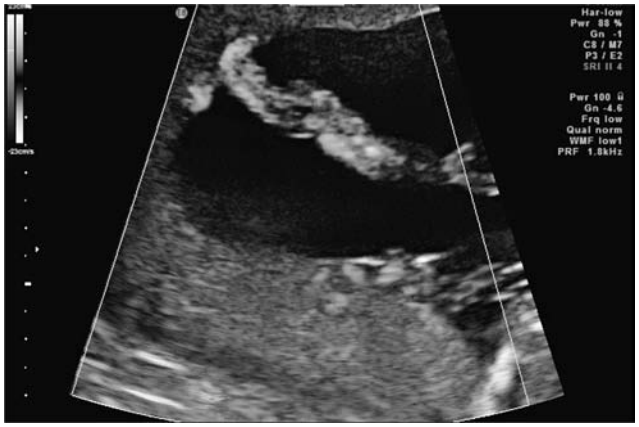

FIGURE 12.3 Ultrasound image shows two umbilical cords inserted without amniotic membrane in-between in monoamniotic twin pregnancy.

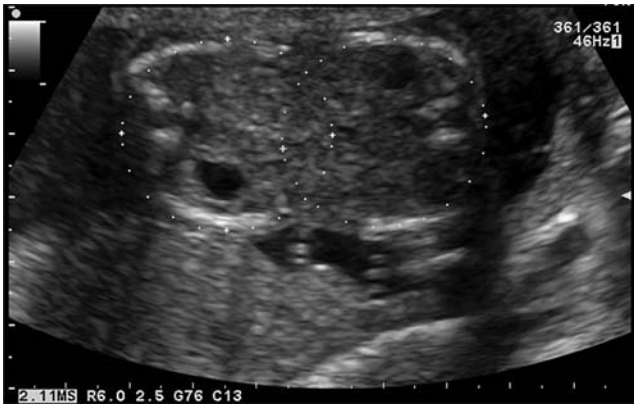

FIGURE 12.4 Omphalophagus conjoint twins.

Fetus in Fetu

Fetus in fetu (FIF) is a rare condition associated with abnormal embryogenesis in a monozygotic pregnancy, wherein a fetus is enclosed within the body of another normally developing fetus.[88] The growth of an FIF initially parallels that of its twin, but stops abruptly either because of vascular dominance of the host twin or an inherent defect in the parasitic twin.[89] FIF is mostly anencephalic, but its vertebral column and limbs are present in almost all cases (91% and 82.5%, respectively). Its lower limbs are more developed than the upper limbs.[90]

ANTEPARTUM MANAGEMENT

Gestational Age Determination

Routine dating of pregnancy from a first trimester crown-rump length (CRL) is superior to the use of menstrual dates.[91] There are two main concerns in twin pregnancy dating. Firstly, whether CRL charts derived from singleton pregnancies can be used to accurately date twin pregnancy. Secondly, which twin's measurement should be considered for dating? Dias and coworkers concluded that singleton CRL charts can be used reliably to date twin pregnancy with the difference of 1–2 days.[92] Furthermore, larger twin's CRL is more pragmatic for dating as pathological largeness in early pregnancy is not biologically plausible but smallness.[93] After 14 weeks as for singletons, head circumference can be reliably used for twin pregnancy dating in second trimester up to 25 weeks.[94]

Chorionicity Determination

Chorionicity can be accurately determined during first trimester ultrasonography. Monochorionic twin pregnancy can be diagnosed in the presence of the T-sign and dichorionic twins with the presence of lambda sign or when two separate placental masses are present (Fig. 12.5).[95] The

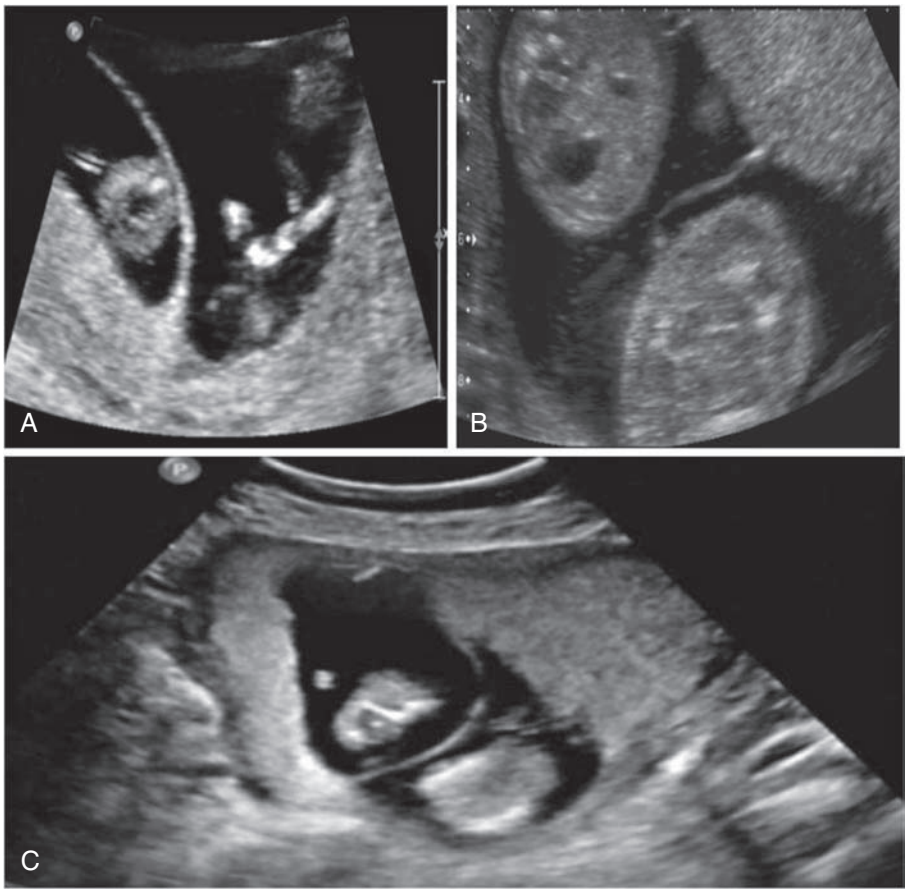

FIGURE 12.5 Ultrasound determination of chorionicity during first trimester. A: Lambda sign, B: T-sign, C: Two different placental masses.

lambda sign was first described by Bessis and Papernik (1981), and referred to the triangular tissue projection extending from the base of the intertwin membrane in early dichorionic pregnancies with a single fused placenta.[96] The term lambda sign has been used interchangeably with the 'twin peak' sign.[97] The absence of the lambda sign leads to the finding of the T-sign characteristic of monochrorionicity. Largest study ofthe accuracy of the T/Lambda signs and number of placentas in the first trimester diagnosis of chorionicity has shown that chorionicity determination is feasible and very accurate at 11–14 weeks gestation.[94] Dias and coworkers in that study reported the sensitivity of T/Lambda signs and number of placentas for the detection of monochrorionicity was 100% with only one dichorionic pregnancy incorrectly assigned as monochorionic.[94] Chorionicity is confirmed by histology at birth (Fig. 12.6). As the pregnancy advances into the second trimester, regression of the chorion-frondosum leads to the gradual loss of the lambda sign. This change explains the observation that the lambda sign is not visible in about 7% of dichorionic pregnancies by 20 weeks' gestation.[95] Therefore, it is mandatory to assign chorionicity in the first trimester. If there is uncertainty about the chorionicity, thermal image of the membrane attachment to the placenta should be retained in the case notes and a second opinion should be sought or the woman should be referred to a specialist without delay, as chorionicity is best determined before 14 weeks.[98]

Systematic Labelling of Twins

A reproducible method for antenatal labelling of twins is important in the management of all twin pregnancies. This is to ensure that biometry from longitudinal growth scans are consistently allocated to the same twin at each visit. Inconsistent allocation of twin in each visit may result in the 'yo-yoing' of fetal growth as smaller and larger twin sizes are swapped repeatedly during the course of the pregnancy. Additionally, when screening for aneuploidies is undertaken, there must be a reliable and accurate system in place to ensure that invasive prenatal diagnosis or selective fetal reduction is carried out on the at-risk or affected twin, respectively RCOG). Each fetus within the twin pregnancy can be orientated at the 11–14 week ultrasound assessment, the fetus contained in the gestational sac closest to the maternal cervix is designated as twin one.[99] The relative orientation of the fetuses to each other is then defined as

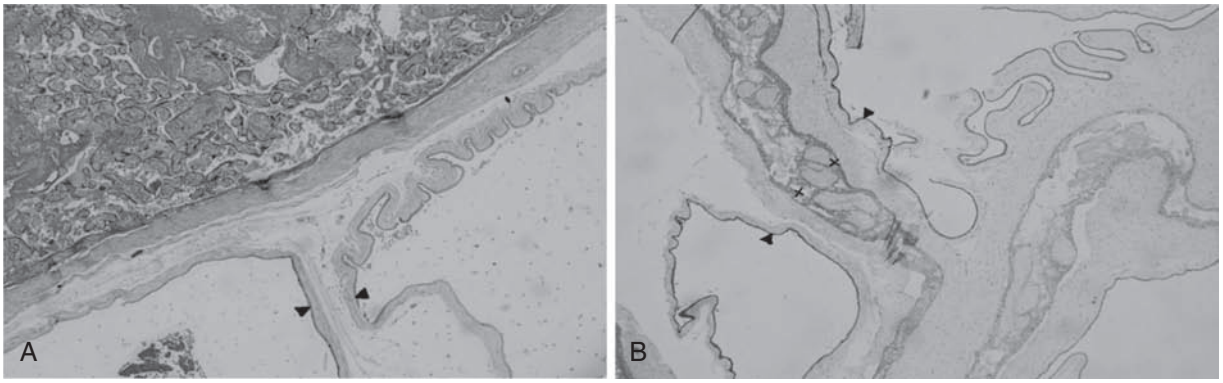

FIGURE 12.6 **(A)** Dividing membrane of monochorionic placenta showing two layers of amnion (arrow heads) on either side. H & E stain X100; **(B)** Dividing membrane of dichorionic placenta showing two layers of chorion (X) sandwich between two layers of amnion (arrow heads) on either side. H & E stain X100.

either lateral (left/right) or vertical (top/bottom) (Fig. 12.7). Lateral fetal orientation is associated with an intertwin membrane running vertically along the longitudinal axis of the uterus and a vertical fetal orientation is associated with an intertwin membrane running horizontally across the longitudinal axis of the uterus.

Screening for Chromosomal Aneuploidy

Risk of underlying chromosomal problems in each fetus depends on zygocity. In dizygotic twins, the maternal age-related risk for chromosomal abnormalities for each fetus is the same as in singleton pregnancies. As majority of dichorionic twins are dizygotic, the chance that at least one fetus is affected by a chromosomal defect is twice as high as in singleton pregnancies. Since all the monochorionic twins are monozygotic their risk for a chromosomal abnormality affecting both fetuses is the same as in singleton pregnancies (Table 12.3). Risk assessment for chromosomal abnormalities in twin pregnancies can be effectively done by a combination of maternal age, fetal NT thickness, fetal heart rate and maternal serum free beta-hCG and PAPP-A.[99,100] Most importantly standardized values of serumbiochemistry should be used in the risk calculation formula in twin pregnancy.[95] In dichorionic twins, the fetus specific risk for trisomy 21 is determined by the differences in NT. The detection rate (>90%) and false positive rate (3% per fetus or 6% per pregnancy) are similar to those in singleton pregnancies.[99] Increased NT in at least one of the fetuses could be an early manifestation of TTTS in monochorionic twins.[102] Therefore, the false positive rate of screening

TABLE 12.3 Risk of Trisomy 21 at 12 Weeks in Twins

	Risk for Trisomy 21 at 12 Weeks		
Age (yrs)	Singleton	Monozygotic	Dizygotic
20	1100	1100	550
25	1000	1000	500
30	650	650	325
31	550	550	275
32	450	450	225
33	400	400	200
34	300	300	150
35	250	250	125
36	200	200	100
37	150	150	75
38	120	120	60
39	90	90	45
40	70	70	35
41	50	50	25
42	40	40	20

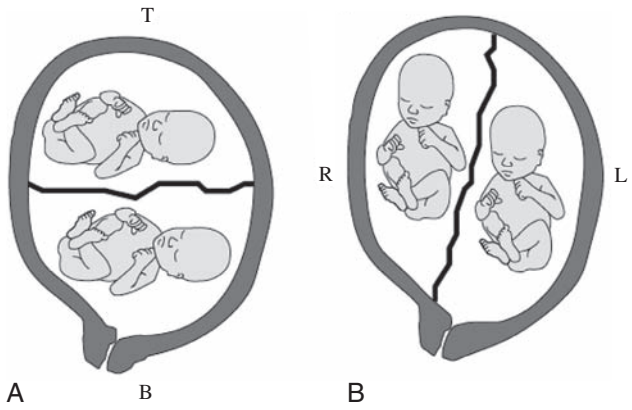

FIGURE 12.7 Diagrammatic representation of twin orientation relative to the longitudinal axis of the uterus. The twins may **(A)** top/bottom [T/B, vertical] or **(B)** right/left [R/L, lateral] orientation.

(8% per pregnancy) is higher than in DC twins. As all monochorionic twins are monozygotic, they invariably concordant for fetal karyotype. In monochorionic twins, the risk for trisomy 21 is calculated for each fetus, based on maternal age, fetal NT and maternal serum biochemistry and then the average risk between the two fetuses is considered to be the risk for the pregnancy as a whole.[103] Amniocentesis in twins is effective in providing a reliable karyotype for both fetuses and the procedure related fetal loss rate is about 2%. In the case of chorionic villous sampling, the procedure-related fetal loss rate is also about 2%, but in about 1% of cases there may be a diagnostic error, either due to sampling the same placenta twice or cross-contamination. In pregnancies discordant for chromosomal defects the main options are either selective fetocide or expectant management. Selective fetocide after 16 weeks of gestation is associated with three-fold increase in risk of spontaneous abortion compared to reduction before 16 weeks. Consequently, if the parents request invasive testing it is preferable to perform CVS rather than amniocentesis.

Prediction and Prevention of Preterm Labour

Prematurity is responsible for adverse perinatal and infant outcomes among twins and triplets compared to singletons. Therefore, the prediction and prevention of spontaneous preterm birth is important goals to optimise outcomes of twin and triplet pregnancies. It has been recognised that cervical length assessment at 22 weeks could be used to screen women with singleton pregnancy that are at risk of preterm birth.[104] Majority of singleton pregnancies with cervical length <1.5 cm at 22 weeks will deliver before 34 weeks.[40] In contrast, there is evidence that cervical length less than 25 mm at 18–24 weeks of gestation in twin pregnancies is a good predictor of preterm birth at up to 35 weeks of gestation.[105] Moreover, recent evidence suggests that a cervical length less than 25 mm measured at 14–20 weeks in triplet pregnancies was associated with spontaneous preterm birth before 32 weeks.[105] Cervico-vaginal fetal fibronectin has very high negative predictive value in screening for preterm birth in singleton pregnancies. However, there is no association between a positive fetal fibronectin test result and the risk of spontaneous preterm birth in twin pregnancies.[105] Similarly as for singleton pregnancies, there is no evidence that home uterine activity monitoring in twin pregnancies is effective in predicting spontaneous preterm birth.[105]

An effective treatment with improved infant morbidity for preterm labour has not been found yet. The administration of progestogens has been proposed as a strategy to prevent preterm birth in women with singleton pregnancies at high risk of preterm delivery. Progesterone reduces the risk of preterm birth particularly singletons with a mid-trimester short cervix, or in women with a documented history of a previous spontaneous birth at <34 weeks of gestation. However, progesterone does not appear to decrease the incidence of preterm birth in multiple pregnancies.[104] Paradoxically, cervical circlage increases the risk of preterm births in multiple pregnancies.[105]

Antepartum Fetal Surveillance

Antenatal fetal surveillance is intended to identify high-risk pregnancies and to intervene appropriately. Since multiple pregnancies are at greater risk of pregnancy complications than singletons, they need frequent care than singletons.

Screening for Complications in Monochorionic Twins

In order to identify TTTS, early serial ultrasound assessments are needed for monochorionic twins. It is recommended to offer ultrasound examinations once in 2 weeks from 16 weeks until 24 weeks and findings should be interpreted according to Quintero classification.[105] In case of suspected TTTS, patient should be referred to regionally commissioned centres with the experience and expertise for management of complicated twin and triplet pregnancies. Routine fetal cardiac assessment is indicated in monochorionic twins as the prevalence of congenital cardiac anomalies is common in monochorionic twins.[106]

Fetal Growth and Well-being Assessment

Symphysis fundal height measurement is not recommended as a method of fetal growth assessment in multiple pregnancies. Serial ultrasound fetal biometry is the method of choice in assessing fetal growth in multiple pregnancies. It is recommended to offer serial growth scans once in 4 weeks from 28 weeks onwards for multiple pregnancies. It is also recommended to refer to a tertiary referral centre when the discordant fetal growth in twins with estimated fetal weight differences of more than 25% as it is associated with increased perinatal mortality and morbidity, which can lead to difficult clinical situations that require decisions to be made relating to investigation and potential delivery with risks to one or both fetuses.

Summary of Antepartum Management

First trimester scan at 11–14 weeks is important in multiple pregnancies in terms of assessing gestational age, chorionicity, labelling and aneuploidy risk assessment. In monochorionic pregnancies 2 weekly ultrasound assessments from 16 weeks is indicated to screen TTTS. As a screening method of preterm labour routine cervical length assessment is not recommended for multiple pregnancies as there is no effective treatment to prevent preterm labour. Serial 4 weekly ultrasound fetal growth case of suspected TTTS and discordant fetal growth >25%, referral to a regional referral centre is recommended.

MANAGEMENT OF LABOUR AND DELIVERY

Timing of Delivery

Timing of delivery of twins should be decided when the benefit of prolonging the pregnancy is outweighed the risk of stillbirth. Perinatal mortality of singletons is increased significantly after 42 weeks.[107] In contrast, perinatal mortality of twins starts to become significantly high after 38 weeks and after 35 weeks for the triplets.[30] Recent, large cohort studies have demonstrated significantly higher stillbirth rates near term even in apparently low-risk monochorionic twin pregnancies.[108] This would justify a differential policy for the timing of delivery in monochorionic versus dichorionic twin pregnancies. Risk of stillbirth in dichorionic twins does not appear to be different between 28 and 38 weeks.[108] Therefore, uncomplicated dichorionic twins should be managed expectantly and delivery can be arranged around 38 weeks. Whereas, in case of prematurity and discordant fetal well-being exists, timing of delivery should be based on parameters of healthy twin. Stillbirth risk in monochorionic twins is five times higher than dichorionic twins and this risk remains high throughout the pregnancy.[109] However, there is no statistically significant increase of stillbirth between 32 weeks and 37 weeks in uncomplicated monochorionic twins. It is justified that otherwise uncomplicated monochorionic twins could be monitored until delivery at 37 weeks.[108] In case of discordant fetal well-being or an anomaly, timing of delivery should be based on the condition of the compromise fetus. This is because of high mortality and morbidity in surviving twin is apparent in co-twin death.[110] In view of uncomplicated triplet pregnancies, continuing beyond 36 weeks 0 days increases the risk of fetal death. Therefore, elective birth from 35 weeks 0 days is recommended for uncomplicated triplets after a course of antenatal corticosteroids has been offered.[105]

Malpresentations

The changes in fetal presentation throughout pregnancy were observed in twins. It has been reported that 78% of the leading twins were vertex at 26–30 weeks' gestational age, 75% at 31–34 weeks and 81% at 35–38 weeks.[111] The incidence of non-vertex presentation for either twin was 73.0%, 64.5% and 59.5% at the same gestational ages.[111]

Mode of Delivery

The decision of which twins should be delivered vaginally or by caesarean section is varied from place to place. The effect of birth order should also be considered as potential risk factor of perinatal death among twins.[112] The second twin is at increased risk of labour complications than first twin mainly due to difficulties in fetal monitoring and at the time of the delivery of the second twin.[113] Smith and coworkers reported an overall five times higher intrapartum death rate in second twin (OR for second twin 5.00, 95% CI 2.00–14.70) in cohort 8073 twins.[113] They also reported that the odds ratio for death of the second twin due to intrapartum anoxia was 21 (95% CI 3.4–868.5) and these associations were similar for twins delivered following induction of labour and for sex discordant twins. In contrast, they demonstrated that there was no association between birth order and the risk of death among 1472 deliveries by planned caesarean section.[113] Armson and coworkers also reported that the second twin was at greater risk of composite adverse outcome (RR 1.62, 95% [CI] 1.38-1.9) than the first twin and this excess risk was evident independent of presentation, chorionicity or infant sex but was associated with planned vaginal delivery, birth weight discordance, and prolonged inter-delivery interval.[113] Furthermore, they showed term *second twins* were less likely to suffer excess morbidity with elective caesarean (RR 1.0, 95% CI 0.14–7.10) than with planned vaginal delivery (RR 3.0, 95% CI 1.47–6.11). However, the available evidence is inconclusive to suggest the best method of delivery in twin gestations to optimize maternal and fetal outcome.

MANAGEMENT OF HIGHER ORDER MULTIPLE PREGNANCY

Women with higher order pregnancies are at increased risk of all the fetal and maternal complications than twin pregnancy. Therefore, they need more frequent check-ups throughout pregnancy. Women with higher order multiples should receive a first trimester ultrasound scan when crown-rump length measures from 45 to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days). The purpose of this scan is to estimate gestational age, determine chorionicity and screen for Down syndrome.[105] Determining chorionicity should be based on the number of placental masses, the lambda or T-sign and membrane thickness. All higher order multiples should be labelled according to the relative position of each fetus (for example, upper and lower, or left and right) and this should be documented clearly in the woman's notes to ensure consistency.[105] Fetal growth restriction is more common in higher order multiples and they should receive serial ultrasound scans to estimate fetal weight discordance using two or more biometric parameters at every ultrasound scan from 20 weeks onwards. A difference in size of 25% or more between twins or triplets should be considered as a clinically important indicator of intrauterine growth restriction and offer referral to a tertiary level fetal medicine centre. Delivery of uncomplicated triplet pregnancies should be undertaken electively from 35 weeks 0 days by caesarean, after a course of antenatal corticosteroids.[105]

Multifetal Pregnancy Reduction

Multifetal pregnancy reduction (MFPR) was initially used as a procedure to selectively terminate fetuses with congenial abnormality or genetic disorders. Subsequently, its usage was extended to terminate one or more fetuses of a multiple gestation pregnancy while allowing some fetuses to remain alive. Risks associated with multifetal pregnancy reduction and the ethical issues related to it are still a debate. Therefore, sensitive counselling before the procedure is very important. When multifetal pregnancy reduction is considered, the decision of how many fetuses to be reduced should be made by considering combination of financial, social and emotional aspects. A reduction to a singleton may be a choice for some patients but there is some controversy as to whether women pregnant with twins should be offered reduction to a singleton.[114] MFPR is usually carried out through transabdominal route with ultrasound guidance. A 22 gauge needle is inserted into the fetal thorax under direct transabdominal ultrasonographic visualization and 2–3 mEqKcl are injected to each fetus that is to be terminated. Asystole should be observed for 3 min before the needle is removed. MFPR is associated with 5–7% risk of miscarriage.[115]

Important Points

- Multiple pregnancies are at increased risk of pregnancy complications than singletons.
- Pregnancy outcome of the multiple pregnancy is mainly determined by the chorionicity.
- First trimester ultrasonography is very reliable in determining accurate pregnancy dating, chorionicity, orientation and abnormal twin gestation.
- Monochorionic twins should be monitored more often between 16 and 24 weeks for early diagnosis of fetal transfusion syndromes.
- Fetal growth of the multiple pregnancy should be monitored 4 weekly from 26 to 28 weeks.
- In case of suspected fetal transfusion syndrome, discordant growth >25%, MCMA and higher order twins should be managed in specialized centre.
- Uncomplicated DC twins should be delivered at 38 weeks, whereas in an uncomplicated MC twins should be delivered after 37 weeks.
- Mode of delivery is decided by the presentation of presenting twin, gestation of delivery, chorionicity and fetal well-being at the time of delivery.
- Multifetal pregnancy reduction is an option to improve pregnancy outcome in higher order multiples.

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Chapter 13

Hypertensive Disorders in Pregnancy

Vandana Bansal and Kaizad R. Damania

Chapter Outline

INTRODUCTION

Hypertensive disorders represent the most common medical complication of pregnancy affecting between 7–15% of all gestations and account for approximately a quarter of all antenatal admissions.[1] According to World Health Organization's (WHO) systemic review on maternal mortality worldwide, hypertensive disease remains a leading cause of direct maternal mortality. Together with haemorrhage and infection, hypertension forms the deadly triad that contributes to morbidity and mortality during pregnancy and childbirth.[2]

Although maternal mortality is much lower in high-income countries than in developing countries, the incidence of preeclampsia has risen in US.[3] This might be related to an increased prevalence of predisposing disorders such as chronic hypertension, diabetes and obesity.[4] About 16% of maternal deaths were attributed to hypertensive disorders in developed countries and over half of these hypertension-related deaths were preventable.[5] Recent confidential enquiry into maternal deaths in UK found hypertensive disorders to be the second leading direct cause of maternal death.[6]

Hypertensive disorders are responsible for not only maternal deaths but also substantial morbidity for the pregnant women. One-third of severe maternal morbidity was a consequence of hypertensive conditions in UK.[7] Long-term impact of hypertension in pregnancy in the form of chronic hypertension and increased lifetime cardiovascular risk is also present.

Hypertensive disorders also carry a risk for the baby. Hypertension and/or proteinuria is the leading single identifiable risk factor in pregnancy associated with stillbirth. In the most recent UK perinatal mortality report, 1 in 20 (5%) stillbirths in infants without congenital abnormality occurred in women with preeclampsia. Preeclampsia is strongly associated with fetal growth restriction, low birthweight, spontaneous or iatrogenic preterm delivery, respiratory distress syndrome and admission to neonatal intensive care.[8]

Preeclampsia contributes significantly to overall preterm birth rate, both spontaneous and iatrogenic. About 1 in 250 primigravidas (0.4%) will give birth prior to 34 weeks as a consequence of preeclampsia and 8–10% of all preterm births result from hypertensive disorders. Half of women with severe preeclampsia give birth preterm.

Growth restriction arising from placental disease is common, with 20–25% of preterm births and 14–19% of term births in women with preeclampsia being less than the 10th centile of birthweight for gestation.

DEFINITIONS

Hypertension

The following thresholds, used by National High Blood Pressure Education Program Working Group (NHBPEP) and the American College of Obstetrician and Gynecologists (ACOG), to define "hypertension" have been accepted by most international organizations.[9,10] Hypertension in pregnancy is defined as:

- Systolic pressure level of 140 mmHg or higher and/or
- Diastolic blood pressure of 90 mmHg or higher (Korotkoff V)

These measurements have to be confirmed on at least two occasions 4 to 6 hours apart but within a maximum of a week period. Elevation of more than 30 mmHg systolic or more than 15 mmHg diastolic above the patients' baseline has been abandoned from the diagnostic criteria of hypertension as it has not proved to be a good prognostic indicator. Available evidence does not support the notion that these women have an increased risk of adverse outcomes.[11] Nevertheless such a rise, without an absolute value above the diagnostic criteria, may be significant in pregnant women with hyperuricemia and proteinuria. Close monitoring of such patients may be appropriate.

Diastolic blood pressure is determined as a disappearance of sound (Korotkoff phase V). Korotkoff phase V (disappearance) as opposed to Korotkoff phase IV (muffling) was chosen as it is more reproducible and showed better correlation with true diastolic blood pressure in pregnancy. Where KV is absent, KIV should be accepted. For accuracy, mercury sphygmomanometer is preferred. Automated systems for blood pressure measurements have been shown to be unreliable in severe preeclampsia and tend to under-record the true value particularly the systolic blood pressure.[12]

The blood pressure level should be taken with an appropriate size cuff (length 1.5 times the upper arm circumference or a cuff with a bladder that encircles 80% or more of the arm) with the patients in an upright position with their right arm supported in horizontal position at the level of the heart, after a 10 minute or longer rest period. For patients in the hospital, the blood pressure can be taken when the patient is sitting or left lateral recumbent position with the arm at the level of the heart. The cuff should encircle and

cover two-thirds of the length of the arm. A large cuff should be used for obese patients. When the patients lie on their left side and the blood pressure is taken on their right arm, the blood pressure is falsely low by as much as 15 mmHg.

Proteinuria

It is defined as the urinary excretion of 300 mg or more of protein in 24 hours urine collection or a urine protein/creatinine ratio of ≥ 30 mg/mmol. This usually correlates with ≥30 mg/dl (≥1+ by qualitative estimation using reagent strips) in at least two random urine samples collected 4 to 6 hours apart, with no evidence of urinary tract infection. 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. Urine concentrations vary widely during the day; hence the diagnosis should be based on a 24-hour urine protein determination. Urine protein/creatinine ratio has not been found to be an accurate method of quantifying protein excretion and cannot replace 24 hour urine excretion. However, this ratio may be used when assessment for proteinuria needs to be done on outdoor basis.

Although the visual dipstick test has a poor predictive value, it still remains an important screening test due to easy availability, convenience and low cost. Approximate equivalence is Trace=0.15 to 0.3 g/l, 1+ = 0.3 g/l, 2+ = 1g/l, 3+ = 3g/l.

CLASSIFICATION OF HYPERTENSIVE DISORDERS IN PREGNANCY

The clinical classification adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP) reflects the pathophysiology of the disorder as well as the potential maternal and perinatal risks and outcomes.[9]

Hypertensive disorders during pregnancy can be included into four well-defined groups:

- Gestational hypertension
- Preeclampsia, eclampsia
- Chronic hypertension
  - Essential
  - Secondary
- Preeclampsia superimposed on chronic hypertension

Gestational hypertension: New onset hypertension developing after 20 weeks of gestation, during labour, or in the first 24 hour postpartum, without proteinuria, or any other systemic features of preeclampsia, in a previously normotensive nonproteinuric woman and the blood pressure resolves within 3 months postpartum.

Preeclampsia: Hypertension associated with proteinuria greater than 0.3g/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).

Chronic hypertension is defined as hypertension present before 20th week of pregnancy or that is diagnosed preconceptionally. Hypertension should be documented on at least two occasions, measured at least 4 hours apart. Blood pressure elevation that persists > 12 weeks postpartum is also retrospectively considered as chronic hypertension.

- ***Essential hypertension*** is diagnosed when there is no apparent underlying cause for chronic hypertension.
- ***Secondary hypertension*** may be caused by renal parenchymal disease or scarring, renovascular disease, endocrine disorders or coarctation of aorta.

Preeclampsia superimposed on chronic hypertension: It is diagnosed when one or more features of preeclampsia (e.g. elevated liver enzymes, low platelets, proteinuria) develop for first time during pregnancy after 20 weeks, in a woman with pre-existing chronic hypertension.

As per the NICE guidelines, for the purpose of management, hypertension is further divided as per the severity into mild, moderate and severe hypertension.[7]

- ***Mild hypertension:*** Systolic blood pressure 140–149 mmHg, diastolic blood pressure 90–99 mmHg.
- ***Moderate hypertension:*** Systolic blood pressure 150–159 mmHg, diastolic blood pressure 100–109 mmHg.
- ***Severe hypertension:*** Systolic blood pressure 160 mmHg or greater, diastolic blood pressure 110 mmHg or greater.

GESTATIONAL HYPERTENSION

Gestational hypertension is the most frequent of the hypertensive disorders of pregnancy with prevalence between 6 and 15% in nulliparous and 2–4% in multiparous.[13] 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.[14] 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. The condition is more frequent in obese women with multiple gestations, diabetes and a previous history of preeclampsia.

Gestational hypertension was earlier referred to as "pregnancy-induced hypertension," or "PIH" and considered to be a relatively benign condition. The old name was a source of confusion because it was also used to denote all forms of hypertension during pregnancy. Also, the condition is not benign and pregnancy outcomes in severe gestational hypertension are worse than in mild preeclampsia.[15]

It is recognized that some women classified as gestational hypertension may have undiagnosed chronic hypertension which may become evident only when hypertension does not return to normal after 3 months postpartum.

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 on two occasions at least 4–6 hours apart.

Maternal and Perinatal Outcome

Maternal and perinatal morbidity are increased in women with gestational hypertension. Women with mild gestational hypertension have an increased incidence of obstetrical interventions such as induction of labour and caesarean section. Women with severe gestational hypertension have a higher incidence of preterm birth and small for gestational age (SGA) newborns than in those with normal pregnancy or with mild preeclampsia.[15]

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 subsequently progress to develop the clinical syndrome of preeclampsia.[16] The likelihood of progression to preeclampsia depends on severity of hypertension and the gestational age at the time of diagnosis. The earlier the gestation at presentation and more severe the hypertension, the higher the risk of developing preeclampsia and associated morbidity. 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. Early gestational hypertension shares with preeclampsia a high incidence of poor placentation with histologic evidence of placental ischaemia and haemodynamic changes characterized by vasoconstriction and decreased cardiac output. Gestational hypertension near term (after 35 weeks) is associated with only 10% risk of preeclampsia and little increase in risk for adverse pregnancy outcome and results in good perinatal outcome.[16]

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 (2002) also found difference in outcome depending on ethnicity with African-American showing higher incidence of placental abruption, stillbirths and neonatal deaths than in White women.[17]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 placental insufficiency, fetal growth restriction, iatrogenic prematurity, admission to neonatal intensive care unit and placental abruption.[15] Overall, their outcome is quite similar to that in women with severe 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 13.1). There are major and minor risk factors. The first and most important major risk factor to be considered in such evaluation is the degreeof blood pressure 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, oligohydramnios, and abnormal uterine and umbilical Doppler assessment.

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 clinic visit. They are given a blood pressure threshold, usually systolic ≥ 150 or diastolic ≥100 that requires clinic or hospital evaluation. They also need to be

BOX 13.1 Criteria to Identify High-Risk Women with Gestational Hypertension

- Blood pressure ≥ 150/100
- Gestational age less than 30 weeks
- Evidence of end-organs damage (elevated serum creatinine, liver enzymes, LDH, decreased platelet count)
- Oligohydramnios
- Fetal growth restriction
- Abnormal uterine and/or umbilical Doppler velocimetry

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 clinic or hospital if the result is ≥ 1+. 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 clinic visits every week. The weekly assessment of patients with gestational hypertension and no risk factors must include a systemic review of the maternal and fetal status. From the maternal side, the review includes assessment of 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. Performance of nonstress test (NST) is probably unnecessary if the fetal growth and uterine, umbilical and cerebral fetal Dopplers are normal at initial assessment.

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 hypocalcuiria 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 it is 0.20 ± 0.18 and in preeclampsia it is 0.03 ±0.03. A 24-hour urine collection for significant proteinuria (≥ 300 mg) although cumbersome may be advised.

The development of proteinuria, elevation of the blood pressure above the threshold, decreased fetal movements, poor fetal growth or development of other signs of preeclampsia, 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 to 39 weeks. At this time, labour may be induced using 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 13.1, 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 a24-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.[18] 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 outcomes of pregnancy. However, there are some studies suggesting benefits. Tuffnell et al (1992) in a small trial randomized women to care in a day care 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 care unit.[19] 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.[20] It is common to observe that the blood pressure decreases significantly and edema decreases or disappears after a few days rest in hospital. However, complete bed rest may do more harm than good. Prolonged bed rest is associated with venous stasis and risk of venous thromboembolism, bone demineralization and muscle disuse atrophy.

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 oedema) associated with uncontrolled hypertension. The recent NICE guidelines on hypertension in pregnancy suggests need to treat moderate hypertension (BP 150/100 mmHg) and above with antihypertensives with an aim to keep diastolic blood pressures between 80–100 mmHg and systolic BP less than 150 mmHg.[7] Fetal surveillance is of the greatest importance in the expectant management of women with severe gestational hypertension. NST and AFI 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 abruption placentae, arrest of fetal growth, worsening of Doppler evaluation with absent or reversed umbilical artery (UA) diastolic flow and development of severe alternations in the fetal heart rate (FHR) monitoring.

Delivery

Gestational hypertension is not by itself an indication for caesarean section except in severe cases unresponsive to

treatment or with fetal growth restriction. 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. If the cervix is unripe and the cervical length is ≥ 2.5 cm, it is better to deliver by caesarean and avoid a prolonged induction. If the cervix is ripe, vaginal delivery will be the best option. For women with mild gestational hypertension, induction of labour after 38–39 weeks and vaginal delivery is appropriate.

Long-Term Prognosis

The risk of recurrence of gestational hypertension ranges between 16–47%. Chance of the patient developing preeclampsia in future pregnancy is low (2–7%).[7]

CHRONIC HYPERTENSION AND PREGNANCY

Chronic hypertension complicates about 0.5–3% of all pregnancies. With the current trend of childbearing at an older age and the epidemic of obesity, the incidence of chronic hypertension in pregnancy is expected to rise.

Chronic hypertension in pregnancy is defined as hypertension before pregnancy or before the 20th week of gestation, on more than one occasion, at least 4–6 hours apart. Hypertension is defined as systolic blood pressure of 140 mmHg or greater, or diastolic blood pressure of 90 mmHg or greater or both. Persistence of hypertension for 12 weeks postpartum is also retrospectively described as chronic hypertension.[21]

Establishing the diagnosis of chronic hypertension is straightforward if the patient is already on antihypertensives before pregnancy. However, problem with this definition is that in many patients it 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 undiagnosed chronic hypertension exhibit a physiological fall in blood pressure in the second trimester and are erroneously classified as gestational hypertensive when their blood pressure increases in the third trimester.

Chronic hypertension in pregnancy is subclassified as:

- **Mild hypertension:** Systolic blood pressure of 140–159 mmHg or Diastolic blood pressure of 90–109 mmHg.
- **Severe hypertension:** Systolic blood pressure of 160 mmHg or greater or diastolic blood pressure of 110 mmHg or greater.[22]

Pregnant women with chronic hypertensive disorder, regardless of their cause, may develop superimposed preeclampsia in up to 30% of cases. Superimposed preeclampsia usually presents earlier in gestation than pure preeclampsia and tends to be more severe and often associated with fetal growth restriction. Criteria for diagnosis of superimposed preeclampsia on chronic hypertension include[9]:

- New onset proteinuria ≥ 300 mg/24 hours in hypertensive women with no proteinuria before 20 weeks gestation.
- Sudden increase over baseline proteinuria or baseline hypertension or platelet count < 100,000 in women with chronic hypertension and proteinuria before 20 weeks gestation.

Aetiology

Essential hypertension, i.e. elevated blood pressure without an underlying cause, is responsible for 90% of cases of chronic hypertension in pregnancy. In 10% of cases, chronic hypertension is secondary to one or more underlying disorders such as chronic renal disease, endocrine disorders, collagen vascular disease or other causes (Box 13.2).

Pathophysiology

Normal pregnancy is characterized by increased plasma volume (preload), increased cardiac output, and decreased peripheral vascular resistance (PVR). These changes result in a physiologic decrease in mean blood pressure during the second trimester. Chronic hypertension will modify the normal haemodynamic 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 cardiac output and PVR. These haemodynamic parameters

BOX 13.2 Aetiology of Chronic Hypertension

1. Primary or essential hypertension
2. Secondary hypertension
   - Renal
     - Renal parenchymal disease (glomerulonephritis, reflux nephropathy, adult polycystic disease)
     - Renovascular hypertension (renal artery stenosis)
   - Endocrine
     - Diabetes with vascular involvement
     - Thyrotoxicosis
     - Pheochromocytoma
     - Primary aldosteronism
     - Cushing syndrome
   - Collagen vascular disease
     - Systemic lupus erythematosus
     - Scleroderma
   - Others
     - Aortic coarctation
     - Increased intracranial pressure

are, in turn, the result of multiple influences. Peripheral vascular resistance is affected by humoral factors such as angiotensin and catecholamines, nervous sympathetic activity, and local factors such as endothelin and nitrous oxide. Cardiac output 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 reason unknown at present, essential hypertension starts with increased cardiac output and normal PVR. This phase is followed by a gradual increase in PVR and fall in cardiac output. 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 cardiac output and normal or mildly elevated PVR and rarely show evidence of end organ damage. However, a normal PVR in the presence of elevated cardiac output is abnormal because the physiologic response during pregnancy to the increase in cardiac output 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 increased cardiac output, 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 cardiac output that starts at end of first trimester and peaks at about 28–30 weeks gestation. Women with chronic hypertension have a limited ability to counterbalance this increase in cardiac output by further decreasing their PVR and maintain their blood pressure under normal limit. Subsequently as a consequence of this limited ability, their blood pressure starts to rise. The aggravation of chronic hypertension during the third trimester of pregnancy differs from preeclampsia because of the absence of proteinuria or presence of other end-organ injury.

Effect of Chronic Hypertension on Pregnancy

The most important risks confronting pregnant patients with chronic hypertension are the development of severe hypertension, superimposed preeclampsia, fetal growth restriction, premature births, fetal demise, placental abruption and caesarean delivery. Adverse fetal and maternal outcome are directly proportional to the duration of hypertension, severity of hypertension, associated end organ damage and presence of superimposed preeclampsia.

For management and counseling purposes, chronic hypertension in pregnancy is categorized as low risk or high risk. Low risk are women with mild hypertension without any organ involvement. The BP criteria is based on initial blood pressure values at first visit irrespective of treatment with antihypertensive medication. A patient initially classified as low risk may become high risk later in pregnancy if she develops severe hypertension or preeclampsia.[23]

Most women with chronic hypertension conceive when the disease is mild. Mild chronic hypertensives either have an uncomplicated course of pregnancy or encounter minor complications. Maternal and perinatal morbidity and mortality rates are not generally increased for patients with uncomplicated mild chronic hypertension.

However, the risk to mother and fetus increases dramatically when the pregnancy is complicated by severe disease or superimposed preeclampsia. Other risk factors include maternal age more than 40 years, hypertension lasting longer than 15 years (long-standing hypertension), BP greater than 160/110 in early pregnancy (severe hypertension), diabetes classes B through F, connective tissue disease, coarctation of aorta (secondary hypertension) and concurrent cardiovascular and/or renal disease (end organ damage).[24]

Maternal risks include exacerbation of hypertension, superimposed preeclampsia, congestive cardiac failure and pulmonary oedema, intracerebral bleed, acute renal failure, abruption placentae with disseminated intravascular coagulation (DIC) and death as a result of any of the above complications. Serious maternal outcomes have been reported in a population-based study of 30,000 pregnant women, leading to a fivefold rise in maternal mortality over normotensives.[25]

The two most common complications are superimposed preeclampsia and placental abruption. The risk of preeclampsia in mild hypertension is upto 20%, but this increases to 50% with severe hypertension and 75% if hypertension is in the high-risk category (severe hypertension, end organ disease, or secondary hypertension).[24,25,26] Those classified as severe, even in the absence of superimposed preeclampsia, have substantially increased maternal and fetal morbidity. The incidence of abruptio placentae is 0.5–2% with mild chronic hypertension and increases to 3–10% in severe hypertension.[24]

Fetal morbidity and mortality is directly related to the severity of hypertension and presence of preeclampsia. Decreased placental perfusion leads to SGA fetus. The risk of SGA infants is reported as 16% in uncomplicated nonproteinuric hypertension which increases to 50% in the setting of superimposed preeclampsia. Prematurity, both iatrogenic and spontaneous, is as high as 62–70% in severe chronic hypertension in the first trimester. Perinatal mortality is two to four times higher than in general population.[27]

Duration of disease is directly related to the amount of end organ damage, specially cardiac and renal involvement. Women with long-standing hypertension are likely to have cardiomyopathy, cardiomegaly, ischaemic heart disease, renal impairment and hypertensive retinopathy. Such hypertensive patients with significant left ventricular hypertrophy and abnormal function (poor ejection fraction) are prone to develop cardiac decompensation and heart failure as pregnancy

progresses, as a result of increased intravascular volume and cardiac demand. Renal dysfunction may increase the risk of preterm delivery and SGA infants. Pregnant hypertensive women with significant renal impairment (serum creatinine > 1.4 mg/dL) may have further deterioration of renal function.[27]

Effect of Pregnancy on Chronic Hypertension

The physiological decrease in systemic vascular resistance in normal pregnancy results in a decrease in blood pressure, which has a nadir at 16–18 weeks of gestation and returns to pre-pregnant levels by the third trimester.

Management of Chronic Hypertension in Pregnancy

The primary aim of management of chronic hypertension in pregnancy is reducing maternal risks and improving perinatal survival. This can be achieved by preconceptual evaluation and counseling, early prenatal care, frequent antenatal monitoring of maternal condition, fetal surveillance, timely delivery and proper postpartum management.

Initial Evaluation (Preconception or Early in Pregnancy)

Ideally, women with chronic hypertension should be evaluated pre-conceptionally in order to determine aetiology and severity of hypertension, identify possible presence of end organ disease, coexistence of other medical disease and counsel the patient accordingly. Unfortunately, the majority of these patients are seen after conception.

The history and physical examination should be directed to determine the duration of disease, the antihypertensive medications used, 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 cardiac, renal disease, diabetes, thyroid disease 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. A detailed obstetric history should be directed at determining outcomes in previous pregnancies including presence of hypertension, development of superimposed preeclampsia or abruption, preterm or SGA fetus and neonatal morbidity and mortality.

Chronic hypertensives of long-standing duration are likely to have cardiac, renal involvement and retinopathy and hence require preconception or early pregnancy evaluation of heart, kidneys and eyes.

The majority of these women do not require extensive laboratory testing (Box 13.3). Complete blood count with platelets and baseline renal function assessment is recommended for all patients with chronic hypertension. Renal impairment is one of the earliest manifestations of end organ damage and presence of proteinuria is important for diagnosing superimposed preeclampsia and its associated morbidity. Urinalysis for protein and microscopy should be done for diagnosis of renal disease. Renal function test mentioned in the ACOG guidelines on chronic hypertension include serum creatinine, blood urea nitrogen, 24-hour urine protein excretion or spot urine for protein/creatinine ratio and creatinine clearance.[27] However, practically creatinine clearance may be 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 may be done if the patient shows 1+ or more albumin on spot checks. Ultrasound of the kidneys for structure, size and pelvic dilatation may be considered when clinically relevant for screening for renal pathology (e.g. chronic pyelonephritis).

Long-standing hypertensives are predisposed to cardiomegaly, hypertensive cardiomyopathy and ischaemic heart disease. An electrocardiogram and echocardiography should be considered.

Young women in whom hypertension is severe or there are signs and symptoms suggesting secondary hypertension or those who have not been evaluated before or diagnosed in pregnancy for the first time, may require further evaluation in search for secondary and/or reversible causes. Pheochromocytoma should be suspected in young women with paroxysmal hypertension, frequent hypertensive crisis, seizures or panic attacks, palpitations and headaches. They should undergo determination of plasma metanephrines, urinary vinyl mandelic acid and metanephrines in a 24-urine collection. If

BOX 13.3 Investigations for Chronic Hypertensives Presenting Prior to 20 Weeks of Gestation

All patients

- Establish baseline blood pressure values
- Complete blood count with platelets
- Establish baseline renal function tests (serum creatinine, blood urea nitrogen, serum uric acid, serum electrolytes)
- Complete urinalysis for microscopy for albumin, sugar, WBCs, RBCs and casts
- Urine culture and sensitivity
- Spot urine for protein/creatinine ratio for screening or 24-hour urine protein
- ECG and echocardiography
- Ophthalmic examination (Fundus)
- Glucose tolerance test

Selected patients

- Renal ultrasound, renal Doppler flows (if feasible as in early pregnancy)
- Fasting free plasma metanephrine or 24-hour urine metanephrine
- Serum potassium levels or plasma renin activity

biochemical results are suggestive of pheochromocytoma, then MRI or CT after the first trimester may be useful for localization of the tumour which is commonly present in the adrenal gland. If disease is diagnosed pre-pregnancy or early to midpregnancy, it can be treated surgically or pharmacologically with good obstetric outcome. Renal artery Doppler or magnetic resonance angiography or renal biopsy may be asked for if there is suspected renal pathology or renal artery stenosis on ultrasound or biochemistry. Serum electrolytes may be done to rule out primary hyperaldosteronism if suspected. ANA (antinuclear antibody) titers are important if the patients' history or examination suggests the possibility of autoimmune disease. Evaluation of secondary hypertension should be done in collaboration with a medical subspecialist.

Prepregnancy Counseling

Prepregnancy counseling will be useful to introduce lifestyle modifications that will improve pregnancy outcome including weight loss for obese women, avoiding alcohol and smoking. An appropriate diet that curtails heavy salt intake is recommended. It is important to establish baseline lab tests and teach patients on self-monitoring of blood pressure. Prepregnancy evaluation is also important to establish adequate control of hypertension, medications reviewed and changes made in the antihypertensive drugs that are unsafe in pregnancy. Patients on diuretics and angiotensin converting enzyme inhibitors should be advised to discontinue use of these medications before conception or as early as possible, if patient reports after conceiving. Diuretics should be avoided as they reduce the blood flow to the placenta. Angiotensin converting enzyme inhibitors are known as *teratogens*, classified by FDA as Class D with warning about its association with fetal growth restriction, fetal and neonatal renal failure, oligohydramnios and fetal anomalies including severely underdeveloped calvaria, renal dysgenesis, pulmonary hypoplasia and fetal or neonatal death with exposure any time during pregnancy. Similarly angiotensin receptor blockers have been associated with renal abnormalities, dysmorphia and neonatal death. 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. Women with significant renal impairment (serum creatinine $>$ 1.4 mg%), diabetes with vascular involvement (Class R/F), cardiomyopathy, collagen vascular disease, coarctation of aorta should be counseled in depth about the increased risk of maternal and perinatal complication. They should be made aware that pregnancy can exacerbate their condition with potential for causing renal failure, cardiac failure or even death. Such patients if still plan to conceive should be managed in a tertiary care centre under a maternal fetal medicine specialist and in conjunction with a medical specialist.

General Care during Pregnancy

There is no substitute for frequent clinical observations in the antepartum care of pregnant patients with chronic hypertension. Since patients with chronic hypertension are at risk for superimposed preeclampsia and growth restriction, close monitoring for maternal and fetal manifestations is necessary. They should have prenatal clinic visits very 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 in addition to standard prenatal care are:

1. Blood pressure measurement along with home BP monitoring
2. Monitoring for signs of superimposed preeclampsia
3. Assessment for proteinuria using dipstick test or spot urine protein /creatinine ratio
4. Lab tests for renal function, urine microscopy, complete blood count if worsening hypertension or proteinuria
5. Fetal growth and well-being assessment

Self-monitoring of blood pressure: Blood pressure monitoring is of critical importance. The patients should measure their blood pressure at home twice daily and bring the written results at each office visit. Patients should be asked to call on the doctor if the diastolic blood pressure is consistently above 100 mmHg or the systolic is above 150 mmHg. 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 patients' 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. The majority of patients with chronic hypertension have lower blood pressure readings at home than at the clinic reflecting their BP reading in their own environment. The reverse situation is rare and when the blood pressure rises at home it will usually be elevated at the clinic. The blood pressure measurements at home are also the best index to measure the patient's response to therapy. Self monitoring reduces the use of antihypertensives and need for hospitalization.[28]

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 give a better understanding of an individual need for or response to treatment.

Monitoring maternal weight is also important in the prenatal follow-up of patients with chronic hypertension. Too much or too little weight gain is a concern. 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.

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. Platelet count is necessary for assessing thrombocytopenia. There is no need for monthly or periodic creatinine clearance tests and quantitative urinary protein determinations unless the serum creatinine level is greater than 0.8 mg/dL or there is 1+ or more protein in qualitative examination of the random urine specimen.

Fetal evaluation includes a baseline ultrasonography for dating and an 18–20 weeks anatomical survey. Chronic hypertensives are prone for uteroplacental insufficiency. Poor fetal growth secondary to placental insufficiency affects 15–25% of pregnancies with chronic hypertension. Clinical evaluation of the fetal growth is imprecise, hence close surveillance with ultrasound for fetal growth, liquor with assessment of uterine and umbilical artery Doppler monitoring is necessary at 28–30 weeks. There is no consensus on the most appropriate method of fetal surveillance or the frequency of monitoring. ACOG guideline mentions the use of twice weekly nonstress test or biophysical profile biweekly and the use of umbilical artery Doppler in patients with fetal growth restriction.[27] It is customary to initiate fetal well-being tests at 34 weeks and earlier if fetal growth restriction or maternal complications develop. However, if growth restriction is not present and superimposed preeclampsia is excluded, these tests of fetal well-being have not shown improved outcome. 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 amniotic fluid volume. The MBPP is performed twice 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 is a reassurance 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 umbilical artery 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 arteries Doppler is good. In contrast, an abnormal umbilical and 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 an indication for delivery except when exhibiting absent or reversed diastolic flow. A high resistance flow in the umbilical artery Doppler has only prognostic value and indicates the need for closer fetal surveillance.

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.

Chronic hypertension in pregnancy is subclassified (ACOG 2012, NICE 2010, SOMANZ 2008 clinical guidelines) as[27,7,29]:

- **Mild hypertension:** Systolic blood pressure of 140–159 mmHg or Diastolic blood pressure of 90–109 mmHg.
- **Severe hypertension:** Systolic blood pressure of 160 mmHg or greater or diastolic blood pressure of 110 mmHg or greater.

Determination of the severity of the hypertension is important to establish a prognosis. More severe the hypertension, the worse the prognosis and the greater the potential for complications. Failure of blood pressure to normalize in the second trimester is also an indicator of poor prognosis. 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. Other factors which place the patient at high risk for complications and poor outcome are listed in Box 13.4. Women with chronic hypertension with risk factors should be clinically managed in conjunction with a medical specialist.

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

BOX 13.4 Patients with Mild Chronic Hypertension at High Risk for Complications and Poor Outcome

- 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
- History of severe hypertension in pervious pregnancies
- History of abruptio placentae
- History of stillbirth of unexplained neonatal death
- History of previous deliveries of small for gestational age infants
- Older than 35 years or more than 15 years of hypertension
- Marked obesity
- Secondary hypertension

output, decreases peripheral oedema, and improves placental perfusion.

Complete bed rest on the other hand may predispose to venous thrombosis, bone demineralization, muscle atrophy, pulmonary atelectasis, financial and psychological burden. Therapeutic bed rest may do more harm than good. Hence, these women should be advised restricted non-strenuous activity with extra 1–2 hours of rest in a day.

Salt Restriction

Women with chronic hypertension should be encouraged to keep their dietary sodium intake low as it can reduce blood pressure. 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. 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 salt/day). The 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.

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 is 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 antihypertensive therapy is necessary in patients with severe hypertension (systolic BP $\geq$ 160 and diastolic BP $>$ 110 mmHg) to reduce the risk of maternal cardiac and cerebrovascular complications. In addition, control of severe hypertension may permit prolongation of pregnancy and thereby improve perinatal survival. However, there is no evidence that treatment of severe hypertension has any impact on reducing the risk of superimposed preeclampsia or abruption placentae.

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 abruption placentae. The fetus may be affected by growth restriction, antepartum and intrapartum hypoxia and acidosis. Benefits of therapy for the treatment of mild chronic hypertension in pregnancy have not been proven. Metanalysis of randomized trials of antihypertensive treatment in 2409 patients with mild to moderate hypertension during pregnancy (systolic BP 140–169 mmHg, diastolic BP 90–109 mmHg) reported a 50% reduction in risk of developing severe hypertension but no reduction in the risk of superimposed preeclampsia, perinatal mortality, preterm delivery or growth restricted fetus.[30] Antihypertensive therapy has shown to reduce the risk of progress to severe maternal hypertensive crisis but has not shown improvement in overall perinatal outcome. Possible benefits include reduction in hospital admission and prolongation of gestation when uncontrolled hypertension would result in early delivery.

However, as opposed to benefits of antihypertensive therapy in mild hypertensives, another meta-analysis of treatment versus no treatment in mild chronic hypertensives have shown an increase in the frequency of SGA infants associated with treatment-induced reduction in mean arterial pressure.[31]

American College of Obstetricians and Gynecologists in their practice bulletin have recommended pregnant women with hypertension in the blood pressure range of 150–160/100–110 mmHg should be treated with antihypertensives and their blood pressure to be kept lower than 150/100 mmHg.[27]

NICE guideline on hypertension also mentions that pregnant women with uncomplicated chronic hypertension should aim to keep blood pressure lower than 150/100 mmHg. Such uncomplicated chronic hypertensives should not lower diastolic blood pressure below 80 mmHg.[7]

In pregnant women with end organ damage secondary to chronic hypertension such as left ventricular hypertrophy or renal insufficiency, it is recommended that antihypertensive treatment should be given to maintain blood pressure in the normal range, lower than 140/90 mmHg, thereby reducing the risk of further end organ damage.[7,27]

Considering the above recommendation, it would be reasonable to withhold antihypertensive therapy in mild chronic hypertension patients who become pregnant unless their blood pressure is above 150/100 mmHg or they have other complicating factors (cardiac or renal) and to either stop or reduce medications in women who are already taking antihypertensive therapy.[32] Aim is to keep BP lower than 150/100 mmHg (140/90 mmHg if there is target organ damage). In women with severe chronic hypertension (systolic BP 160 mmHg or more, diastolic BP 110 mmHg or more), antihypertensive should be started or continued to reduce the risk of maternal complications like stroke, intracranial bleed, left ventricular failure and pulmonary oedema and renal failure.

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 and it should have no side effects. This optimal medication does not exist. However, several medications have been prescribed for the treatment of chronic hypertension during pregnancy but data on safety and efficacy are limited to few medications. The largest experience has been with methyldopa. Recently, beta-blockers have surfaced as first line medications.

Beta-Blockers

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 predominately bind to beta-1 receptors or as noncardioselective when they bind to both beta-1 and beta-2 receptors. Atenolol is predominately a beta-1 or cardioselective type of beta-blocker while propranolol is noncardioselective.

Our present understanding of the haemodynamics of mild chronic hypertension in pregnancy indicates that the majority of these patients have increased cardiac output and hyperkinetic circulation. Propranolol reduces cardiac output between 15 and 30% and suppresses rennin 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 cardiac output. These haemodynamic 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.

Propranolol is an effective drug for the treatment of chronic hypertension during pregnancy. Several prospective studies have demonstrated the safety of its administration during pregnancy. Propranolol 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. The medication lowers the blood pressure within hours, and 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.

Most of the side effects and contraindications for the use of propranolol 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 propranolol may cause fluid retention.

Atenolol is selective beta-1 adrenergic blocking agent that has significant advantages over propranolol 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 (α_1 and nonselective β-blocker) has been extensively studied and is increasingly being prescribed during pregnancy. Due to low rate of adverse effects and good efficacy, labetalol is a good option for first line treatment of chronic hypertension.

Different from other beta-blockers, labetalol acts by decreasing PVR with little or no effect on cardiac output. The drug has beta-1 and 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. Once 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, headache, 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. Maximum dose per treatment cycle is 220 mg.

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 to a maximum of 1200 mg/day. The maintenance dose is usually 200–400 mg twice daily.

Nifedipine (Calcium Channel Blocker)

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 like labetalol or methyldopa in the treatment of chronic hypertension during pregnancy. It can also be used in acute hypertensive situations.

- For severe hypertensive crisis, 10 mg initial oral dose is given followed by repeat dose if necessary after 30 minutes.
- The usual oral dose is 10–30 mg orally every 6 hours. It can be increased up 20 mg every 4 hours (maximum 90 mg/day).

The medication is absorbed immediately and reaches a peak level serum concentration in 30 minutes. 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 or postural hypotension. There is also a theoretical risk of potential synergy between magnesium (used as a treatment or prophylactic agent against eclamptic seizures) and calcium channel blockers, resulting in severe hypotension or neuromuscular blockade leading to respiratory failure.

There were concerns about occasional precipitation of angina and myocardial infarction with the use of sublingual nifedipine. However, there has not been evidence for the same in healthy young population. Caution is necessary in use of sublingual nifidepine in older mothers or those with family history of coronary artery disease at a young age and women who are heavy smokers. Sublingual administration is no longer recommended as it causes sudden maternal hypotension and fetal distress due to placental hypoperfusion.

Methyldopa (Central Acting Adrenergic Agonist)

Methyldopa has been the most widely used antihypertensive drug during pregnancy for decades 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 reducing systemic vascular resistance with little effect on the heart rate and cardiac output. The medication causes dilatation 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. The drug is primarily excreted in the urine and may accumulate in patients with severe impairment of renal function.

- The usual starting dose in 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.

Methyldopa is one antihypertensive medication that has been submitted to controlled trials during pregnancy and has been shown to have beneficial effects. It is the only drug whose safety profile has been tested in a 7.5 year follow-up of newborns exposed in utero, which demonstrates no detrimental effects on the exposed offspring.[33]

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 associated with methyldopa may limit uptitration. It should be avoided in women with a prior history of depression, because of increased risk of postnatal depression.

Positive Coombs and abnormal liver tests occur in approximately 10% of all patients. Haemolytic anemia is an uncommon complication. In some patients, long-term administration of methyldopa causes salt water retention. Apparently, the kidneys of patients with chronic hypertension react to decrease 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, oedema and haemodilution. This situation may progress to a point at which "rebound" hypertension caused by the large intravascular volume expansion observed. In these cases, a diuretic should be added to the treatment. The result will be increased urinary output, decreased oedema, 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.

Although NICE guidelines recommends stopping the use of hydrochlorthiazide in pregnancy due to possible risk of fetal and neonatal complications, the American guideline suggests that diuretics does not adversely affect perinatal outcome and they do not need to be discontinued in pregnancy.[7,27] 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. Depletion of intravascular volume by diuretics, which is often already reduced in pregnancy-induced hypertension, may lead to decreased placental perfusion. This effect of diuretics limits its use primarily for treatment of pulmonary oedema in antenatal and immediate postnatal period.

- Initially, diuretics decrease blood pressure by increasing urinary sodium excretion, decreasing intravascular plasma volume and the extracellular fluid, and decreasing the cardiac output. After 6–8 weeks of therapy, the cardiac output 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.

Hydralazine (Peripheral Vasodilator)

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 fibres 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 severepreeclampsia and hypertensive crisis. The medication is unsuitable as a first choice antihypertensive for long-term use during pregnancy.

Hydralazine increases cardiac output and plasma volume by vasodilation and reflex stimulation of the rennin angiotensin system. Consequently, resistance to treatment or treatment failures is 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 in 10 minutes after intravenous injection. The target response is a decrease in diastolic pressure to not below 90–100 mmHg.

- The drug is usually given in 5–10 mg intravenous doses that are repeated at 15–20 minutes intervals until the desired level of blood pressure is achieved. The upper limit of total dose per treatment cycle is 30 mg.
- 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 relativelyresistant to the hypotensive effect of the drug.

Up to 50% of patients treated with hydralazine may demonstrate tachycardia, hypotension, palpitations, 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. Fetal heart decelerations due to uteroplacental insufficiency are encountered if there is a rapid and drastic fall in blood pressure which improves with rapid crystalloids infusion. 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.

Hydralazine is certainly effective but due to its maternal side effects and high incidence of overshoot hypotension with the subsequent fetal distress, it is no longer a preferred drug.

Prazosin

Prazosin is a peripheral vasodilator that works by blocking postsynaptic alpha receptors. The medication does not cause changes in cardiac output 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.

- The initial dose should be 1.0 mg at bedtime to avoid first dose hypotension. The dose may be increased according to the patient's response but usually 2–4 mg twice daily is necessary to achieve adequate blood pressure control.

Prazosin is a safe drug for pregnant patients. The main side effect of prazosin is postural hypotension which affects

approximately 1% of the patients. Dizziness and lightheadedness are also frequent complaints.

Delivery

As per a recent consensus panel recommendation (also mentioned in the ACOG practice bulletin number 125), women with chronic hypertension, not on medications may be allowed to deliver at 38–39 weeks, women whose hypertension is controlled with medications should give birth at 37–39 weeks and women with severe hypertension difficult to control should deliver at 36–37 weeks of gestation.[34,27]

Women with chronic hypertension and a previous adverse pregnancy outcome, may be candidates for early delivery as per the clinical situation. Also those with uncontrolled severe hypertension or superimposed preeclampsia may need to be delivered prematurely for fetal or maternal indications. Chronic hypertension by itself is not an indication for caesarean delivery. However, the incidence of caesarean is high because of the development of complications and the need to delivery prematurely.

Continuous fetal monitoring should be done in labour. Epidural analgesia is ideal for labour. Antihypertensives need to be continued in labour to keep blood pressure below 150/100 mmHg.

Figure 13.1 summarizes the plan of management for women with chronic hypertension during pregnancy.

Postnatal Investigation, Monitoring and Treatment

Postnatal women with mild chronic hypertension must be monitored with blood pressure daily for the first 2 days after birth, at least once between day 3 and day 5 and as per clinical indication.[7] High risk women with chronic hypertension should be monitored more closely for the first 48 hours because of the risk of hypertensive encephalopathy, pulmonary

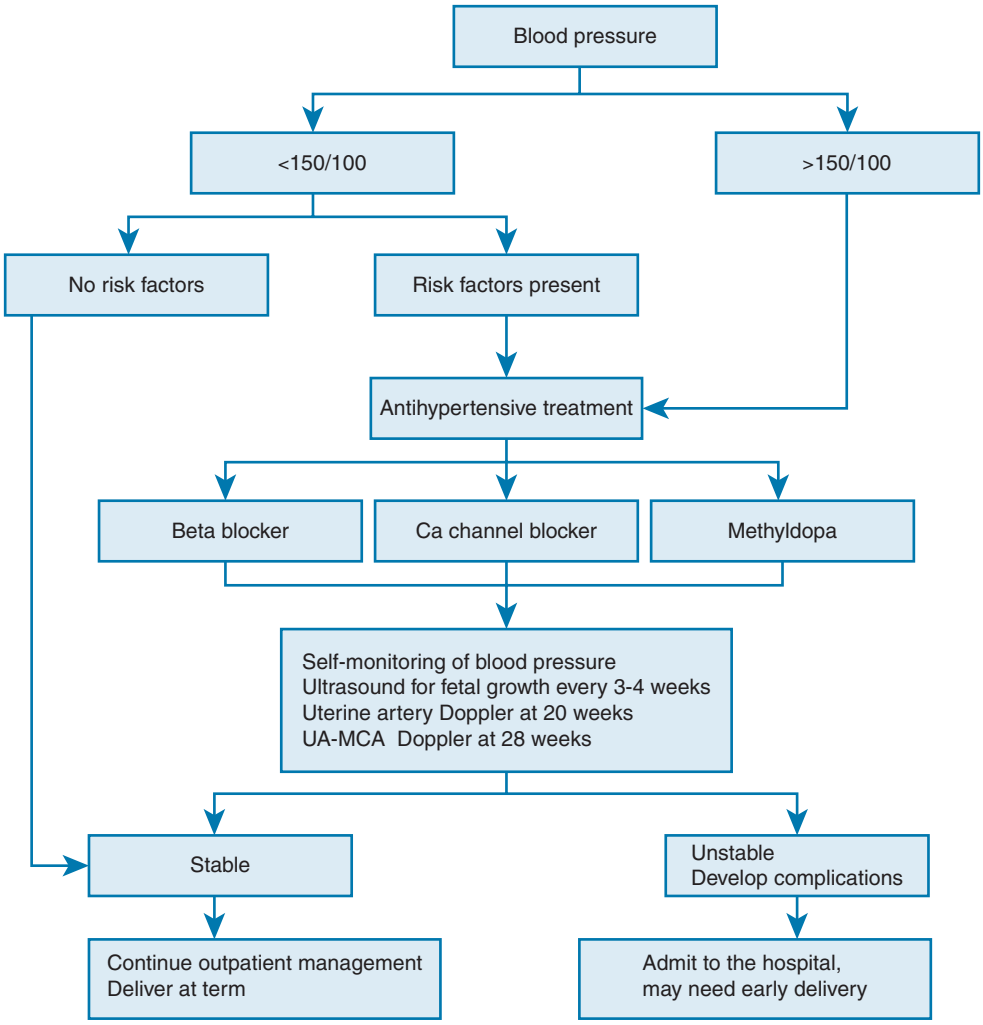

FIGURE 13.1 Management of chronic hypertension during pregnancy.

oedema and renal failure. In many women with chronic hypertension, BP may remain unstable for one to two weeks after delivery and may require increase in medications. Diuretic therapy can be used in patients with evidence of circulatory congestion or pulmonary oedema. All antihypertensives are found in small quantity in breast milk. All of them are allowed during breast feeding including labetolol, hydralazine, methyldopa, calcium channel blockers, captopril, enalapril and ACE inhibitors.

Women with chronic hypertension may be allowed to continue antenatal antihypertensive treatment after birth with an aim to keep blood pressure lower than 140/90. Need for long term antihypertensive treatment can be reviewed at 2 weeks after the birth. However, if a woman is on methyldopa during pregnancy, it should be stopped within 2 days of birth and restarted on the pre-pregnancy antihypertensive regime.

All chronic hypertensives should be called for a medical review at postnatal 6–8 weeks with the pre-pregnancy medical specialist.

PREECLAMPSIA

Preeclampsia is a multiorgan disease process of unknown aetiology characterized by de novo development of hypertension and proteinuria after 20 weeks of gestation, sometimes progressing into a multiorgan cluster of varying clinical features. It is a pregnancy-specific syndrome that can affect virtually any organ system. Classically, it was defined as a triad of hypertension, oedema and proteinuria. Modern definition does not include oedema because of lack of specificity. Oedema is neither sufficient nor necessary to confirm the diagnosis of preeclampsia. The clinical findings of preeclampsia can manifest as either maternal syndrome alone (Hypertension and proteinuria $>$ 0.3 g/24 hour-urine with or without other multisystem dysfunction) or in association with fetal syndrome (fetal growth restriction, oligohydramnios). Appearance of proteinuria remains an important diagnostic criterion to differentiate from gestational hypertension. Proteinuria is defined as a 24-hour urinary protein excretion exceeding 300 mg, a urine protein:creatnine ratio of $>$ 0.3, or persistent 30 mg/dL (1+ on dipstick) protein in random urine samples.

Atypical Preeclampsia

The traditional criteria of hypertension and proteinuria may not always be seen in all patients who develop signs and symptoms or other lab abnormalities of preeclampsia or eclampsia. In the absence of proteinuria, the syndrome of preeclampsia should be considered when gestational hypertension is present in association with persistent cerebral symptoms of severe headache, epigastric or right upper quadrant pain with nausea or vomiting, fetal growth restriction or abnormal laboratory test such as thrombocytopenia and elevated liver enzymes. Criteria for atypical preeclampsia is given in the Box 13.5.[23] Women with severe gestational hypertension are associated with adverse maternal and perinatal outcome and may also be considered as atypical preeclampsia and managed.

The incidence of preeclampsia ranges between 2–7% in healthy nulliparous women. In these women, the disease is usually mild with onset near term or intrapartum (75%) with minimal risk of adverse fetal outcome. However, the incidence and severity of disease is substantially higher in women with multifetal gestation, chronic hypertension, previous preeclampsia, pregestational diabetes or preexsisting thrombophilia.[23]

Mild preeclampsia is defined when the diastolic BP remains below 110 mmHg and the systolic BP remains below 160 mmHg. Criteria for severe preeclampsia are given in Box 13.6.[23] Headache or visual symptoms of scotomas are premonitory symptoms of impending eclampsia. Epigastric or upper quadrant pain is characteristically seen with hepatocellular necrosis, ischaemia, haemorrhage or oedema causing stretch on the Glisson capsule. This pain is frequently accompanied by elevated liver enzymes. Thrombocytopenia is caused by platelet activation and microangiopathic haemolysis induced by severe vasospasm causing disorder known as HELLP syndrome. Cardiac or renal dysfunction or fetal growth restriction in the presence of preeclampsia also places the disease in the severe category.

As per most accepted guidelines, severe preeclampsia is preeclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment. Severe preeclampsia is confirmed by a diastolic BP of $\geq$110 mmHg on two occasions, or a systolic BP of $\geq$160 mmHg on two

BOX 13.5 Criteria for Atypical Preeclampsia

Gestational hypertension plus one or more of the following:

- Symptoms of preeclampsia
- Haemolysis
- Thrombocytopenia ($<$ 100,000/mm^3)
- Elevated liver enzymes: two times the upper limit of the normal values for aspartate transaminase (AST) and alanine transaminase (ALT)

Gestational proteinuria plus one or more of the following:

- Symptoms of preeclampsia
- Haemolysis
- Thrombocytopenia ($<$ 100,000/mm^3)
- Elevated liver enzymes

Early signs and symptoms of preeclampsia–eclampsia at $<$ 20 weeks

Late postpartum preeclampsia–eclampsia ($>$ 48 hours postpartum)

BOX 13.6 Criteria for Severe Preeclampsia*

1. Blood pressure of ≥ 160 mmHg systolic or ≥110 mmHg diastolic, recorded on at least 2 occasions at least 6 hours apart with the patient on bed rest
2. Proteinuria of ≥ 5g in 24 hours
3. Oliguria < 500 mL in 24 hours
4. Cerebral visual disturbances
5. Epigastric pain, nausea and vomiting
6. Pulmonary oedema
7. Impaired liver function of unclear aetiology
8. Thrombocytopenia
9. Convulsions (eclampsia)
10. Fetal growth restriction

*Adapted from Sibai BM. Hypertension. In: Textbook of Obstetrics: Normal and Problem Pregnancies.[23]

BOX 13.7 Risk Factors for Preeclampsia

Couple related risk factors:

- Primipaternity
- Limited sperm exposure
- Pregnancy after donor insemination, donor egg, donor embryo
- Dangerous male partner

Maternal or pregnancy related risk factors:

- Extremes of age
- Obesity and insulin resistance/gestational diabetes
- Smoking
- Multifetal pregnancies
- Preeclampsia in previous pregnancy
- Maternal low birth weight
- Family history of preeclampsia

Pre-existing medical disease:

- Pre-gestational diabetes
- Chronic hypertensive or renal disease
- Maternal immunological disease
- Preexisting thrombophilia, antiphospholipid antibody syndrome

occasions, together with significant proteinuria (at least 1g/L). However, the recent RCOG greentop guideline No 10 (A) which has been reviewed in 2010 defines severe preeclampsia with a systollic BP of ≥170 mmHg. Clinical features of preeclampsia are[35]:

- Severe headache
- Visual disturbances
- Epigastric pain and/or vomiting
- Signs of clonus
- Papilloedema
- Liver tenderness
- Platelet count below 100 x 10^6/l
- Abnormal liver enzyme (ALT or AST rising to above 70 IU/L
- HELLP syndrome

Epidemiological Risk Factors

Factors which have been identified to be associated with increased risk for preeclampsia have been given in Box 13.7.[36] Preeclampsia is a disease of first pregnancy. A previous abortion or a healthy pregnancy reduces the risk. This protective effect is lost if there is a change of partner. The risk increases in women with limited sperm exposure with the same partner before conception as in teenage pregnancy. There is data on paternal risk factors for preeclampsia, the so called dangerous father, where men who fathered a preeclamptic pregnancy are nearly twice as likely to father another such pregnancy with a different woman. Increased incidence of pregnancies after assisted reproductive techniques have also increased the risk of preeclampsia as these women are generally older in age, obese, polycystic ovarian disease, pregnancies from donated gametes and multiple gestation. The risk of preeclampsia typically doubles with each 5 to 7 kg/m^2 increase in prepregnancy BMI. There is an overall higher rate of acquired (primary antiphospholipids) and genetic thrombophilia in women with severe early onset preeclampsia compared with controls.

Aetiopathogenesis

Two-Stage Disorder Hypothesis[37]

The exact nature of the primary event causing preeclampsia is not known. However, abnormal trophoblastic invasion of spiral arteries, inappropriate endothelial cell activation, exaggerated inflammatory response are key features in the pathogenesis of preeclampsia. The preeclamptic syndrome has been hypothesized as a two-stage disorder.

Primary stage involves abnormal placentation. In normal pregnancy, the wall of the spiral arteries is invaded by endovascular trophoblastic cells. This migration transforms the small, musculo-elastic spiral arteries into large, tortuous channels that carry a large amount of blood to the intervillous space and are resistant to the effects of vasomotor agents. Although this starts in the first trimester, this invasion is completed in the second trimester after the second wave of trophoblastic invasion. 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 (*incomplete trophoblastic invasion*). This deficiency results in decreased uteroplacental perfusion. In addition to failure of demuscularization, the arteries maintain their response to the vasomotor influences.

The second stage of preeclampsia involves the conversion of this earlier described uteroplacental maladaptation to the maternal systemic syndrome of preeclampsia. Stage 2 is amenable to modification by preexisting maternal conditions like cardiac, renal disease, diabetes, obesity or hereditary influences.

This secondary stage of systemic maternal disease is associated with an exaggerated endothelial cell activation and a generalized hyper-inflammatory state. Episodes of placental hypoxia or reperfusion result in oxidative stress, subsequent apoptosis and necrotic disruption of syncytial architecture. The anatomic and physiologic disruption of normal placentation is thought to lead to release of placental debris from the intervillous space into the maternal circulation, thereby inciting a systemic inflammatory response by stimulating the synthesis of inflammatory cytokines, products that affect angiogenesis and abnormal lipid perioxidation. These products will affect the endothelial system with the production of signs and symptoms of multiple organ compromise.[37]

Vascular Endothelial Activation

In response to placental factors released by ischaemia, a cascade of events is set into motion finally provoking endothelial cell injury. This endothelial cell dysfunction is due to an extreme activated state of leucocytes in the maternal circulation. Cytokines like tumour necrosis factor-α (TNFα) and interleukins (IL) contribute to the oxidative stress by formation of free radicles and self-propagating lipid peroxides that injure endothelial cells, modify their nitric oxide production and interfere with prostaglandin balance. This oxidative stress presents as **atherosis** by production of lipid-laden macrophages, as microvascular coagulation manifested as thrombocytopenia, and increased permeability manifest as oedema and proteinuria.

Angiogenic Imbalance

This is used to describe production of excessive amounts of antiangiogenic factors by the trophoblastic tissue, stimulated by worsening hypoxia at uteroplacental interphase, in patients destined for preeclampsia. Soluble Fms-like tyrosine kinase 1 (sFlt-1) is a protein produced by the placenta. It acts by binding to the receptor binding domains of vascular endothelial growth factor (VEGF) and placental like growth factor (PLGF). Increased maternal levels of sFlt-1 levels inactivate and decrease circulating free PLGF and VEGF concentration resulting in endothelial cell dysfunction. The magnitude of increase in sFlt-1 levels correlate with disease severity.

Genetic Factors

Preeclampsia is a disorder with multifactorial aetiology. The hereditary predisposition cannot be due to a single gene. It is likely the result of interaction of multiple genes inherited from both maternal and paternal sides. Genetic conflict theory suggests that fetal genes are selected to increase transfer of nutrients to the fetus and increase blood pressure, while maternal genes are selected to limit transfer in excess of an optimal level by lowering blood pressure.[38]

Increased Pressor Response

Pregnant women normally develop refractoriness to the pressor response of angiotensin 2. Women predisposed to preeclampsia have increased vascular reactivity to infuse angiotensin 2 and norepinephrine.

Nitric Oxide

This is a potent vasodilator produced by the endothelial cells from L-arginine. Preeclampsia is associated with decreased endothelial nitric oxide synthase expression.

Prostaglandins

Prostanoids are also implicated in the pathophysiology of preeclampsia. The blunted pressor response seen in normal pregnancy is due to increased production of endothelial prostacyclin. In preeclampsia, there is decreased production of prostacyclin (PGI_2) mediated by phospholipase A_2. The secretion of Thromboxane A_2 by the platelets is increased simultaneously. The prostacyclin:thromboxane A_2 ratio decreases leading to increased sensitivity to vasopressor response.

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 labour and premature rupture of the membranes. Also, some women with preeclampsia, particularly those who are obese, diabetic, chronic hypertensive, and with multifetal pregnancies may have placentas of normal or large size without the characteristic features of abnormal placentation. 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 with preeclampsia.[39] 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 adaptive 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 aetiology and the mechanism of disease, there are several important pathophysiologic changes in preeclampsia. These changes include haemodynamic changes due to alternations in blood volume and PVR, alternations of the haemostatic system and abnormal renal function.

Maternal Changes in Preeclampsia

Haemodynamic Changes

Haemodynamic 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 cardiac output rather than increased PVR is the most common haemodynamic feature in mild preeclampsia. However, once preeclampsia becomes severe, there is a switch to normal or decreased cardiac output and elevated PVR as a manifestation of systemic vasoconstriction.[40] Women with preeclampsia have increased cardiac output and normal PVR before the onset of clinically severe disease. However, with worsening of the disease, there is a haemodynamic crossover to low cardiac output and elevated PVR causing a rise in both systolic and diastolic blood pressures. High cardiac output along with increased PVR may result in traumatic intravascular haemolysis (microangiopathic haemolytic anaemia).

Increased sympathoadrenal activity mediates increase in cardiac output. This in turn increases cardiac work load which is generally well tolerated by young patients, but it may occasionally precipitate left ventricular failure. Decrease in renal perfusion, increased hydrostatic pressure and proteinuria induced decreased oncotic pressure may precipitate pulmonary oedema if compounded by fluid overload.

Severe preeclampsia characterized by vasoconstriction with a leaky microcirculation results in fluid shift into extracellular interstitial space causing a depleted intravascular compartment and thus relative hypovolaemia. Thus, an abnormally high haematocrit level is a surrogate measure of the amount of hypovolaemia and correlates with low birthweight, prematurity and perinatal mortality. Oedema, although not a reliable sign for preeclampsia, is the clinical expression of this extravasation of fluid into the interstitial compartment. Physiological oedema of pregnancy, as we know, is due to increased intracapillary hydrostatic pressure. In preeclampsia, an increased precapillary resistance causes decrease in intracapillary hydrostatic pressure. Hence the pathological oedema of preeclampsia is caused not due to increased intracapillary pressure but due to increased capillary permeability to plasma proteins and a reduction in plasma colloid osmotic pressure. Pathological oedema appears suddenly, more often facial and periorbital, and presents as accelerated rate of weight gain ($>$ 1kg/wk over 2–3 weeks or $>$ 2kg in 1 week).

Changes in Intravascular Volume

Haemoconcentration is the hallmark of severe preeclampsia and eclampsia. The physiological expansion of plasma volume in normal pregnancy is about 40% and is highest at 30 weeks and remains stable until term. Women with gestational hypertension have normal expansion of intravascular volume. In patients with established preeclampsia, the average plasma volume is about 9% below expected values and falls by 30–40% in cases of severe preeclampsia. The reduced plasma volume results in haemoconcentration as the disease progresses. Hypovolaemia in preeclampsia is particularly associated with growth restriction, oligohydramnios and preterm labour.

After delivery, the plasma volume increases and the haemoglobin and haematocrit values decrease because of decreased vasospasm, excessive blood loss during delivery, and mobilizations of extracellular fluids into the intravascular compartment. In women with severe haemoconcentration, an acute fall in haematocrit post delivery may not just be resolution of preeclampsia as always taught earlier. It is extremely important to remember that a substantial fall in haematocrit could also be due to blood loss at delivery. Women with severe preeclampsia/eclampsia are unduly sensitive both to vigourous fluid therapy in an attempt to expand the hypovolaemia as well as to blood loss at delivery.

Changes in Peripheral Vascular Resistance

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 24–26 weeks gestation women who will remain normotensive require 12–14 ng/kg/min of angiotesnsin 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/min 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.

Haematological Abnormalities

Overt haematological abnormalities exist in only a minority of patients with severe preeclampsia. The most common is mild thrombocytopenia, which affects 7–10% of the cases. Overt thrombocytopenia (platelet count $<$ 100,000/μL) indicates severe disease. In most cases, delivery is advisable as thrombocytopenia usually continues to fall and improves after a day of delivery reaching normal levels after 3–5 days in 90% of cases. Lower the platelet count, higher is the maternal and fetal morbidity and mortality.

Subtle haematological changes similar to mild intravascular coagulation may occur in preeclampsia. The levels of factor VIII plasma clotting factors may be decreased and levels of fibrin degradation products are mildly increased due to consumptive coagulopathy. Except for thrombocytopenia, coagulation aberrations are generally minimal and present only in association with abruption. Routine laboratory assessment of coagulation including prothrombin time,

activated partial thromboplastin time, fibrinogen levels may be unnecessary except in patients suspected with placental abruption.

The most serious haematologic complications of preeclampsia is the HELLP syndrome that is a form of severe preeclampsia which presents with haemolytic anemia, thrombocytopenia, and elevated liver enzymes. Presence of haemolysis is semiquantified by elevated serum lactate dehydrogenase and by presence of schizocytosis, spherocytosis and reticulocytosis in peripheral blood. HELLP syndrome is a manifestation of microangiopathic haemolysis caused by endothelial disruption with platelet adherence and fibrin deposition and not a form of DIC. The localised increase in intravascular coagulation is secondary to endothelial cell injury. In a case of HELLP syndrome , microangiopathic hemolysis and thrombocytopenia preceeds the appearance of consumptive coagulopathy and DIC. Occasionally and only in advanced stage of HELLP with platelet count less than 50,000/mm^3 and lactate dehydrogenase levels $>$ 600 IU/L do the coagulation profile shows derangement in the form of decreased fibrinogen, increased fibrin degradation products, prolongation of prothrombin time and activated partial thromboplastin time.

A diagnosis of HELLP syndrome needs confirmation of haemolysis, either by elevated LDH levels or by peripheral blood film showing fragmented red cells. An AST or ALT above 70 IU/L is seen as significant and a level above 150 IU/L is associated with increased maternal morbidity. The platelet count would have to be below $100x10^6$ to support the diagnosis.[35]

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 large population study and meta-analysis[41] suggests the existence of the association between severe preeclampsia and thrombophilia, particularly favour V Leiden and to a lesser extent MTHFR C6771 mutations. This systematic review did not find an association between thrombophilia and mild preeclampsia or gestational hypertension. However, women with thrombophilia had increased risk for very early onset severe disease compared with those without thrombophilia. 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

In a normal pregnancy, renal perfusion and glomerular filtration rate are increased. But with development of preeclampsia, there is about fivefold increased renal afferent arteriolar resistance causing a reduction in renal blood flow and diminished glomerular filtration.

The hallmark renal lesion in preeclampsia characterized by swollen intracapillary endothelial cells in the glomeruli 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 immunoflourescent techniques. It has been found that these deposits correspond to a material that reacts which antibodies against fibrinogen and fibrin. The excess sFlt-1 probably plays a major role in causation of glomerular endotheliosis. Glomerular endotheliosis, by blocking the filtration barrier, diminished effective renal plasma flow and diminished glomerular filtration together reduce filtration fraction. Preeclampsia is associated with increased uric acid concentration and diminished urinary calcium excretion.

Although acute renal failure (ARF) is a rare complication of preeclampsia(1 in 10,000), preeclampsia is a major cause of obstetric acute renal failure. Acute renal failure in preeclampsia is most commonly due to acute tubular necrosis (ATN) and rarely as a result of bilateral cortical necrosis. Acute tubular necrosis is rarely caused by preeclampsia alone except in few neglected cases. Acute renal failure in preeclampsia is invariably induced by a coexisting haemorrhagic hypotension due to obstetric haemorrhage without adequate blood replacement. Renal failure due to preeclampsia in antenatal period will almost always prompt delivery.

Hepatic Changes

Excessive fibrin deposition in hepatic sinusoids which obstruct blood flow and hepatic vasoconstriction mediated hypoxaemia causes release of hepatic enzymes in the circulation and hepatic capsular distension which may present as epigastric and right upper quadrant pain. Liver edema and hepatocellular damage increases the serum transaminase and LDH levels while bilirubin is rarely raised.

The characteristic lesion in severe preeclampsia/eclampsia are periportal haemorrhages in the liver periphery. Hepatic vasculature in the subcapsular region is particularly susceptible to injury resulting in subcapsular haemorrhages. In combination with DIC, these haemorrhages can become larger and cause major subcapsular haematomas and liver rupture. In a patient with HELLP, this clinically manifests as severe epigastric pain, shoulder pain, shock, massive haemoperitoneum and respiratory difficulty. If the rupture or haematoma is contained within the capsule, the patient will be haemodynamically stable with excruciating pain.

Brain

In response to acute and severe hypertension, there is cerebrovascular overregulation leading to vasospasm, ischaemia, cytotoxic oedema and eventually tissue infarction. The motor

cortex is susceptible to cellular injury with resultant convulsion. Hyperreflexia and clonus are hallmarks of severe preeclampsia and are due to neurological irritability. Eclamptic seizures are grand mal in character with tonic/clonic phases. Vasoconstriction in different region cause different clinical manifestations: Vasospasm of frontal cortex causes frontal headache unrelieved by analgesics and is described as throbbing headache. Constriction in the occipital cortex causes visual disturbances and cortical blindness. Blindness may also develop due to retinal detachment. Cerebrovascular accidents occur due to cerebral vasospasm, vascular damage due to hypoxaemia and systolic hypertension leading to mechanical disruption of vessel wall. Most common hypertension-related maternal mortality is due to cerebrovascular accident, hence well controlled systolic blood pressure is of utmost importance.

Clinical Diagnosis

Blood Pressure Elevation

Persistent elevation in blood pressure is the hallmark of preeclampsia and reflects the severity of the disease. The diagnostic cut off values and the right technique for measuring blood pressure were described in the beginning of the chapter. Unfortunately, mistakes are frequently made due to lack of consistency in the measurement of the blood pressure. One common error is taking the blood pressure in an obese patient with 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 pregnant 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.[9,10]

Proteinuria

Proteinuria is a sign of preeclampsia which is defined as $\geq$ 300 mg of protein in a 24-hour urine collection. This usually correlates with 30 mg/dL or a 1+ reading dipstick in a random urine specimen. Proteinuria is also valuable as a sign of severity and a value $\geq$ 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. Urine dipsticks can be affected by variable excretion, maternal dehydration and bacteriuria. The correlation of the dipstick with the 24 hours excretion of protein was studied by Meyer et al.[42] A 1+ dipstick has a 92% positive predictive value to predict > 300 mg of protein. Approximate equivalence is 1+ = 0.3g/l, 2 + = 1g/l, 3+ = 3g/l.

A second rapid method for evaluation of proteinuria is the protein/creatinine ratio that in the nonpregnant state, 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.[43] 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 summary, a protein/creatinine ratio $\geq$ 0.3 almost always indicates significant proteinuria and a ratio $\leq$ 0.2 almost always indicates absent or nonsignificant proteinuria. Intermediate values have elevated percentages of false negative and false positive results.

The definitive test for diagnosing proteinuria is a quantitative measurement of total protein excretion in 24-hour urine sample. As per the NICE clinical guideline, if anautomated reagent-strip reading device is used to detect proteinuria and a result of 1+ or more is obtained, a spot urinary protein:creatinine ratio or 24-hour urine collection to quantify proteinuria should be done. Significant proteinuria is diagnosed if the urinary protein:creatinine ratio is greater than 30 mg/mmol or a validated 24-hour urinecollection result shows greater than 300 mg protein.[7]

The proteinuria of preeclampsia is "nonselective," meaning that it is a mixture of several proteins of different molecular weight. Proteinuria in preeclampsia characteristically occurs in the absence of either a nephritic (red cells, red cells 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.

Excessive Weight Gain and Oedema

Excessive weight gain and oedema are no longer considered a diagnostic criteria for preeclampsia as both are commonly seen in normal pregnancies with no increase in the incidence of preeclampsia. 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.

Signs and Symptoms

Neurological manifestations of preeclampsia always signify severe involvement and require immediate attention. Headache may be mild to severe and intermittent to constant. The pain may be frontal or occipital, may be pulsatile or dull, may occur simultaneously with visual symptoms, especially when preceding eclamptic convulsions. Headache and scotomas are thought to arise from cerebrovascular hyperperfusion that has a predilection for the occipital lobes.

The most common visual symptom appearing in patients with severe preeclampsia is scotomas, a transient perception of bright or black spots. This may progress to a sudden inability to focus, diplopia, blurred vision and in severe case, 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. Blindness is uncommon and is usually reversible with complete recovery following delivery. Occipital blindness, also called amaurosis, occurs due to occipital lobe vasogenic oedema. Blindness secondary to retinal ischaemia or infarction is called Purtscher retinopathy. Blindness following retinal detachment is commonly unilateral and partial.Surgical treatment is seldom indicated and vision usually returns to normal in a week post-delivery.

Epigastric or right upper quadrant pain is also common in patients with severe forms of the disease, particularly HELLP syndrome. This complaint is frequently attributed to indigestion or gallbladder disease and treated with antacids. When such pain occurs in patients with severe hypertension, it is frequently a harbinger of impending eclampsia. It is often accompanied by marked alterations in AST (aspartate aminotransferase), ALT (alanine aminotransferase) and LDH values.

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. Tonic clonic convulsions are diagnostic of eclampsia.

Clinical symptoms are important for assessing worsening disease especially development of headache and abdominal pain. Increasing oedema, is not in itself, a sign for decision making. Maternal tendon reflexes are not of value in determining risk of convulsions, however, presence of clonus is useful pointer for impending eclampsia.

Laboratory Findings

Women with preeclampsia may vary in severity and the laboratory findings may be unrevealing in cases of mild preeclampsia to derangements of multiorgan systems in severe forms. The laboratory changes reflect the effects of the disease on the renal, hepatic, haematologic systems and the fetoplacental unit.

Altered Renal Function

As discussed earlier, renal plasma flow and GFR are increased in normal pregnancy causing a fall in serum creatinine, blood urea and uric acid. In severe preeclampsia, an average reduction in GFR of about 25% results in a mild elevation in serum creatinine, blood urea nitrogen (BUN), and uric acid levels. The serum creatinine almost never exceeds 1.2mg/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 may fall to nonpregnant level. It should be noted that a creatinine clearance of 100 mL/min is abnormal during gestation when the lower limit of normal is 130 mL/min.

Renal functions are generally maintained in preeclampsia until late stage or HELLP. If creatinine is elevated in early in the disease process, underlying renal disease should be suspected. Serum creatinine may rise with worsening disease. Renal failure is uncommon in preeclampsia unless associated with haemorrhage, HELLP or sepsis.

Some investigators have postulated that an elevated serum uric acid is a specific laboratory finding in preeclampsia. Clinical significance of elevated uric acid levels in preeclampsia has been confusing. 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. Hyperuricemia is associated with renal dysfunction, glomerular endotheliosis and decreased renal tubular secretion. Uric acid levels are frequently elevated in pregnancies with preeclampsia. However, this test is neither sensitive nor specific for the diagnosis of preeclampsia or for predicting adverse perinatal outcome. Elevated uric acid levels should not be used as an indication for delivery in women with preeclampsia.

Changes in Liver Function Test

Hepatic involvement is observed in only about 10% of patients with severe preeclampsia. Patients with mild preeclampsia show little or no alteration in hepatic enzyme levels. When liver dysfunction does occur in severe preeclampsia, mild elevation in serum transaminases is most common. An AST or ALT levels of about 70 IU/L is seen as significant and a level above 150 IU/L is associated with increased morbidity to the mother.[35] Bilirubin is rarely elevated and if it is, as in HELLP syndrome, the indirect fraction predominates.

There is an elevation in the serum levels of LDH, usually the result of an increase in the hepatic isoenzyme. When haemolytic 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.

Haematologic Abnormalities

The only haematologic change that may be observed in patients with mild preeclampsia is an elevation of haemoglobin and haematocrit caused by decrease in plasma volume. The plasma fibrinogen concentration rises progressively in a normal pregnancy, and it is unusual to find a fibrinogen level below 200 mg/dL unless preeclampsia is complicated by abruptio placentae.

Thrombocytopenia is the most common haematological abnormality seen with severe preeclampsia and correlates with the disease severity and presence or absence of placental abruption. A falling platelet count is associated with worsening disease. However, not until the count falls below 100,000/mm^3 that there may be associated coagulation abnormalities. Coagulation profile including fibrinogen, prothrombin time and activated partial thromboplastin time should only be done if platelet count falls below 100,000/mm^3.

Ophthalmic Assessment

Direct evidence of vasoconstriction may be obtained by ophthalmologic examination. The most common findings in patient 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. Papilloedema is not a common finding in preeclampsia, and it suggests the possibility of a brain tumour, causing an increase 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 haemorrhages, exudates, or extensive arteriolar changes suggests chronic hypertension.

Fetal Growth Assessment

Shallow and defective trophoblastic invasion of spiral arterioles is a hallmark of preeclampsia. This defective placentation may lead to pathological fetal growth restriction in patients with moderate-to-severe preeclampsia. Fetal growth restriction (FGR) occurs in around 30% of preeclamptics and is usually asymmetric. Abdominal circumference below 5th centile is a good predictor of asymmetric growth restricted fetus. The finding of abnormal fetal biometry, poor growth trajectory on growth charts and oligohydramnios in women with preeclampsia demands evaluation with uterine, umbilical(UA) and middle cerebral artery (MCA) Doppler. The uterine artery Doppler will provide assessment of the uteroplacental circulation and is a screening test for prediction of growth restriction. An abnormal uterine Doppler (increased pulsatility index (PI), 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 women at risk for reeclampsia at 20–24 weeks but has no value in the follow-up of these cases.

The umbilical artery Doppler provides an assessment of the placental–umbilical circulation. A normal umbilical artery PI is indicative of a normal blood flow on 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 umbilical artery PI, absent diastolic flow and reversed diastolic flow are increasingly worsening indicators of resistance to blood flow in the fetal side of the placental circulation.

An elevated umbilical artery PI with diastolic flow still preserved, it is necessary to assess Doppler in the middle cerebral artery flow for presence of brain sparing effect as evidenced by low PI. In presence of hypoxia, the fetus attempts to divert blood flow from the periphery to the vital organs like the brain. When MCA S/D ratio is larger than the UA S/D ratio (MCA/UA $>$ 1.0), known as the cerebroplacental ratio (CP ratio) the placenta still has adequate reserves and the fetus is not under significant hypoxemia or acidosis. When the cerebroplacental ratio falls to less than 1 (MCA/UA ratio $<$ 1.0), 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, this cerebral redistribution (CP ratio $<$ 1) 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 best delivered before they reach a more advanced state of acidosis, manifested by reversed UA blood flow or by severe alterations of the FHR monitoring. Reversed UA diastolic flow reflects a later 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.

Doppler studies of venous side of the circulation has emerged as an important decision maker in FGR. Venous Dopplers (ductus venosus, umbilical vein) are indicators of cardiac decompensation secondary to hypoxia. Monitoring of ductus venosus Doppler helps clinicians in gaining valuable time prior to delivery in cases with abnormal umbilical artery flow with forward flow in ductus venosus. Ferrazzi et al (2002) have studied the temporal sequence in Doppler changes in FGR. Early Doppler changes in umbilical and

middle cerebral artery were seen in 50% of patients 15 to 16 days prior to delivery. Late changes like reversed diastolic flow in umbilical artery and abnormal venous Doppler occurred about 4–5 days prior to delivery. Reversed 'a' wave in the ductus is significantly associated with increased perinatal mortality.[44]

The NST (Nonstress test) and the MBPP (Modified biophysical score - NST plus ultrasound assessment of the amniotic fluid volume) are the most useful tests to periodically assess fetal well-being in the patients with preeclampsia and increased UA resistance.

The frequency of testing has to be individualized to every fetus and would depend upon the severity of growth restriction, the initial Doppler status and the gestational age. Since preeclampsia is a progressive condition, the tests of well-being should be performed weekly to fortnightly if initial growth and Doppler flows are normal. More frequent testing may be required if there is deterioration in maternal status, worsening preeclampsia, fall in amniotic fluid volume and Doppler showing absent or reversed diastolic flows in UAs.

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 as shown in Box 13.6.

Management

The only effective definitive treatment of preeclampsia is delivery. All other ancillary treatments are not directed at the underlying pathology. Although delivery is always beneficial for the mother, it may not be optimal for the premature fetus. Once the diagnosis of preeclampsia is established, subsequent therapy would depend upon severity of preeclampsia, gestational age of the fetus, maternal and fetal status at the time of initial evaluation, presence or absence of labour and the level of specialized neonatal services.

Mild Preeclampsia

Women with mild preeclampsia are at risk of progression to severe disease with end organ damage and associated adverse outcome. This risk is higher at gestational age remote from term. These pregnancies require close supervision either by hospitalization or frequent antenatal visits. The initial belief that bed rest after admission in patients with preeclampsia diminishes frequency of disease progression has not been validated. On the other hand, prolonged bed rest and hospital stay may increase the risk for thromboembolism. The disadvantages associated with a prolonged hospital stay are increased cost, disruption of family life, boredom, exogenous depression, and the monotony of hospital food. Advantage of hospitalization is early detection and prompt intervention in case of sudden disease progression, abruption placentae, impending eclampsia or hypertensive crisis. The recent NICE guidelines supports the fact that all patients diagnosed with preeclampsia must be admitted to the hospital.[7] Unfortunately, there are no randomized clinical trials indicating that one is better than the other, and in majority of cases of mild preeclampsia, the decision to keep a patient in the hospital or close day-care management is depending on individual hospital setup and a well-informed patient.

Initial Evaluation

The first step in the management of women with mild preeclampsia is an assessment of gestational age.

Gestational Age ≥ 37 Weeks: Pregnant women with mild preeclampsia at 37 weeks or more 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. The Hypertension and Preeclampsia Intervention Trial at term (HYPITAT) showed that women with gestational hypertension or mild preeclampsia had better maternal outcomes and equivalent neonatal outcomes with induction at ≥ 37 weeks compared with expectant management.[45] 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.

Gestational Age Between 24 and 36 Weeks: Management of the patient with mild preeclampsia between 24 and 36 weeks depends on maternal and fetal status at initial clinical and laboratory observations. Fetal assessment includes a NST and an ultrasound examination to determine estimated fetal weight, amniotic fluid index and color Doppler of uterine, umbilical and middle cerebral arteries.

Maternal laboratory evaluation includes measurement of haematocrit with platelet count, liver function tests (AST, ALT, LDH), renal function tests (serum creatinine, BUN, uric acid) and a 24-hour urine collection for proteinuria.

The presence of persistently elevated blood pressure ≥ 150/100, thrombocytopenia, elevated liver enzymes, oligohydramnios, fetal growth restriction, elevated resistance 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. 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 and there is absence of disease progression to severe preeclampsia, women with mild preeclampsia can continue pregnancy until 37 weeks of gestation.

General Measures

The goal of management in women with mild preeclampsia remote from term is early detection of progression to severe preeclampsia and organ dysfunction. 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 may be repeated if dipstick proteinuria worsens drastically.
5. CBC with platelet count, AST, ALT weekly/twice per week depending on maternal condition and ensuing clinical progression. Coagulation profile is not necessary in the presence of normal platelet count.
6. Questioning the patients for ominous symptoms at each contact like severe headache or scotomas, altered mentation, epigastric or right upper quadrant pain, nausea/vomiting, shortness of breath and decreased urine output. Patient is asked to maintain a daily fetal kick count. Women should be made aware of symptoms which she needs to report immediately like pain in the abdomen, uterine contractions, bleeding per vagina or decreased fetal movement.

Fetal surveillance includes:

1. Daily fetal movement count
2. FHR monitoring (NST) with liquor assessment (AFI) weekly/biweekly
3. Fetal biometry every 3 weeks
4. Umbilical and cerebral Doppler fortnightly/weekly if associated with growth restriction

During expectant management, the patients are instructed to eat a regular diet with ample protein and calories with no dietary salt and fluid restriction. They should not receive medications other than vitamin and iron supplements. Bed rest is unnecessary. Reduced physical activity throughout the day is likely to be beneficial. 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 compression stockings need to be used when the patient is in bed.

Most women admitted with mild preeclampsia at less than 36 weeks quickly improve with hospitalization 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.

Antihypertensive Treatment

Antihypertensive treatment is frequently used in women with moderate preeclampsia in a plan of expectant management at home or at the hospital. The NICE clinical guidelines suggest treating moderate hypertension (BP 150/100–159/109 mmHg) with antihypertensives to keep BP $<$ 150/80–100 range.[7] The benefits or disadvantage 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 reduce incidence of severe hypertensive crisis and tend to prolong pregnancy by an average of 15 days. There may be a small reduction in infant birthweight with antihypertensives. The first line antihypertensive in this situation is oral labetalol. It may be given orally in doses of 100–400 mg every 8–12 hours. Alternatives are methyldopa or nifedipine, the choice of which have been left on the clinician as per their familiarity of use.[7]

There is a consensus that if the blood pressure is below 150/100 mmHg, there is no immediate need for antihypertensive therapy. An exception may be, if mild hypertension is associated with markers of potential severe disease or signs of organ dysfunction (heavy proteinuria, liver dysfunction, haematological dysfunction).[35] Also women with mild to moderate hypertension with co-morbid conditions (diabetes, chronic hypertension, renal disease) should have antihypertensive therapy to lower systolic BP to 130–139 mmHg and their diastolic BP to 80–90 mmHg.[46]

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, adding multiple antihypertensive medications in an attempt to further prolong the pregnancy must be weighed against the risk of worsening disease. 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 could be 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, creantinine or uric acid levels and decreased creatinine clearance are not indications for delivery unless they occur simultaneously with an elevated blood pressure.

Termination of pregnancy is the only cure for preeclampsia. Mild preeclampsia after 37 weeks, moderate preeclampsia not improving after hospitalization and worsening preeclampsia or organ dysfunction, delivery is advisable for the welfare of both mother and fetus.

Role of Glucocorticoids for Fetal Lung Maturity

If birth is likely prior to 34 weeks, two doses of betamethasone 12 mg intramuscularly 24 hours apart is recommended. It may also be considered for fetuses between 35–36 weeks. There is no doubt that neonatal complications including RDS, intraventricular haemorrhage and death are significantly reduced with use of betamethasone prior to delivery. This treatment with steroids do not worsen maternal hypertension. Thiagarajah and colleagues (1984) suggested role of glucocorticoids to ameliorate HELLP syndrome.[47] However, Fonseca in 2005 randomized patients with HELLP to steroid or placebo and found no significant difference in outcomes including duration of hospital stay, recovery time of laboratory tests, recovery of clinical parameters and complication like acute renal failure, pulmonary edema, eclampsia and death. Steroids are not recommended for treatment of thrombocytopenia in HELLP syndrome.[48]

Delivery

Induction of labour and vaginal delivery should be attempted in women with mild preeclampsia, once delivery is indicated or the pregnancy reaches 37 weeks. Labour induction is usually carried out by prostaglandins as majority of these women are primigravidas with an unripe cervix due to their early gestational age. As a consequence thereof, the incidence of caesarean birth is also high. During intrapartum period, the antihypertensive therapy should be continued, maintaining systolic BP $<$ 160 mmHg and diastolic BP $<$ 100. Frequent monitoring of BP one hourly in labour is necessary. Continuous electronic fetal monitoring is indicated in cases suspected to have FGR. Ergometrine is to be avoided in third stage. Third stage can be actively managed with oxytocin or prostaglandins to prevent postpartum haemorrhage. Epidural analgesia/anaesthesia is the procedure of choice in labour and caesarean delivery.

A summary of the overall plan of management for patient with mild preeclampsia is shown in Figure 13.2.

Severe Preeclampsia

If the patient has severe preeclampsia (Box 13.6), the management will depend on the gestational age at the time of diagnosis.

Gestational Age $\geq$ 34 Weeks

If the gestational age is $\geq$ 34 weeks, the best approach is to treat with magnesium sulfate for the prevention of seizures, given antihypertensive to control the blood pressure and deliver after stabilization. Prime objectives are to forestall convulsion, prevent intracranial haemorrhage and serious damage to other vital organs and to deliver a healthy infant.

Prevention of Seizures

Magnesium Sulfate Magnesium sulfate is the medication most commonly used worldwide for the prevention and treatment of seizure activity in patients with severe preeclampsia, impending eclampsia and eclampsia. As recommended by the American College of Obstetricians and Gynecologists (2002a), all women judged to have severe preeclampsia should be given magnesium sulfate prophylaxis.[10] However, if conservative management of a woman with severe hypertension and a premature fetus is decided, it would be reasonable not to treat with magnesium sulfate until decision to deliver is made.[35]

There is robust evidence indicating the effectiveness of magnesium sulfate in the prevention of seizures in women with severe preeclampsia. The largest comparative study was the Magnesium Sulfate for Prevention of Eclampsia (Magpie trial, 2002). About 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 58% reduction in risk of eclamptic seizures.[49] The multinational Eclampsia Trial Collaborative Group study summarized that magnesium sulfate is associated with lower incidence of recurrent seizures as compared to women given alternative anticonvulsants. Maternal death rates of 3.1% with magnesium sulfate were significantly lower than 4.9% with other regimes.[50]

The mechanism of seizure control by magnesium sulfate is not clear but most clinical studies suggest that magnesium most likely exerts a specific anticonvulsant action on the cerebral cortex. Some investigators believe that magnesium is a peripheral anticonvulsant because of its ability to block neuromuscular transmission by decreasing the acetylcholine release in response to nerve action potentials.

Magnesium also decreases systemic vascular resistance and mean arterial pressures and at the same time increases cardiac output without myocardial depression. Magnesium sulfate is not used as an antihypertensive but it does have a lowering effect on blood pressures in severe hypertension.

Magnesium sulfate can be administered either by continuous intravenous infusion (Box 13.8) or intramuscular by intermittent injection (Box 13.9). Intramuscular route is as effective as intravenous administration. A loading dose of 6 g of magnesium sulfate given over approximately 20 minutes causes an immediate elevation of the normal

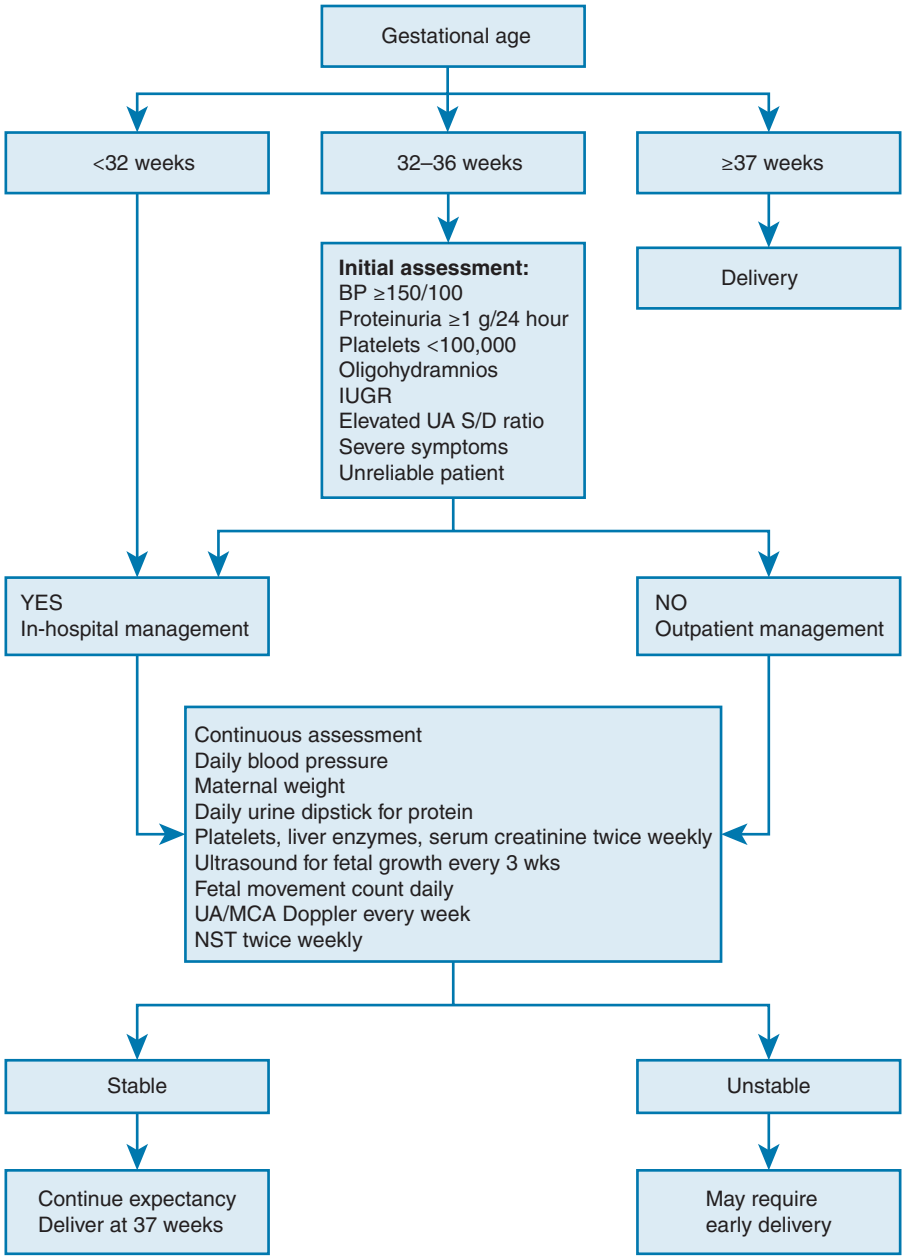

FIGURE 13.2 Management of mild preeclampsia.

magnesium 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.[51] At this elevated plasma level, about one-third of the magnesium is protein bound, and its renal clearance is very similar to the glomerular filtration rate. Eclamptic convulsions are almost always prevented or arrested with plasma magnesium levels of 4–7 mEq/L or 4–8 mg/dL. In most case of eclampsia, the initial loading dose is enough to arrest the convulsion. When given for eclamptic seizures 10–15% may have a subsequent convulsion. An additional 2 g of magnesium sulfate may be repeated slow intravenous. Alternately, if the maintenance infusion rate is 1 g/hr, the rate of infusion can be increased to 1.5–2 g/hr for recurrent seizures.

Magnesium sulfate is not an innocuous drug, and it is necessary to carefully monitor patients who are receiving the medication to prevent serious side effect. The clinical variables to be monitored are urinary output, patellar reflex, respiratory rate and pulse oximetry.

BOX 13.8 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. RCOG guidelines recommend a lower dose of 4 g as loading.[35]

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). RCOG guideline recommends 1g/hour maintenance dose.

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.

Magnesium sulfate is discontinued 24 hours after delivery or after last convulsion.

BOX 13.9 Guidelines for Intramuscular Magnesium Sulfate (Pritchard's Regime)

Intravenous loading dose (only in patients with eclampsia):

- Give 20 mL of 20% magnesium sulfate (4 g) slow intravenous in 3–5 minutes at a rate not exceeding 1 g/min

Intramuscular loading dose:

- 10 mL of 50% magnesium sulfate (5 g) deep intramuscular in the upper outer quadrant of each buttock using a 3 inch, 20 gauge needle. The intramuscular injection should immediately follow the intravenous loading dose in patient with convulsions. Patients without convulsions may receive only the intramuscular loading dose.

Maintenance dose:

- Give 5 g magnesium sulfate (10 mL of 50% solution) deep IM injection in alternate buttock every 4 hours.

Monitoring for magnesium toxicity:

- Urine output should be at least 30 mL/hour or 100 mL in 4 hours
- 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

Magnesium sulfate is discontinued 24 hours after delivery or after last convulsion.

Since magnesium is eliminated by the kidneys, monitoring of the urine output is extremely important. Magnesium intoxication is unusual when the glomerular filtration rate is maintained. Adequate urine output correlates well with preserved GFR. A urine output of at least 30 mL/hour is necessary for the continuous administration of magnesium sulfate. Routine measurement of Magnesium levels are not recommended.[10,35]

The urine output is frequently decreased in patients with severe preeclampsia. This may lead to an abnormally high serum magnesium concentration resulting in respiratory or cardiac arrest. Administration of diuretics to a preeclamptic patient with impaired renal function does not prevent magnesium accumulation to toxic levels despite the increase in urine output. Serum creatinine must be done to detect signs of declining GFR. The initial loading dose of 4 g can be safely administered regardless of renal function. The standard loading dose should not be reduced under the mistaken conception that decreased renal function requires a reduced dosage. Reason being the loading dose after redistribution achieves the desired therapeutic levels and the infusion maintains the steady state levels. Hence the maintenance rate should be altered in patients with decreased GFR (serum creatinine > 1 mg/mL) depending on the serum magnesium levels. If the urine output falls below 20 mL/hour, the magnesium infusion should be stopped.

Disappearance of the patellar reflex is important because it is the first sign of impending toxicity. The patellar reflex is usually lost when plasma magnesium 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. For severe respiratory depression and arrest, immediate tracheal intubation and mechanical ventilation is life saving.

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 oedema. 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.

The medication may cause maternal death from overdose leading to respiratory failure or pulmonary oedema

and its toxicity is associated with decreased myometrial activity, slow cervical dilatation, increased blood loss at delivery. High levels of serum magnesium may depress myometrial contractility by its effect on intracellular calcium. Inhibition of uterine activity is dose dependent and serum levels of at least 8–10 mEq/L are needed to show this effect. With the plasma levels achieved with the regimes used for prevention and treatment of eclampsia, no evidence of myometrial depression has been observed beyond a transient decrease in activity during and immediately after the initial intravenous loading dose. Magnesium sulfate does not affect either the duration of labour or the rate of caesarean delivery.

Maternal administration of magnesium crosses the placental barrier and equilibrates in the fetal serum. Neonatal respiratory depression and hyporeflexia is observed only with severe hypermagnesemia at delivery. Nonstress test done during magnesium sulfate administration should be interpreted cautiously. Magnesium causes a decrease in fetal heart rate variability. This is a frequent reason to misinterpret decreased variability on FHR tracings as fetal compromise and unnecessary caesarean section is done. On the other hand, 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.

Recent studies done in patient given magnesium for prevention of eclampsia or preterm labour showed neuroprotective effect of magnesium. A meta-analysis of five randomized trials that enrolled 6145 infants born to women with/without magnesium showed decreased rates of gross motor dysfunction in magnesium exposed group.[52] Overall, a protective effect of magnesium has been suggested against the development of cerebral palsy in very low birth infants.

Magnesium sulfate acts synergistically with the muscle relaxants used for general anaesthesia. Obstetrical anaesthesiologist are aware of this fact and prescribe a smaller dosage of such medications when giving general anaesthetics 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.[53] 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/min. 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 for Acute Management of Severe Hypertension

Dangerous hypertension can cause cerebrovascular haemorrhage, hypertensive crisis, congestive heart failure, trigger eclamptic seizures and abruption. The objective of antihypertensive treatment in severe preeclampsia is to prevent intracranial bleed 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 oedema or by inhibiting the cerebral arterial vasospasm that causes tissue ischaemia and per capillary bleeding.

Royal College of Obstetrician and Gynecologists in their greentop guidelines recommend antihypertensive treatment to women with systolic blood pressure of $>$ 160 mmHg or a diastolic BP of $>$ 110 mmHg.[35] Martin and associates highlighted the importance of treating systolic blood pressure as the risk of haemorrhagic strokes were more common in women with systolic BP $>$ 160 mmHg than those with diastolic BP $>$ 110 mmHg.[54] Nearly half of these serious haemorrhagic strokes associated with preeclampsia were seen in patients with chronic hypertension. Chronic hypertension results in development of Charcot-Bouchard aneurysms in the deeply penetrating arteries of the lenticulostriate branch of middle cerebral artery. These aneurysmal weakening predisposes these small arteries to rupture with sudden severe hypertension.

Drugs used for rapid lowering of elevated blood pressure in hypertensive crisis are hydralazine, labetalol and nifedipine.

Labetalol Labetalol is the medication of choice for 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. Because of its beta-blockade action, it is to be avoided in asthmatics and in patients with heart failure. Rarely, it may cause bradycardia and hypoglycemia in neonates.

Labetalol is effective in the treatment of severe hypertension and can be given by continuous or intermittent

intravenous infusion. For intermittent dosing, 20 mg should be given intravenous bolus initially 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 per treatment cycle. The maximum effect of IV labetalol is usually reached 5 minute after injection.

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 in 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 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 was commonly used for the rapid lowering of elevated blood pressure in obstetrics. Hydralazine acts directly on arteriolar smooth muscle to reduce PVR. The blood pressure response is almost immediate. 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. 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.[55] Hydralazine causes more maternal tachycardia and palpitation while labetalol causes bradycardia and hypotension. Effectiveness of both are similar. Hydralazine is contraindicated in women with myocardial insufficiency and heart failure.

Nifedipine Nifedipine is a calcium channel blocker used for the treatment of chronic hypertension. It has gained popularity because of its efficacy for control of acute pregnancy-related 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 NHBPEP Working group and the RCOG recommend a 10 mg initial oral dose to be repeated after 30 minutes if necessary. 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. Nifedipine given sublingually is no longer recommended.

The risk of neuromuscular blockade with concomitant use of magnesium sulfate and nifidepine is less than 1%. The blockade may be reversed by the use of 10 mg of intravenous calcium gluconate.

Other Antihypertensive Agents Methyldopa is used frequently in pregnant women with chronic hypertension and in gestational hypertension/mild preeclampsia but is not used in severe 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 < 24 Weeks

An attempt at expectant management of severe preeclampsia in extremely preterm pregnancies before 24 weeks have shown extraordinary high maternal and perinatal morbidity and mortality rates as published in five studies since 2000.[56] Sibai et al (1985) reported on 60 patients with severe preeclampsia between 18 to 27 weeks managed conservatively. They found serious maternal complications including eclampsia is 16.7%, HELLP syndrome in 16.7%, ATN in 5.0% and individual cases of hypertensive encephalopathy, intracerebral haemorrhage, and liver haematoma. The overall perinatal mortality was 87%.[57] The accumulated evidence indicates that conservative management for severe preeclampsia developing before 24 weeks is not adequate. Maternal morbidityis severe and perinatal survival is less. Hence in the face of serious

maternal complication approaching almost 50%, it is advisable to allow early delivery in these patients with mid-trimester severe preeclampsia to reduce maternal risk and avoid severe maternal morbidity and prolonged hospitalization.

Gestational Age 25–33 Weeks

Traditionally, severe preeclampsia has been an indication for delivery of the fetus irrespective of the gestational age. Although delivery is always beneficial to the mother, the fetal consequences of early delivery are also severe, and most investigators have looked at the possibility of prolongation of pregnancy to achieve better perinatal outcomes. A systemic review of management of women remote from term with severe preeclampsia have concluded in 2009 that expectant management, as compared to stabilization and delivery, confers some perinatal benefit with a minimum amount of additional maternal risk.[58] On the other hand, a recently concluded randomized, multicenter clinical trial of expectant management of severe preeclampsia remote from term, the MEXPRE Latin Study, does not demonstrate any significant neonatal benefit with expectant management of severe preeclampsia from 28 to 34 weeks. Additionally, it suggested that a conservative approach may increase the risk of abruption and SGA.[59] However, straightforward recommendations for either expectant or interventionist care cannot be given and policies should be individualized.

The decision between delivery and expectant management would depend on fetal gestational age, maternal and fetal status at the time of initial evaluation, presence of labour or ruptured membranes and the level of available neonatal and maternal services. Only patients with severe preeclampsia by blood pressure criteria and whose maternal condition is stable and fetal status is reassuring are candidates for expectant management. Such expectant management should only be practised at tertiary care institutions with adequate maternal and neonatal intensive care facilities and under specialists who are experienced in management of preeclampsia and its complications.

The women on expectant management should be counseled and made aware of the anticipated maternal, fetal and neonatal risks and that the decision to continue such management will be made on a daily basis and that the average prolongation of pregnancy is about 7 to 10 days. Maternal consequences of delayed delivery may include placental abruption (20%), pulmonary oedema (4%), eclampsia, HELLP syndrome, cerebrovascular haemorrhage, acute renal failure and maternal death. Fetal risks of hypoxaemia and perinatal death must be explained.

However, prompt delivery is indicated at any gestational age if there is imminent eclampsia (persistent severe symptoms), eclampsia, multiorgan dysfunction, severe intrauterine growth retardation (IUGR), suspected abruption or nonreassuring fetal testing.

Expectant Management of Severe Preeclampsia at <34 Weeks Gestation

Strict patient's selection criteria and adequate patient and neonatal care facilities are essential to avoid a major disaster when women with severe preeclampsia are managed expectantly. Presence of severe disease mandates immediate admission. Prior to initiation of expectant management, these patients should remain in a high risk antepartum area for intensive fetal and maternal monitoring and be carefully evaluated for a minimum of 24 hours.

During the observation period, maternal conditions evaluated are blood pressure monitoring, urine output, cerebral status, presence of epigastric pain/tenderness, shortness of breath, labour or vaginal bleeding. Laboratory tests include complete blood count with platelets, liver enzymes, serum creatinine and 24-hour urine protein. Fetal assessment by ultrasound for growth, liquor and Doppler studies and daily cardiotocography (NST) is done.

Antihypertensives are administered with an aim to lower systolic blood pressure between 140–155 mmHg and diastolic blood pressure between 90 and 105 mmHg. The present Cochrane review does not support the choice of any one antihypertensive agent over another and concludes that the choice should depend on the clinician's experience with a specific drug.[30]

All patients with gestational age less than 34 weeks, during the period of their initial evaluation must receive corticosteroids to accelerate fetal lung maturity and prevent intracranial bleed and hence improve fetal survival. Steroids are administered as 12 mg of betamethasone IM every 24 hours for two doses. Delivery should be accomplished at least if possible 12–24 hours after the second steroid dose. Treatment with steroids does not worsen maternal hypertension.

After an initial assessment, the need for immediate delivery versus the potential neonatal benefits and relative risk to mother and the fetus of expectant management is weighed. Once the decision for delivery is made, the patient should receive prophylactic magnesium sulfate in labour and for 24 hours postpartum.

The main aspects of expectant management are shown in Box 13.10.

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 13.11. The obstetrician should always remember that immediate delivery is the only measure that interrupts the progression of this disease. In a study (Hibbard, 1973), 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:[60]

- Underestimation of the severity of the disease
- Masking of symptoms with medications

BOX 13.10 Guidelines for the Expectant Management of Severe Preeclampsia Less Than 34 Weeks

- Hospitalization
- 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, creatinine, bilirubin, 24-hour urinary protein.
- Daily fetal movement count
- Weekly to as frequently as daily NST depending upon fetal growth status and liquor
- Umbilical and middle cerebral Doppler twice every week
- Amniotic fluid volume twice every week
- Ultrasound for fetal growth every 2 weeks.

BOX 13.11 Criteria to Interrupt Expectant Management and Move to Delivery

Maternal

- Persistent severe headache or visual changes, eclampsia
- Shortness of breath, chest tightness with rales and/or SpO2 $<$ 94% at room air; pulmonary oedema
- Uncontrolled severe hypertension despite treatment
- Oliguria $<$ 500 mL in 24 hours or serum creatinine $\geq$ 1.5 mg/dL
- Persistent platelet count $<$ 100,000/mm^3
- Suspected abruption, progressive labour and/or ruptured membranes

Fetal

- Severe growth restriction $<$ 5th centile for gestational age
- Reversed or end diastolic flow in umbilical artery Doppler
- Persistent severe oligohydramnios (AFI $<$ 5cm)
- Biophysical profile $\leq$ 4 done 6 hours apart
- Fetal death

- Failure to aggressively use antihypertensive drugs to combat extreme elevations of blood pressure

Criteria to interrupt expectant management and deliver women with severe preeclampsia as recommended by Sibai and Barton (2007) has been tabulated in Box 13.11.[61]

Delivery

The mode of delivery is determined after considering the presentation of the fetus, the fetal condition, the gestational age together with the likelihood of success of induction of labour after assessment of cervical bishop. Vaginal delivery is generally preferred. All women with severe preeclampsia should receive continuous electronic fetal monitoring in labour so as to early diagnose distress, hyperstimulation or abruption. Vaginal prostaglandins are preferred mode of induction of labour. Maternal pain relief during labour can be provided with systemic opioids or epidural analgesia. Restrict intravenous maintenance fluid to 80mL/hour unless there are other ongoing losses.

However, in most cases of severe preeclampsia before 34 weeks, induction of labour is unsuccessful and approximately 80% of these women will end up having a caesarean delivery.[62] If the fetus is growth restricted, the incidence of abnormal FHR monitoring patterns during labour is high. The high probability of operative delivery must be discussed with the mother, and many of them will opt for caesarean to avoid prolonged and usually unsuccessful inductions.

Third stage should be actively managed with the use of oxytocin. Ergometrine or its combination with oxytocin is best avoided for prevention of haemorrhage as it can further increase blood pressure. Haemorrhage is poorly tolerated in the severe preeclamptic patient due to the constricted intravascular volume. A blood loss of 1000 mL during a caesarean section corresponds to approximately 35–40% of the blood volume of a pregnant woman with severe preeclampsia.

Regional anaesthesia is the anaesthesia of choice in patients with severe preeclampsia, and in the hands of a competent obstetric anaesthesiologist, spinal and epidural anaesthesia are safe for the preeclamptic patient. The main contraindication to regional anaesthesia in these patients is the presence of coagulopathy or severe thrombocytopenia (platelet count $<$ 50,000 mm^3). In some cases, the sympathetic blockade associated with regional anaesthesia causes venous dilatation, significant blood pooling and a reduced preload. These haemodynamic effects may be avoided by administration of intravenous fluid, use of crepe bandage or elevating the lower extremities, and assumption of the lateral decubitus position to improve venous return.

The management of severe preeclampsia based on seizure prophylaxis, antihypertensive treatment and timed delivery involves adherence to some basic rules shown in Box 13.12. An overall management plan for severe preeclampsia is summarized in Figure 13.3.

Postpartum Care

All women with preeclampsia should be closely monitored postpartum with blood pressure measurement at least four times a day for the first 2 days followed by once daily for next 2 weeks or more till they are off antihypertensive and the blood pressure normalizes. If the patients are not on antihypertensives and the blood pressure is 150/100 mmHg or higher, they may be started on antihypertensives. Those patients on antihypertensives in the antenatal period need to continue same postpartum. Dosage can be reduced once blood pressure falls below 130/80 mmHg. Antihypertensives can be stopped once blood pressure remains normal for at least 48 hours. Women with persistent hypertension

BOX 13.12 Useful Guidelines for the Management of Patient 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 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.
- **May give diuretics after delivery**. Administration of cystalloids 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 oedema which may be avoided by diuretics.
- **Do not give diazepam to stop an eclamptic seizure**. Seizures are self- limiting and rarely last more than 1–2 minutes. Rapid administration of diazepam may produce apnea and facilitate aspiration. The management of seizures involves 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 the patients biting their tongue during the seizure. If it is pushed to the back of the throat, it will stimulate a gag reflex and vomiting with increased danger of aspiration.

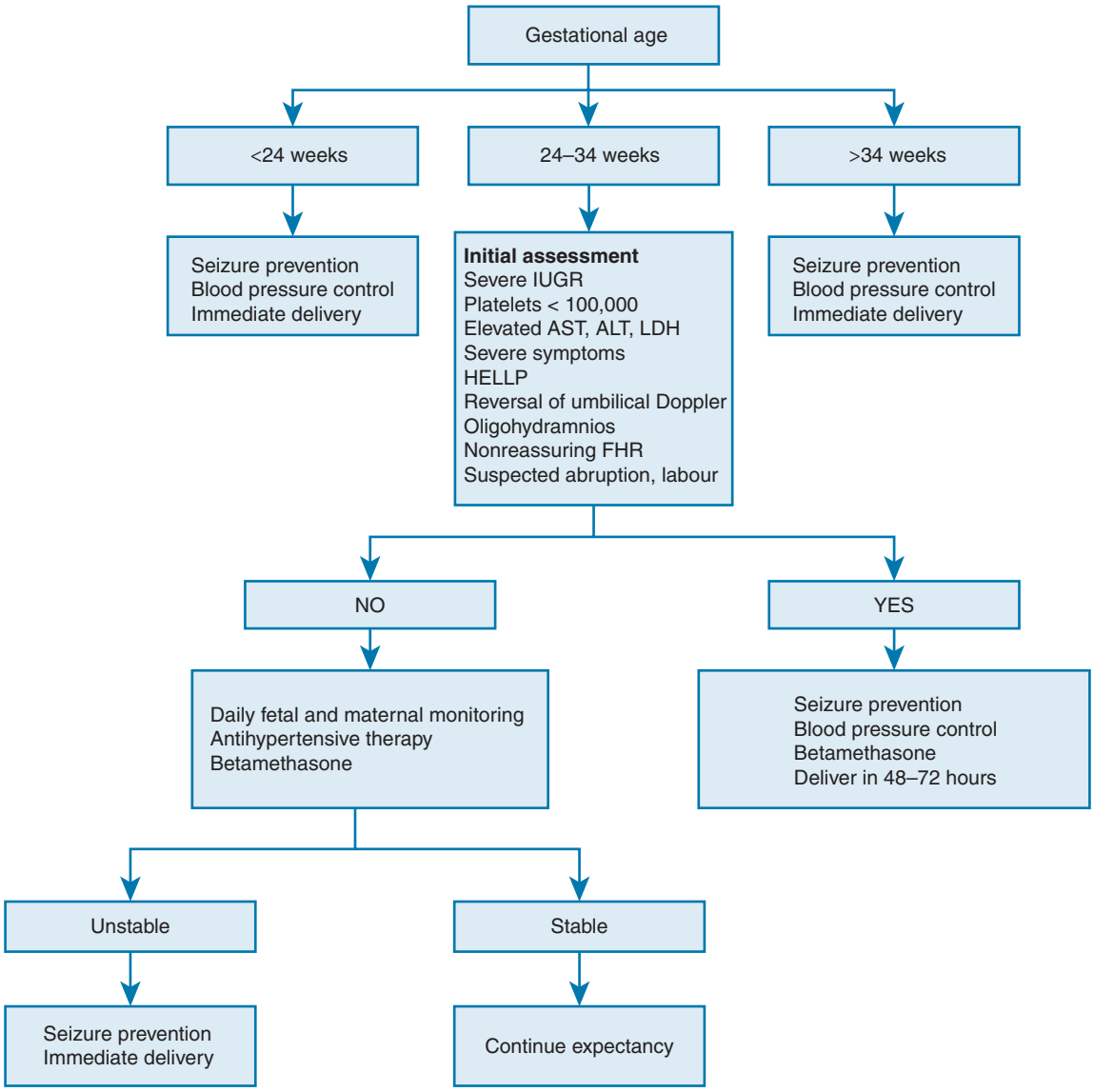

FIGURE 13.3 Management of severe preeclampsia.

and/or proteinuria at 6 weeks postpartum should be evaluated by a medical specialist.

In general, gestational hypertension resolves during the first postnatal week. However, preeclampsia takes longer to resolve. There may be an initial decrease followed by rise in hypertension between 3rd to 6th day postpartum.

Patients should also be asked about any signs and symptoms of severe hypertensive disease, pulmonary oedema, stroke and thromboembolism. Careful evaluation of intake, output and chest auscultation is necessary in the postpartum period. Women with severe preeclampsia especially those with deranged renal function and those with early onset disease are at increased risk of pulmonary oedema and exacerbation of hypertension postpartum. Mobilization of extracellular fluids into intravascular compartment that occurs post-delivery coupled with the large amount of intravenous fluids given during labour makes immediate postpartum period high risk for pulmonary oedema.

ECLAMPSIA

Eclampsia is an extremely severe form of preeclampsia. It is characterized by sudden onset of generalized tonic-clonic convulsion or coma in pregnancy or postpartum, unrelated to other cerebral conditions, in patients with signs and symptoms of preeclampsia. This condition affects between 1 in 2000 and 1 in 3448 pregnancies in the Western world but the incidence may be several times higher in developing countries.[63]

Depending on time of occurrence of convulsions before, during or after labour, eclampsia is designated as antepartum, intrapartum or postpartum. The frequency of timing of eclampsia reported in literature ranges from 38–53% antepartum, 15–20% intrapartum and 11–44% in the postpartum period.[64] Most antepartum eclampsia occurs in the third trimester (90%). Eclampsia occurring before 20 weeks is usually associated with molar pregnancy. Recent years have shown an increase in the incidence of postpartum eclampsia probably due to better prenatal care and prophylactic use of magnesium sulfate in severe preeclampsia during antepartum and intrapartum period. Most postpartum eclampsia occurs within the first 48 hours, few cases may present beyond 48 hours to as late as 4 weeks postpartum. In such cases of atypical eclampsia (presentation before 20 weeks of gestation or more than 48 hours after delivery, eclampsia refractory to adequate magnesium sulfate therapy) as also women with focal neurological deficits, prolonged coma, extensive neurological evaluation including cerebral imaging must be done to rule out other intracranial pathology.

Pathophysiology

The pathophysiology of eclampsia is still not conclusively elucidated. Autopsy studies have shown cerebral oedema, cortical and subcortical 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 oedema involving the posterior portions of the cerebral hemispheres bilaterally. Additional findings are areas of petechial haemorrhage and ischaemia 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 innervations 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. In these cases, vasogenic oedema 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. In the severely hypertensive women, the normal autoregulatory response to increase blood pressure is vasoconstriction, but once the upper limit of autoregulation is exceeded, vasodilatation occurs with hyperperfusion, causing endothelial capillary damage and interstitial vasogenic oedema. The level of cerebral perfusion pressure required to cause barotraumas and seizures varies between individuals.

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 exaggerated vasoconstriction and ischaemic changes with rupture of the vascular endothelium and pericapillary haemorrhages with development of foci of abnormal electrical discharges that generalize and cause convulsions. The practical implication of these ideas is that an agent that decreases perfusion pressure will be the ideal seizure prophylatic 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.[65]

Maternal and Perinatal Outcome

Eclampsia is associated with elevated maternal and fetal morbidity and mortality. Preeclampsia and eclampsia are the causes of approximately 20% of all maternal deaths in USA and approximately one-half of them are associated with eclampsia.[66] Case fatality rate in eclampsia as reported in UK is 1.8% and another 35% have severe morbidity.[67] Major maternal complications include placental abruption (7–10%), –DIC (7–11%), HELLP syndrome (9.7–20%), acute renal failure (5–9%), pulmonary oedema (3–5%), aspiration pneumonia

(2–3%), cerebral haemorrhage and cardiopulmonary arrest (2–5%).[68] The most common causes of maternal death are intracranial bleeding and acute renal failure secondary to abruption placentae. The risk of death is higher for women developing antepartum eclampsia, more than 30 years of age and those without prenatal care but it is greatest when eclampsia develops before 28 weeks of gestation.

Perinatal mortality occurs in about 5–12% of the cases.[68] The most common causes of perinatal death are prematurity and fetal asphyxia. Perinatal morbidity is substantial and correlates strongly with preterm birth, abruptio placentae, and FGR.

Diagnosis

The diagnosis of eclampsia is usually clear when women present with seizures, hypertension and proteinuria. Hypertension is the hallmark for the diagnosis of eclampsia. Hypertension may be severe (20–54% of cases) or mild (30–60% of cases).[68] Unfortunately, in approximately 15% of the cases, hypertension and proteinuria may not be present. However, when seizures develop in a pregnant woman without a history of seizures disorders, eclampsia should be the diagnosis unless proven otherwise. In the majority of cases, the onset of convulsions is preceded by persistent occipital or frontal headache, throbbing in nature, visual symptoms, epigastric or right upper quadrant pain or altered mentation. Presence of these clinical symptoms helps in establishing the diagnosis as eclampsia. The presence of haemoconcentration, elevated liver enzymes, elevated LDH, and thrombocytopenia also help in correct diagnosis when high blood pressure and proteinuria are not present.

Typically, the convulsions are tonic clonic and rarely last more than 1 to 2 minutes. They usually start with facial twitching and then progressing to the body becoming tonically rigid with generalized muscular contractions. This is followed by a phase of alternate contraction and relaxation of muscles of the body in rapid succession. These contractions are extremely forceful and it is not possible to restrict these contractions manually or abolish the convulsion. The patients in the event can injure themselves by falling off of the bed or biting their own tongue. Post seizure, the patient usually regains some degree of consciousness. She may enter into a semiconscious combative state and become agitated. In severe cases, she may be in coma for variable duration. Coma may persist from one convulsion to the next and death may result. This persistent coma is due to cerebral oedema and transtentorial herniation. Rarely convulsions continue unabated and this is called as status epilepticus.

The eclamptic patient ceases to respire during the seizure followed by hyperventilation during the immediate postictal state in response to lactic acidosis, hypercarbia and hypoxia. Urine output may reduce and there may be significant proteinuria and haemoglobinuria.

Pulmonary oedema may occur either secondary to aspiration of gastric contents during the seizure or due to ventricular failure from increased afterload due to overzealous intravenous fluid administration in a hypertensive patient. It is more common in obese and patient with chronic hypertension.

A 10% of women experience varying degrees of loss of vision secondary to either retinal detachment or occipital lobe ischaemia and cerebral oedema. Blindness is reversible and returns within a few days to a week postpartum.

Sudden death may occur during or after a seizure which is often due to massive cerebral haemorrhage. Sublethal intracranial haemorrhage may present as haemiplegia. Hyperthermia following seizure is ominous as it is suggestive of cerebral haemorrhage. This is seen more often in older women with underlying chronic hypertension.

Management

Eclampsia is a major obstetric emergency that requires mobilization of efforts and adequate management to avoid catastrophic events. Basic principles of management of eclampsia fall under three major categories:

- Control of convulsion
- Control of hypertension
- Delivery of the fetus

Control of Convulsion

Principle of management of seizures follows the principle of ABC of resuscitation (Airway, breathing and circulation). The initial step is to prevent maternal injury and maintain cardiorespiratory function. Patients should never be left alone. The bedside rails should be elevated to avoid maternal injury during the convulsion. To decrease the risk of aspiration the patients should be placed in the lateral decubitus position and oral secretions or vomitus are suctioned if needed. Assess and establish airway patency to ensure maternal oxygenation. Supplement oxygen by face mask at 8–10 L/minute during the seizure. The seizure usually lasts only 1–2 minutes during which there is apnea. After the convulsion has ceased, patient starts breathing again, so oxygenation is not seriously compromised. It is good practice to monitor maternal oxygenation with pulse oximeter. Management of eclamptic seizure is summarized in Box13.13.

Magnesium sulfate is the drug of choice in treatment of eclampsia. The efficacy of magnesium sulfate as an anticonvulsant has been compared with diazepam, phenytoin and lytic cocktail regime in collaborative eclampsia trial in 1995 where it was concluded that magnesium sulfate is associated with significantly lower recurrent seizures as well

BOX 13.13 Treatment of Eclamptic Seizures

- Do not try to stop seizure
- If suitable, an oral airway may be inserted without trauma to mouth and teeth
- Suction oral secretion
- Give oxygen by mask at 8–10 L/minute
- Elevate bedside rails and pad them to avoid injury
- Use physical restraints if necessary
- Pulse oximetry to monitor hypoxaemia
- Once the seizure end, start IV fluids (125 mL/hour)
- Give loading dose (6 g) of magnesium sulfate over 15–20 minutes followed by maintenance dose of 2 g/hour as 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

as lower maternal mortality than the others.[50] 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 infusion. 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 refractory cases, intubation may be necessary.

In the majority of cases, it is unnecessary to monitor magnesium plasma levels. However, this 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. When magnesium toxicity is suspected, an effective antidote is 10 mL of 10% calcium gluconate, given IV over 10 minutes. Treatment with magnesium sulfate should continue for at least 24 hours after delivery in order to avoid postpartum eclampsia.

Treatment of Hypertension

Treatment of elevated blood pressure is of the largest importance in eclamptic patients. Treating severe hypertension helps prevent congestive heart failure and cerebral haemorrhage and also has an important role in the treatment and prevention of seizures. The first line antihypertensive drug is labetalol followed by nifedipine. The goal should be to maintain systolic blood pressure between 140 and 160 mmHg and diastolic blood pressure between 90 and 105 mmHg. Antihypertensives that can be used have been detailed in the previous section on severe hypertension.

Diuretics

Use of diuretics in the antepartum period should be limited to eclamptic women with concomitant pulmonary oedema. However, they may form an integral part of the postpartum care. Furosemide 20–40 mg IV every 10–12 hours can be initiated shortly after vaginal or caesarean 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 setup for congestive heart failure and pulmonary oedema particularly in women with renal function impairment. These is one randomized clinical trial indicating that aggressive postpartum stimulation of diuresis with furosemide enhances and speeds the recovery of preeclamptic women.[69]

Fetal Response to Maternal Seizures

During a seizure, there are no maternal respirations for 1 or 2 minutes. Maternal hypoxaemia, hypercarbia and lactic acidosis 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 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 caesarean performed. In these cases, the maternal and fetal prognosis may be poor.

Delivery of the Fetus

Delivery is the only definitive treatment for eclampsia. However, every attempt should be made to stabilize the mother before attempting to deliver the patient. A crash caesarean in an unstable patient would place the mother at grave risk to life. Presence of eclampsia in itself is not an indication for caesarean section.

Following a seizure, labour often ensues spontaneously, progresses fast or can be induced successfully. The mode of delivery should be decided depending on the fetal presentation, fetal condition and likelihood of success of induction of labour. Caesarean delivery may be indicated in the presence of prolonged fetal bradycardia, unripe cervix, gestational age < 30 weeks, FGR, inadequate blood pressure control and poor progress in labour.

The anaesthesia of choice for eclamptic patients is regional, spinal or epidural. The only contraindication to regional block anaesthesia is a platelet count $< 50{,}000/mm^3$.

When general anaesthesia 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. About 44% of eclampsia occur in the postpartum period and it is important to be vigilant. The incidence of postpartum eclampsia declines after 4th postpartum day and the patient may be discharged. As mentioned previously, administration of furosemide and aggressive diuresis should be initiated immediately following delivery and maintained for several days after the patients' discharge from the hospital. Oral administration of antihypertensive agent (labetalol, calcium channel blockers) should continue in the postpartum period until complete normalization of the blood pressure is demonstrated. Patients can be slowly weaned off the antihypertensive therapy as an outpatient. An assessment of blood pressure and proteinuria should be done at 6 weeks postnatal checkup. If the hypertension or proteinuria persists beyond 6 weeks, they should be further evaluated by a medical specialist. Up to 13% of women with preeclampsa have an underlying chronic or essential hypertension that was not suspected antenatally.[35]

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.[70]

Long-Term Prognosis

The seizure characteristics 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 haematologic complications. Haemolysis in these cases results from cell passage through small vessels partially obliterated with fibrin deposits (microangiopathic haemolytic anemia). This complication of preeclampsia is recognized by the acronym HELLP (haemolytic anemia, elevated liver enzymes, low platelet count) syndrome.

Diagnosis

The criteria for the diagnosis of HELLP syndrome are shown in Box 13.14. In most cases, the diagnosis of HELLP syndrome is straightforward. Patients usually present with nausea and vomiting, right upper quadrant or epigastric pain. About 82–85% of patients with HELLP have mild to severe hypertension and 85% have significant proteinuria. Rarely there are differential diagnostic difficulties with fatty liver of pregnancy, haemolytic 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 is the presence of haemolysis. 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 haemolysis is markedly decreased or absent plasma haptoglobin. The elevated liver enzymes include AST and ALT $\geq$ 72 U/L and LDH $\geq$ 600 U/L. Total LDH concentration is the result of the combined activity of several isoenzymes of hepatic and red cell origin and represents both altered liver function and haemolysis. Finally, the platelet count should be $\leq 100{,}000/mm^3$. HELLP syndrome is not a variant of DIC and all coagulation parameters (prothrombin time, partial thromboplastin time and fibrinogen) are normal.

Several studies have tried to classify HELLP syndrome based on laboratory parameters. The Mississippi classification

BOX 13.14 Criteria for the Diagnosis of HELLP Syndrome

Haemolysis

- Abnormal peripheral blood smear (burr cells, schistocytes)
- Elevated bilirubin $\geq$ 1.2 g/dL
- Low serum haptoglobin
- Increased LDH > twice the upper limit of normal (> 600 U/L)

Elevated liver enzymes

- Elevated AST, ALT $\geq$ twice the upper limit of normal ($\geq$ 72 IU/L)

Low platelet count ($< 100{,}000/mm^3$)

categorizes the severity of HELLP syndrome into three categories, according to maternal platelet count.[71]

- **Class I (severe thrombocytopenia):** platelet count below 50,000/mm^3
- **Class II (moderate thrombocytopenia):** platelet count between 50,000 and 100,000/mm^3
- **Class III (AST > 40 IU/L, mild thrombocytopenia):** platelet count between 100,000 and 150,000/mm^3

Tennessee System also classifies HELLP into complete syndrome if there is presence of all three parameters abnormal (AST/ALT, LDH, Platelets) and incomplete syndrome if there are one or two of the three as abnormal.[72]

Maternal and Perinatal Outcome

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 oedema. Maternal morbidity is frequent and severe (Box 13.15). Perinatal mortality and morbidity are also significantly increased in women with HELLP syndrome mainly due to prematurity, growth restriction and abruption placentae. The perinatal mortality changes with the gestational age and may vary between 7 and 30%. 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 haemorrhage, necrotizing enterocolitis, and bronchopulmonary dysplasia is equally high.[23]

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 progressive hypovolaemia will point to intraabdominal bleeding. 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** haematomas. 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 haemostatic agent. One of the sponges is brought outside the abdominal incision to facilitate removal on the 2nd or 3rd postoperative day.

BOX 13.15 Maternal Morbidity Associated with HELLP Syndrome

Abruptio placenta	10–15%
Disseminated intravascular coagulation	10–15%
Pulmonary oedema	6–8%
Acute renal failure	5–8%
Adult RDS	1–2%
Death	1%

Management

The clinical course of women with HELLP is usually progressive with sometimes sudden deterioration of maternal and fetal condition. Hence a diagnosis of HELLP syndrome is an indication for immediate delivery if the pregnancy is ≥ 34 weeks or at any gestational age if pulmonary oedema, renal failure, placental abruption, severe liver dysfunction or bleeding, nonreassuring fetal status, or uncontrollable hypertension is present.

All other cases require administration of magnesium sulfate, steroids for the prevention of intraventricular bleed and RDS in the fetus and delivery within 24 hours after the second steroid dose. In these situations also it may be 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 not be delayed further even if there is some apparent improvement in the patient situation during the time required for steroid administration.

Vaginal delivery is a consideration only if the cervix is ripe, the gestational age is ≥ 32 weeks, the FHR is reactive and there are no indications for caesarean delivery. Labour 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 caesarean 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 haemostasis. 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 platelet in a presumably non-immunized 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. 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 haemodynamics. 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 double blind, placebo controlled clinical trial with adequate number of subjects demonstrated that dexamethasone treatment does not improve the outcome in women with HELLP. Outcomes assessed included duration of hospitalization, recovery time of abnormal lab test results and complications like acute renal failure, pulmonary oedema, eclampsia and death. 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.[73] At present, corticosteroids are not recommended for treatment of HELLP.

SEVERE COMPLICATIONS OF PREECLAMPSIA

Pulmonary Oedema

Pulmonary oedema is a rather common complication of severe preeclampsia and eclampsia, affecting approximately 3% of these patients. Most cases are the results of aggressive use of crystalloid solutions for intravascular volume expansion. Pulmonary oedema usually occurs in the postpartum period and is characterized by profound respiratory distress, severe hypoxaemia, and diffuse rales on auscultation.

There are clinical differences between the pulmonary oedema of organic heart disease and that of preeclampsia. In majority of preeclamptic patients, pulmonary oedema 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 echocardiography.

Respiratory distress, a drop in oxygen saturation, and bilateral rales on auscultation of the lungs are typical findings in preeclamptic women with pulmonary oedema. This usually is associated with the administration of large amounts of intravenous crystalloids in a patient with oliguria.

Treatment consists of propped up position, administering oxygen by nasal prongs or a rebreathing mask, restriction of intravenous and oral fluids, and furosemide 20–40 mg IV every 6 hours. The response to aggressive administration of furosemide is usually dramatic with profuse diuresis and improvement of the respiratory symptoms. Central haemodynamic monitoring (central venous pressure of Swan Ganz catheter) has been recommended by the American College of Obstetricians and Gynecologists (2002a) only in severely preeclamptic women with accompanying severe cardiac disease, renal disease, or both or in cases of refractory hypertension, oliguria and pulmonary oedema.[10]

Acute Renal Failure

Oliguria is not uncommon in patient with severe preeclampsia. Oliguria in women with severe preeclampsia most of the time is pre-renal 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 haematocrit reflecting haemoconcentration need aggressive treatment with vasodilators to effect afterload reduction and decrease renal artery vasospasm. Normotensive or mildly hypertensive women with low haematocrit values have expanded intravascular volume and need aggressive diuresis.

In some patients, usually older and obese, there is large increase in plasma volume with normal or decreased cardiac output. These women are at significant risk of pulmonary oedema 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 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 DIC. 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 caesarean section. In many occasions, delivery is followed by disappearance of the renal vasospasm and brisk diuresis.

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 pre-eclampsia and eclampsia was that the main correlation of this event was the systolic, not the diastolic blood pressure.[54] 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 CT 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 microhaemorrhages and microinfarcts occurring in the occipital lobe. Cortical blindness is equivalent to a seizure, and patients with these symptoms 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 oedema, which frequently is missed in the examination because it begins in the periphery of the retina. Papilloedema in preeclampsia is highly unusual and demands a reevaluation to rule out the possibility of an intracranial tumour or bleeding. Diplopia is a symptom that may occur, and it is caused by functional impairment of the sixth cranial nerve paralysis. This finding requires a CT scan to rule out a tumour in the brainstem area. Like most lesions caused by preeclampsia, sixth nerve paralysis improves after delivery and eventually disappears several weeks later.

Abruption Placentae

About 7% of all patients with eclampsia will have premature separation of the placenta and they are managed on the lines of abruption with DIC.

LONG-TERM PROGNOSIS OF PREECLAMPSIA AND ECLAMPSIA

When counseling women who had preeclampsia or eclampsia, the main questions are the possibilities of recurrence in a future pregnancy and the development of chronic hypertension later on in life.

The probability of recurrence of preeclampsia is approximately15% and this probability increases in inverse relationship to the gestational age at which the patient developed the disease. Risk of preeclampsia rises to 25% if the index pregnancy was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and about 1 in 2 (55%) pregnancies if it led to birth before 28 weeks.[7] Women who develop preeclampsia as multiparous 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 onset of symptoms, and severity of the hypertension are factors significantly associated with the probability of developing recurrent preeclampsia.

Women who develop preeclampsia especially those remote from term are at high risk for chronic hypertension later in life. A Cohort study in Scotland 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.[74] However, women who develop preeclampsia are not at high risk of developing hypertension when using oral contraception.[75]

In addition, women with preeclampsia, particularly those with recurrent preeclampsia are more likely to have an underlying renal disease. Women with pregnancy complicated with preeclampsia have a lifetime increased risk of coronary artery disease and stroke. Such patients must be counseled on lifestyle and risk factor modification to alter their risk of complications.

PREDICTION OF PREECLAMPSIA

Prediction of preeclampsia may help in stratifying women into high risk group so that surveillance can be intensified and prophylactic therapies can be initiated. Several tests have been proposed to identify women at risk of developing preeclampsia.[76] Biochemical markers that have been proposed to identify women destined to develop preeclampsia were chosen on the basis of specific pathophysiological abnormalities that have been found in association with preeclampsia. These biochemical markers include markers of placental dysfunction, endothelial cell activation and

dysfunction, coagulation activation, angiogenesis and markers of systemic inflammation. Biophysical tests such as the cold pressor test, the isometric hand grip exercise and the roll over test also depend on the pathophysiologic changes that occur in preeclampsia. However, none of these tests are sufficiently reliable for use as a screening test in clinical practice. Combination of these tests are being evaluated for their predictive accuracy.

Provocative Pressor Tests

These are tests which assess blood pressure increase in response to a stimulus. They are cumbersome and time consuming. Sensitivities of all these tests range from 55 to 70% with specificities of approximately 85%. They include :

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 labour intensive and has a high incidence of false negative and false positive results. Also, angiotensin II preparations for human use are not available.

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. It measures the hypertensive response in women at 28 to 32 weeks who are resting in the left lateral decubitus position and then roll over to a supine position. A positive test is an elevation of 20 mmHg or more in blood pressure when patients roll over from the lateral to the supine position. Unfortunately, the test has poor sensitivity and poor specificity and is of limited clinical value.

Isometric Exercise Test (Hand Grip Test)

This also employs the same principle by squeezing a handball.

Mean Blood Pressure in the Second Trimester

Mean arterial pressure (systolic + 2 (diastolic)/3) (MAP) $\geq$ 90 mmHg in the second trimester of pregnancy was proposed long time ago as a predictor of preeclampsia. However it has a low sensitivity and low positive predictive values.

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 urinary sample seems to be as accurate as 24-hour collection. In normotensive pregnancies, this ratio is 0.44 $\pm$ 0.32. In case of chronic hypertension, the ratio is lower 0.20 $\pm$ 0.18, but in preeclampsia it is much lower (0.03 $\pm$ 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 patient at risk.

Fibronectin

Patients with preeclampsia have elevated levels of plasma fibronectin—a high molecular weight 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 level of endothelium originated fibronectin precede the clinical signs of preeclampsia and may be useful for prediction of the disease.

Uterine Artery Doppler

The underlying mechanism for the development of preeclampsia is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control. Uterine artery Doppler velocimetry at 22–24 weeks is useful to identify women destined to develop preeclampsia. An abnormal UA velocity waveform is characterized by pulsatility index above the 95th percentile or the presence of early diastolic notching (unilateral or bilateral). Thesepregnancies are associated with sixfold increase in rate of preeclampsia.[77] The sensitivity of abnormal UA Dopplerfor predicting preeclampsia range from 20% to 60%. The sensitivity increases to 80% to 90% for women developing severe forms of these complications requiring delivery before 32 weeks. The positive and negative likelihood ratio of second trimester uterine artery Doppler screening are 6.61 and 0.55, respectively. It seems that, although not a perfect screening tool, UA Doppler ultrasound is the best available test for the early detection of preeclampsia of placental origin. Current evidence does not support routine screening of all pregnant women with UA Doppler but it may be beneficial as a screening test in women at high risk for preeclampsia so as to stratify care into low risk and high risk pregnancies.

Recently lot of research is being done on Doppler studies of the uterine arteries at 11–13 weeks. They have demonstrated that impedance to flow is increased in pregnancies that subsequently develop hypertensive disorders and that the increase is particularly marked for early preeclampsia. The estimated detection rate, at a 10% false-positive rate,in screening by a combination of maternal factor-derived a-priori risk with uterine artery PI was 81% for earlypreeclampsia, 45% for late preeclampsia and 35% for gestational hypertension.[78]

BOX 13.16 Various Tests for Prediction of Preeclampsia

Testing Related To	Examples
Placental perfusion-faulty trophoblastic invasion of spiral arterioles/increased vascular resistance	Roll over test, isometric handgrip or cold pressor test, angiotensin II sensitivity test, midtrimester mean arterial pressure, uterine artery Doppler, Nail bed arterial pressure stiffness test
Fetoplacental endocrine dysfunction	Increased HCG, AFP, estriol, placental protein 13 Low pregnancy associated plasma protein A (PAPPA), Low Inhibin A
Renal dysfunction	Serum uric acid, microalbuminuria, hypocalciuria
Endothelial dysfunction/ oxidative stress	Increased fibronectin, endothelin, C-reactive protein, hyperhomocysteine, antiphospholipid antibodies, plasminogen activator inhibitor (PAI), placental growth factor (PLGF), vascular endothelial growth factor (VEGF), fms-like tyrosine kinase receptor-1 (sFlt-1), low platelet count
Others	Antithrombin III, free fetal DNA

The ability to predict those women at risk for PE in very early pregnancy might decrease maternal and fetal morbidity through closer surveillance and early intervention with low dose aspirin.

Various tests for prediction of preeclampsia are summarized in Box 13.16.

PREVENTION OF PREECLAMPSIA

Prevention of preeclampsia can be theoretically achieved at primary, secondary, or tertiary levels.

Primary prevention is equivalent to avoiding the occurrence of the disease. Primary prevention is a task that is impossible because of our limited knowledge about aetiology and initial mechanisms of the disease. However, modifying the risk factors such as obesity, avoiding pregnancy at extremes of age, and embarking on a pregnancy with a well-controlled diabetes, renal disease, and chronic hypertension preconceptionally may be methods of primary prevention.

Tertiary prevention is synonymous with treatment to avoid complications of the disease which has already been dealt with.

Efforts to prevent preeclampsia have been focused on secondary prevention that consists of correcting the pathophysiology of the process and 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 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.

The three preventative strategies more carefully studied during the last 15 years have been low dose aspirin administration, calcium supplementation, and antioxidant administration. Lifestyle modifications including reduction in stress and regular well-supervised prenatal exercises help in some way. Weight reduction in pregnancy is not recommended.

Low Dose Aspirin

There is substantial evidence indicating that 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 promoter 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 thomboxane 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 protein 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 systematic review of 33,439 women enrolled in 43 trials found that the use of aspirin was associated with a 19% decrease in the risk of preeclampsia, 7% decrease in risk of delivery before 37 completed weeks, 8% reduction in the risk of SGA babies, and a 16% reduction in fetal and neonatal death. 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%).[79] 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. Meta-analysis of 31 randomized trials involving 32,217 patients as published in Lancet 2007 found following inferences[80]:

- Significant decrease in (10%) relative risk of preeclampsia, superimposed preeclampsia, preterm delivery, adverse outcome. However, number needed to treat were high
- No increase in antepartum haemorrhage (APH), postpartum haemorrhage (PPH)
- Risk reduction greater if started prior to 20 weeks, dose > 75 mg

NICE recommends aspirin 75 mg daily to all women at moderate to high risk for developing preeclampsia from 12 weeks to the birth of the baby.[7]

Fish oil supplementation has been another attempt to modify the thromboxane/protacyclin 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 cyclooxygenase, inhibiting the production of thromboxane by the platelets. However, several controlled trials have failed to demonstrate 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 did not find any difference in the incidence of preeclampsia between women randomized to calcium and women taking placebo.[81] In contrast, a systematic review of 11 randomized clinical trials found a significant decrease in the risk of hypertension in general and also in the risk of preeclampsia.[82] 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. Dosage of calcium supplementation in women with low calcium intake is 1.5 g /day for preeclampsiaprevention.

Antioxidant

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.[83] 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 using vitamins C and E in women at 20 weeks, demonstrated a significant decrease in the incidence of preeclampsia in the treated group.[84] A second study again using a small number of cases and assuming a high efficacy of the prevention intervention did not find a significant difference between women taking vitamins C and E and those taking placebo in the incidence of preeclampsia.[85] Prevention of preeclampsia using antioxidant needs to be studied in a large population to better assess the potential benefits and the safety of this treatment.

NICE guideline does not recommend salt restriction during pregnancy solely to prevent hypertension in pregnancy. NICE guideline also does not support the use of following nutritional supplements/pharmaceutical agents with the aim of preventing preeclampsia[7]:

- Magnesium
- Antioxidants (Vitamin C and E)
- Fish oils or algal oils
- Garlic
- Nitric oxide donors
- Progesterone
- Diuretics
- Low molecular heparin

INDIAN EXPERIENCE OF HYPERTENSIVE DISORDERS IN PREGNANCY

Predictive Test

- 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.[86]
- Role of calcium:creatinine ratio in first morning urine 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.[87,88]
- Estimation of serum calcium and magnesium levels by Sawhney et al (2001) were not very helpful in predicting the risks of PIH. These were comparable in both hypertensive and normotensive pregnant patients.[89] Perhaps

estimation of intracellular levels of calcium and magnesium may be more meaningful.

- 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.[90]
- 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.[91] 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.[92]
- Antioxidants play an important role in combating oxidative stress during pregnancy. Estimation of enzymes superoxide dismutase, catalase, RBC glutathione and vitamin E are known to fall in women with PIH indicating increasing peroxidation.[93]
- 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 (multiple of the mean) manifested PIH.[94]
- 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 develop PIH.[95]
- 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 birthweight of 2.88 kg and no perinatal loss. As against the PIH group of patients, in whom 66% delivered AGA babies, with the mean birthweight of 2.44 kg and one perinatal death.[96]
- 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%).[97]

Clinical Aspects of Pregnancy-Induced Hypertension

- 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 birthweight and maternal outcome was better in the actively managed cases.[98]
- 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.[99]
- 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.[100] 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.[101]
- 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.[102]
- 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.[103]
- 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, 21.33% in severe PIH cases.[92]
- 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 case of abruption 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 haemodialysis. Postpartum bleeding occurred in 13.9% and perinatal mortality was reported in 42.2%.[104]

- The role of low dose aspirin in the prevention of PIH was investigated in a randomized controlled trial by Sehgal and Sood. The control trial consisted of two groups. Group 1 consisted of patient 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.[105]
- Banerjee Basu et al conducted a randomized controlled clinical trial comparing 54 cases of PIH treated with nimodipine with the outcome in 57 patients treated with alpha methyldopa. The fall in blood pressure was faster and the platelet count increased quicker with nimodipine as compared to alpha methyldopa, however, the obstetric outcome was comparable in both groups.[106]
- Considering the low body mass index of Indian women, low dose magnesium sulfate therapy for eclampsia and imminent eclampsia has been tailored to Indian women by some authors.[107] Recently another study has been carried out at tertiary care centre in rural area of India where 50 cases of eclampsia were randomly selected to find out the efficacy of low dose magnesium sulfate regime to control eclamptic convulsions. Protocol for low dose magnesium sulfate was as follows:

  Four grams of loading dose of magnesium sulfate (20% solution) given intravenously over 5 minutes. Subsequently, maintenance dose of 2 g magnesium sulfate (50% solution) given deep intramuscularly in alternate buttock every 4 hours till 24 hours after delivery or last convulsion, whichever was later. If there was a recurrence of convulsion after 30 minutes of initial intravenous loading dose, additional 2 g of 20% magnesium sulfate solution was given intravenously. If convulsions were not controlled after repeating such two additional doses, then the case was shifted to standard Pritchard regimen and was labeled as failure of low dose regimen. It was observed in this study that 86% cases responded to initial intravenous dose of 4 g of 20% magnesium sulfate. Eight per cent cases were controlled by additional 2 g of 20% magnesium sulfate. Six per cent cases required shifting to standard Pritchard regimen, as they did not respond to low dose magnesium sulfate regimen. The average total dose of magnesium sulfate required for control of convulsions was 20 g i.e. 54.4% less than that of standard Pritchard regimen. The maternal and perinatal morbidity and mortality were comparable to those of standard Pritchard regimen with no case of magnesium-related toxicity with low dose magnesium sulfate regimen. Hence, low dose magnesium sulfate regimen was found to be safe and effective in eclampsia.[108]
- 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%, (c) Menon's regime – fit recurrence 52.94% and PNMR 58%. They, therefore, endorsed the phenytoin sodium regime for the management of eclampsia.[109] 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 13.1.[110]

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 haemorrhage, hypertensive disorders in pregnancy, and sepsis are the chief indications for admission for critical care obstetrics practice.[111] Complicated hypertension disorders in pregnancy account for over 20% of these admissions. Intensive care

TABLE 13.1 Comparison of the Obstetrics Outcome in Case of Diazepam and Magsulf Regime

Parameter	Diazepam Regime	Magsulf Regime
Recurrence of fits	16%	2.0%
Ventilator support	8%	2.0%
Maternal mortality rate (MMR)	38%	14.0%
Perinatal mortality rate (PNMR)	30%	15.%
Rate of cesarean births – Lower segment ceasarean section (LSCS)	62%	55.0%

units account for 5% of patients in hospitals and account for 20–28% of total hospital costs.[112]

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 birthweight 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 UA 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.[96]

In an interesting study of abruptio placenta from Kolkata, the authors reported an incidence of 1 in 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%.[113]

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Chapter 14

Haematological Disorders and Red-Cell Alloimmunization in Pregnancy

Ann Koschorke, Michael Egbor and Amarnath Bhide

Chapter Outline

INTRODUCTION

Iron-deficiency anaemia is one of the commonest medical disorders encountered in pregnancy. There is not only a physiological drop of haemoglobin due to haemodilution, but also most women enter pregnancy with depleted iron stores. The prevalence of anaemia in women of the reproductive age is 10–12% in the developed world, but is much higher in the underdeveloped world with quoted prevalence of up to 87.2% in some regions of India. Anaemia is associated with increased maternal and fetal morbidity and mortality.

Increasingly many more women with sickle-cell disease and α-thalassaemia major are becoming pregnant due to better overall medical care and health. Antenatal care in these pregnancies should be by a multidisciplinary team including a haematologist with experience in these pathologies and a clearly documented plan of action should be in place. This is also advisable for women with immune thrombocytopaenia.

The most significant changes to the management of red cell alloimmunization include, widespread use of routine immunoprophylaxis with anti-D for rhesus negative women and the use of non-invasive ultrasound-based techniques for detection of fetal anaemia. Invasive techniques are currently used to confirm significant fetal anaemia and also to treat the anaemia by ultrasound-guided intravascular transfusion.

Successful immunoprophylaxis using anti-D antibodies has resulted in a fall in the frequency of alloimmunization due to the D antigen. Antibodies to c, Kell and other non-D antigens are increasingly responsible for red-cell alloimmunization owing to the lack of available prophylaxis for other blood-group antigens.

PHYSIOLOGICAL CHANGES IN PREGNANCY

During pregnancy, the cardiac output increases by about 40% in order to achieve an increase in uterine blood flow and hence placental perfusion. This is mainly achieved by an increase in the stroke volume. The plasma volume, on the other hand, increases by about 50% throughout pregnancy, but mainly in the first two trimesters. This increase in the plasma volume exceeds that of the red cell mass,

which increases by about 25%, leading to a fall in the haemoglobin concentration and haematocrit as a result of haemodilution.

Mean cell volume (MCV) increases minimally and the mean corpuscular haemoglobin concentration (MCHC) remains unchanged throughout pregnancy. Iron requirements increase two to three folds during pregnancy, therefore serum iron and ferritin concentrations fall as they are required for the haemoglobin synthesis.

The white cell count increases, but lymphocytes and monocytes are unchanged during pregnancy. Platelets tend to fall by up to 15% but usually remain within normal limits. Pregnancy causes a hypercoagulable state due to increase in the levels of factors V, VII, X, XII and von-Willebrand factor. Fibrinogen and factor VIII also increase markedly. There are also changes in the levels of anticoagulants. Both antithrombin III and protein C remain unchanged, protein S decreases by about 40%. There is an acquired protein C resistance, and inhibition of fibrinolysis as a result of decreased levels of plasminogen activator inhibitor.

Summary of physiological changes:

- Haemoglobin and haematocrit ↓
- White cell count ↑
- Platelets ↓
- Fibrinogen ↑
- Factors V, VII VIII , X, XII and vWF ↑↑
- AT III and protein C ⟷
- Protein S and plasminogen activator inhibitor ↓

ANAEMIA IN PREGNANCY

Physiology

Haemodilution in pregnancy was first described by Scott and Prichard (1967) who measured the haemoglobin/haematocrit (H/H) concentrations in a large group of healthy young women with proven normal iron and folate stores. They found an average drop in haematocrit of 5 U for a singleton and 7 U for a twin pregnancy during the second trimester. This is a consequence of the intravascular volume expansion, which starts at 8–10 weeks and reaches a maximum during the second trimester as described above. The lower limit for haemoglobin concentration in non-pregnant women is about 11.5–12g/dL. The British Committee for Standards in Haematology considers anaemia to be present in a pregnant woman when the levels drop less than 110 g/L in the first trimester, less than 105 g/L in the second and third trimesters and less than 100 g/L in the postnatal period or if the haematocrit drops below 30%.[1]

Anaemia is the most common haematological abnormality diagnosed in pregnancy. It is most often diagnosed by iron deficiency and occasionally by more complex conditions involving deficient production or accelerated destruction of erythrocytes.

Clinical Features

Most women are already anaemic at the beginning of pregnancy. They are often asymptomatic and only diagnosed during routine full blood count at booking or at 28 weeks of pregnancy. Most cases present with symptoms in the third trimester when the demand for iron is greatest. They present with non-specific complaints like fatigue, shortness of breath, weakness and dizziness. Clinical signs include tachycardia and pallor of non-pigmented areas of the skin such as the nail beds, palms of the hands, the conjunctiva or the oral mucosa. Blood loss at delivery can aggravate symptoms in an anaemic woman that was asymptomatic before delivery.

The fetus tolerates even advanced degrees of maternal anaemia very well. This is due to the high oxygen affinity of fetal haemoglobin (HbF) and the efficacy of the maternal oxygen transport system, which is capable of delivering adequate amounts of oxygen to the tissues despite low levels of haemoglobin. Nevertheless, impaired psychomotor and/or mental development has been reported in infants born to mothers with iron-deficiency anaemia, it is also known to have a negative impact on social and emotional behaviour.[2,3] It has also been reported that iron deficiency is associated with preterm delivery and a low birth weight, possibly placental abruption and increased peri-partum blood loss.[4] Pregnancy can aggravate pre-existing anaemia, so that even mildly symptomatic women will become markedly anaemic and women with severe anaemia will become symptomatic by the end of the second trimester.

Iron-Deficiency Anaemia

Iron Metabolism

The iron concentration in women is approximately 40 mg/kg, which is the result of a balance between absorption and iron losses. Main sources of iron losses in women are menstruation and parturition. A recent pregnancy, particularly with less than one year between delivery and conception can be another reason for depleted iron stores.[5]

Low iron stores and increased haematopoiesis causes increased intestinal absorption of iron. Most of the body iron is contained in the erythrocytes as haemoglobin 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 enterocytes in the proximal small intestine and may be transported into plasma or stored in intestinal cells. Intestinal cells are lost when they are exfoliated. There is a continuous movement of iron from the intestine to transferrin, to ferritin and finally to the erythrocytes; and from the erythrocytes through the monocyte–macrophage system back to transferrin and ferritin. Ferritin, which is the main iron

storage molecule, is a spherical protein shell that can store as many as 4500 iron atoms. Most ferritin is found in the hepatocytes and macrophages. There are specialized macrophages in the bone marrow, liver and spleen that can recognize and breakdown old erythrocytes, destroy their membranes and liberate their haemoglobin, which is rapidly catabolized to haeme. Haeme is further degraded to biliverdin and the iron is released and incorporated into ferritin or transported back to the plasma.

Iron Requirements During Pregnancy

Approximately 80% of all anaemia in pregnancy results from iron deficiency. This is due to a combination of poor iron content of the average diet and the insufficient iron stores in the majority of women during their reproductive years. The total requirement for a pregnancy for a 55 kg woman is approximately 1000 mg. Considering the daily needs, this means approximately 0.8 mg of iron in the first trimester, between 4 and 5 mg every day in the second trimester and over 6 mg/day in the third trimester.

In the UK, the average iron intake from food for women is 10.5 mg of which approximately only 15% is absorbed. This amount of dietary iron suffices for the daily requirements of a non-pregnant woman, but is not enough for the formation of large iron stores. Physical iron requirements are three times higher in pregnancy. Even with an optimal diet in pregnancy, the amounts of iron being absorbed are less than the iron requirements in later pregnancy and a woman would have to enter pregnancy with iron stores of >300 mg if she is to meet her requirements. This is more than most women possess, especially in developing countries. Even if these levels of iron stores were present pre-pregnancy, they will be completely exhausted after pregnancy. Evidence from controlled studies suggests that the deficit can be met by iron supplementation.

Diagnosis and Laboratory Assessments

In women with iron deficiency, iron stores become depleted to maintain the production of erythrocytes. Once the stores are empty, 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 blood cells by the bone marrow decreases. Therefore iron deficiency can be divided into three stages:

(a) Depletion of iron stores,
(b) Iron-deficient erythropoiesis and
(c) Frank iron-deficiency anaemia.

The status of iron stores can be assessed by measuring the concentration of plasma ferritin. The values reported by different laboratories vary. The normal range is 50–155 μg/L, and any value less than 20 indicates deficient iron stores. Levels less than 12 μg/L indicates complete depletion of iron stores and levels <50 μg/L in early pregnancy is an indication for iron supplementation. Normal ferritin levels usually indicate that iron deficiency is unlikely.

Changes in the red cell indices give a good indication of iron deficiency. Mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) are all reduced. The first change is usually a fall in the MCV. At this point, a blood smear shows abundant, small, well-rounded erythrocytes with pale centres.

Another change that occurs simultaneously with microcytosis and hypochromia is an abnormal red cell distribution width (RDW) of >15%. It is an index of the presence of a heterogeneous red cell population with varying cell diameters.

The serum iron concentration decreases and is usually below 60 μg/dl (normal: 60–175 μg/dl), whilst the serum transferrin level increases with the severity of the iron deficiency, and is usually greater than 360 μg/dl (normal: 200–360 μg/dl). The result of these changes is a decrease in transferrin saturation to less than 25% versus 25–60% in women with sufficient iron stores. A drop in the haemoglobin/haematocrit concentration characterizes the final stage of iron-deficiency anaemia.

Treatment

Dietary advice should be given to pregnant women, mainly to maximize their iron intake and absorption, but dietary changes alone are not sufficient to correct iron-deficiency anaemia. The WHO, the United Nations Children's fund and the International Nutritional Anaemia Consultative Group have issued guidelines that recommend routine supplementation of iron to all pregnant women for at least 6 months. In the UK, routine iron supplementation is not recommended. A full blood count is obtained at booking and repeated at 28 weeks. Routine screening with ferritin levels is also not recommended. However in centres with high-risk populations, it has been shown to be useful. Non-anaemic women who are at high risk of developing anaemia should have their ferritin levels checked early in pregnancy, and should be offered oral supplements if levels are less than 30 μg/l.

One tablet of 100–200 mg of elementary iron should be given per day and is usually sufficient to fulfil the daily need in pregnancy. Depending on the severity of the iron-deficiency anaemia, 300 mg of ferrous sulphate containing 60 mg of elemental iron can be given up to three times daily. This dosage provides 180 mg of elemental iron of which 15–25 mg/day are absorbed. The increase in haemoglobin with oral iron is about 0.8 g/dl per week and this is reflected in a significant elevation of the haemoglobin/haematocrit concentration when repeated 2 weeks after initiation of treatment. Ferrous sulphate is the oral preparation of choice but ferrous gluconate (320 mg tablets with 36 mg elemental iron) and ferrous fumarate (200 mg tablets with 67 mg elemental iron) are other options. A common problem with oral iron therapy is

gastrointestinal intolerance, which is reported by about 10% of women undergoing treatment. Commonly reported symptoms include nausea, vomiting, constipation, abdominal cramps and diarrhoea. A lower dose should be tried and slow release or enteric coated preparations should be avoided as iron is not well absorbed. Another useful method is to give the iron tablets with meals rather than 1 hour before meals on an empty stomach. Vitamin C improves iron absorption from the gastrointestinal tract.

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. Once the haemoglobin has normalized, the supplementation should continue for 3 months or 6 weeks postpartum to replenish the iron stores.

Parenteral iron should be considered from the second trimester onwards for women with confirmed iron-deficiency anaemia who fail to respond to oral treatment or are intolerant of oral intake.[6] Compared to oral therapy it replenishes the iron stores more rapidly especially when using iron sucrose (Venofer and Cosmofer).[7-9]

A small test dose should be given before giving the full dose due to the risk of anaphylaxis. Free iron may result in the production of hydroxyl radicals with potential toxicity to tissues. First trimester of pregnancy, chronic liver disease and active acute or chronic infections are contraindications to the usage of parenteral iron.[10] Although iron sucrose has a good safety profile, it is often given in multiple small dose infusions which last between 4 and 6 hours per infusion. Newer preparations like iron (III) carboxymaltose and iron (III) maltose are fast acting preparations that aim to overcome the problem of repeat transfusions.[11]

The dose of parenteral iron is usually calculated based on pre-pregnancy weight aiming for target haemoglobin of 110 g/L. The choice of the preparation used should be based on local facilities and preferences. Intramuscular iron injections are not recommended because of the unpredictability of serious allergic reactions and dark staining of the skin areas.

Megaloblastic Anaemia

Megaloblastic anaemia is characterized by defective DNA synthesis due to folic acid or Vitamin B_{12} (Cobalamin) deficiency. Both are co-factors in the methionine synthase reaction that provides a methylene group to convert deoxyuridylate to thymidylate, which is a fundamental step in the DNA synthesis. As a result, more cells are in the non-resting state trying to slowly complete the doubling of their DNA. Since RNA and protein synthesis are not affected, these cells (megaloblast) exhibit large non-mature cytoplasm. These nuclear and cytoplasmic changes are the basic elements of megaloblastosis and they affect erythroid as well as the myeloid line, producing hypersegmented neutrophils that are characteristic of megaloblastic degeneration.

The incidence of folate deficiency anaemia depends on the socio-economic status and nutrition of the population. Only 3–4% of women with anaemia during pregnancy have megaloblastic anaemia. In the majority, megaloblastic anaemia is the result of folic acid deficiency and only 1 in 8500 pregnant women with anaemia has vitamin B_{12} deficiency. The reason for this low incidence is the abundance of folic acid and vitamin B_{12} in the normal diet. Folate is present in fruits, green vegetables and meat; vitamin B_{12} is present in meat, fish, poultry and dairy products. Folic acid deficiency may result from inadequate intake, poor absorption, increased utilization and all may occur in pregnancy. Prolonged cooking can destroy folic acid. Anticonvulsant drugs or folate antagonists such as sulfasalazine can interfere with folate absorption. Folate malabsorption may also occur when the intestinal pH is too acidic or if an inhibitor of the enzyme that breaks down folic acid to its absorbable state is present in the diet.

Vitamin B_{12} deficiency results from poor absorption due to autoimmune gastritis and auto- antibodies against the gastric intrinsic factor (pernicious anaemia), 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 anaemia of pregnancy were caused by pernicious anaemia. In the last few years, defects of ileal absorption have risen in frequency as a result of the popularization of surgical gastrointestinal procedures to treat morbid obesity.

There are similarities in morphological effects on red blood cells and white blood cells caused by folate and vitamin B_{12} deficiencies. Anaemia caused by the deficiency of one of them can be corrected by administering the other. However, there are fundamental differences between the deficiency of folate and vitamin B_{12}. Vitamin B_{12} deficiency causes progressive demyelinization but folate deficiency does not. Treatment of vitamin B_{12} anaemia with folate does not arrest the progression of neurological damage. Therefore, differential diagnosis between these two major causes of megaloblastic anaemia is important.

Both deficiencies may mask iron deficiency. Red cell synthesis is inhibited during the vitamin deficiency, available iron is underutilized and increased saturation of transferrin occurs. As soon as the therapy with folate or vitamin B_{12} is initiated, red cell synthesis begins again, use of iron is maximal and iron deficiency becomes apparent.

Diagnosis

Folate deficiency causes a macrocytic anaemia with megaloblastic changes in the bone marrow. The first indication of megaloblastic anaemia in pregnancy is usually an elevated red cell MCV found on routine antenatal blood tests. This

can be a feature of normal pregnancy, alcohol or azathioprine use, and in certain cases of hypothyroidism. The presence of hypersegmented neutrophils suggests that megaloblastic anaemia is present, and the diagnosis is usually confirmed by measuring serum and red cell folate.

Most women will be asymptomatic, but their history may reveal poor dietary intake or alcohol abuse in cases of folic acid deficiency and a family history of pernicious anaemia or history of gastric bypass surgery in cases of vitamin B_{12} deficiency. Vitamin B_{12} levels should be checked to avoid missing the rare case of vitamin B_{12} deficiency. The serum vitamin B_{12} level may be low in folic acid deficiency anaemia and vice versa but a serum level of less than 100 pg/ml of vitamin B_{12} is diagnostic of vitamin B_{12} deficiency. A combination of a serum folate level of 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 folate in tissues and is the test of choice for the diagnosis of folic acid deficiency.

Treatment

All women planning a pregnancy are advised to take prophylactic folic acid preparations. 400 mcg is the recommended daily dose because it reduces the risk of neural tube defects and other fetal anomalies. Women with a history of spina bifida or a fetus affected with neural tube defects are advised to take a higher dose (5 mg/day). The high dose is also advised for women on anticonvulsant drugs or folate antagonists. Treatment of folic acid deficiency requires 1 mg of folic acid/day. The treatment of megaloblastic anaemia due to vitamin B_{12} deficiency is vitamin B_{12} injections. Regimes differ but the most commonly used one is 1000 µg of parenteral cyanocobalamin every week for 6 weeks, followed by 1000 µg intramuscular injections every month. The reticulocyte count should show an appropriate response to therapy in 4–6 days and the hypersegmentation of leucocytes normally disappears after 2 weeks.

Haemolytic Anaemia

Haemolytic anaemia may occur because of erythrocyte defects such as abnormalities of the haemoglobin structure, metabolic disturbances or membrane abnormalities. Almost all erythrocyte defects causing haemolysis are hereditary in nature. Haemolysis may also occur due to the presence of substances in the plasma that attack and destroy the erythrocytes, as is the case in autoimmune haemolytic anaemia. The normal erythrocyte lifespan is 120 days; this is shortened in haemolytic anaemia because of premature destruction of red cells. This may occur intravascularly, as in acquired haemolytic anaemia, or extravascularly as in microangiopathic haemolytic anaemia of pre-eclampsia.

Extravascular haemolysis is the most common type of haemolytic anaemia. The red cells are destroyed in the reticuloendothelial system, liberating haemoglobin which is converted to bilirubin. This often leads to an increase in the by-products of bilirubin metabolism, such as faecal and urinary urobilinogen. Thus, an increase in unconjugated bilirubin, urinary urobilinogen and reticulocytosis are the laboratory hallmarks of extravascular haemolysis. Intravascular haemolysis occurs when damage to the erythrocyte membrane is extensive. Haemoglobin is liberated and parts bind to haptoglobin and are rapidly cleared by the liver. Once the haptoglobin becomes saturated, free haemoglobin appears in the plasma and eventually haemoglobinuria occurs. The free plasma haemoglobin develops to methaemoglobin or methaemalbumin. To compensate for haemolysis, bone marrow erythropoiesis increases markedly and the reticulocyte count increases. Thus, the diagnostic hallmarks of intravascular haemolytic anaemia include a decreased or absent haptoglobin, the presence of free haemoglobin, methaemoglobin and methaemalbumin and reticulocytosis. Abnormalities in red cell morphology are often seen in the blood film.

Intra- and extravascular haemolysis both cause a bone marrow response characterized by a marked erythroid hyperplasia and reticulocytosis. Immature blood cells may be found in the blood. In all cases of accelerated red cell destruction, plasma lactic dehydrogenase (LDH) increases as it is from the red cells.

The most common form of haemolytic anaemia seen during pregnancy is the intravascular microangiopathic haemolysis, which is part of the HELLP syndrome. Less frequently haemolytic anaemia can be associated with defects in haemoglobin structure, particularly sickle-cell disease. Extremely rare during pregnancy are the metabolic abnormalities of the erythrocyte such as glucose-6-phosphatase dehydrogenase deficiency or the antibody-mediated haemolysis, which is characteristic of autoimmune haemolytic anaemia.

Aplastic Anaemia

Aplastic anaemia is a disease in which the bone marrow and the blood stem cells which reside within them are damaged. This causes a deficiency of all three blood cell types: red blood cells (anaemia), white blood cells (leucopoenia) and platelets (thrombocytopaenia).

Aplastic anaemia rarely occurs during pregnancy with less than 50 cases reported in the literature. Causes for aplastic anaemia include ionizing radiation, ingestion of myelo-suppressant agents, toxins, immune disorders, infections and malignant diseases. However, no apparent cause is found in most of the cases. The diagnosis requires a bone marrow biopsy. The disease has a serious prognosis and the maternal mortality is about 30%. Recent advances in the treatment for aplastic anaemia using bone marrow transplantation, anti-thymocyte globulin, cyclosporine and high-dose corticosteroids may improve the maternal outcome.

HAEMOGLOBINOPATHIES

Adult haemoglobin (HbAA) is composed of two alpha and two beta chains (α2β2). Most of the haemoglobinopathies of obstetrical interest are the result of abnormalities in the quality or the synthesis of haemoglobin.

Sickle Cell Disease

Sickle cell disease (SCD) is the most important haemoglobinopathy encountered during pregnancy because of the severity of the complications associated with this condition. It has a high prevalence in Afro-Caribbean populations, also people from the Middle East, parts of India and the Mediterranean region. But it has become a disease of global importance with an increasing number of affected individuals in Europe and the US.

SCD includes a group of single gene autosomal recessive disorders caused by the 'sickle' gene which affects the haemoglobin structure. A substitution of valine for glutamine in position 6 in the beta-globin chains of the haemoglobin molecule results in the production of the sickle cell haemoglobin (HbSS) also called *sickle cell anaemia.* The term SCD also includes the heterozygous conditions of haemoglobin S (HbSC), combination with beta-thalassaemia (HbSB thalassaemia) and the combination with haemoglobin D, E or O-Arab.

SCD is the most common inherited condition worldwide. In the UK, it is estimated that 12,000-15,000 individuals are affected and over 300 children with SCD are born each year that are diagnosed as part of the neonatal screening programme. There are about 100–200 pregnancies in women with SCD each year in the UK.[12]

The underlying defect in SCD is the decreased solubility of the sickle cell haemoglobin. When HbSS is oxygenated its solubility is similar to normal haemoglobin, but in the deoxygenated form, its solubility decreases, leading to polymerization and formation of rigid and fragile sickle-shaped cells. Reduced oxygen environments can be caused by hypoxia, cold, acidosis and dehydration. These sickle cells are prone to breakdown which causes haemolytic anaemia and often vaso-occlusion in the small blood vessels. This causes most of the other clinical features, including acute painful crises.

Other complications often reported include, retinopathy, leg ulcers, cholelithiasis, stroke, pulmonary hypertension, renal papillary necrosis leading to renal dysfunction, avascular necrosis, which commonly affects the femoral head and leads to hip replacement, splenic sequestration and acute chest syndrome. The latter presents with fever, tachypnoea, pleuritic chest pain, worsening anaemia and chest infiltrates and is the leading cause of maternal mortality.

Acute chest syndrome frequently complicates a vaso-occlusive crisis and multilobar involvement is common. Causes include infection, infarction and fat embolization, which have a particularly poor prognosis. Acute sickling crises occur in about 37% of pregnant women before delivery and 12% in the postnatal period.

Maternal mortality in SCD has decreased dramatically in the last 40 years. Rates as high as 11.5% reported in 1972 (by Hendrickse and coworkers)[13] have dropped to between 2.1% and less than 1% in recent years (reported by Smith et al. and Sergeant et al.)[14,15] with advances in medical and neonatal care and transfusion medicine, the perinatal mortality has also significantly decreased. There is still four-to-six fold increase compared to normal pregnancies. There is also an increased risk of miscarriage, IUGR, preterm labour, venous thromboembolism, pre-eclampsia, placental abruption and fetal distress in labour with possible causes being sickling events in the placenta, increased blood viscosity and anaemia.[16]

Management

Prior to pregnancy women should be checked for hepatitis B and C, HIV and rubella, and vaccinations should be offered where necessary. The woman should be up-to-date with pneumococcal and hepatitis B vaccinations. Assessment of cardiac function (ECG and echocardiogram), retinal screening and renal function should be checked before embarking on a pregnancy.

Pregnant women with SCD are best managed in combined clinics consisting of obstetricians and haematologists experienced in the management of SCD. There should be a clear plan of care and effective communication between all those involved. Previous medications should be reviewed and stopped if necessary. Women should be reminded of measures to reduce sickle-cell crises, such as keeping warm and hydrated. The women should be given clear information regarding when and where to seek help in an emergency, antenatally and during the postnatal period.

All women should be given high-dose folic acid (5 mg) and penicillin prophylaxis (penicillin V 250 mg twice daily). In the UK, genetic counselling and partner screening is provided as part of the antenatal haemoglobinopathy screening programme which was introduced in 2001. If the partner carries a significant haemoglobinopathy, genetic counselling is required, this should ideally happen prior to pregnancy.

During every antenatal visit, the haemoglobin, haematocrit, platelet count, bilirubin, transaminase and lactose dehydrogenase levels should be checked. This is usually done fortnightly as are blood pressure checks, urine dips to check for protein, infection or haematuria. Regular ultrasound scans are required for assessments of fetal growth and closer monitoring if growth restriction is present.

Although the role of blood transfusion in pregnant women with sickle cell disease remains controversial, it is accepted that transfusions may be necessary for severe anaemia.[17] These women often need postnatal thromboprophylaxis for up to 6 weeks.

A sickle crisis is a serious condition and requires aggressive management with admission to hospital, rehydration, thromboprophylaxis, antibiotic use if an infection is suspected and analgesia, which may involve intravenous or subcutaneous infusions of morphine. It is paramount that the patient is kept well hydrated, oxygenated and warm.

In some circumstances, transfusions may be indicated, such as frequent severe sickling episodes, a low haematocrit below the patient's normal steady level, twin pregnancy or a poor past obstetric history. The target is HbS levels of less than 20% because this is the level at which the potential for oxygen delivery approaches normal. Quite often multiple transfusions are required to achieve this target or a large volume exchange transfusion may be necessary. The donor erythrocytes temporarily suppress the new production of HbS-containing erythrocytes and dilute their concentration which reduces the risk of sickling and vascular obstruction. Multiple blood transfusions are associated with many problems including the risk of transmission of infections, formation of atypical antibodies and the deposition of excess iron in vulnerable tissues.

Sickle Cell Trait

Patients with sickle cell trait are heterozygous for the SCD gene mutation and have only one beta chain affected. They are not at great risk for abnormal reproductive performance. One important problem is the possibility of transmission of the abnormal gene to their offspring. In pregnancy, there is an increased risk of urinary tract infections, venous thromboembolism and pre-eclampsia. Women with sickle cell trait should have pre-conception counselling and the male partner should be tested. If he is a carrier there is a 25% chance of the child being affected and have SCD. In this situation, prenatal genetic diagnosis is important as it will allow the option of pregnancy termination. Another alternative for these couples is the possibility of preimplantation genetic diagnosis using one or two cells obtained by blastomere biopsy.[18]

Thalassaemias

Haemoglobin A, which is the adult form, consists of two alpha subunits and two beta subunits ($\alpha 2\beta 2$). Haemoglobin A2, with two alpha and two delta ($\alpha 2\delta 2$), accounts for less than 3.5% of all adult haemoglobin. The thalassaemias are classified according to the chain of the globin molecule that is affected with defective formation. The two major types are alpha-thalassaemia and beta-thalassaemia.

Alpha Thalassaemia and Alpha Thalassaemia Trait

The alpha globin chain synthesis is determined by two genetic loci of each chromosome 16, and there are four alleles in total. In alpha-thalassaemia, the most common defect is deletion of the genes, and gene mutation is less common. The pattern of abnormalities is related to ethnicity. The greater the number of affected alleles, the more severe the clinical manifestations of the disease. When only one of the four allele is affected (–/α, α/α), three normal alpha-globin alleles are adequate for normal haemoglobin production. Clinical symptoms are not present and RBC indices can be normal. When two alleles are affected, erythropoiesis is can still be maintained with two alpha alleles, although mild microcytic hypochromic anaemia may be present (α -thalassaemia trait). The abnormal/deleted genes may be on the same chromosome (–/–, α/α, $Alpha^0$ thal or alpha-thal-1) or on two homologous chromosomes (–/α, –/α, $Alpha^+$ thal or alpha-thal-2). The former is more common in Asian or Mediterranean population, and the latter more common amongst Africans).

When three alleles are affected (–/α, –/–), the production of alpha globin chain is significantly impaired because only one a normal alpha gene is functional. Beta chains are relatively in excess, and form an unstable tetramer called haemoglobin H (β4). Affected individuals have mild-to-moderate microcytic hypochromic anaemia. They can have normal life expectancy, although top-up blood transfusions may sometimes be required. No synthesis of alpha globin chain is possible when all four alleles are affected (–/–, –/–), and the excessive gamma chains form the unstable and ineffective haemoglobin bart (γ4) in the fetus. The affected fetuses present with features of profound anaemia with cardiomegaly and hydrops. This condition is not compatible with life.

Beta Thalassaemia Trait and Beta Thalassaemia Major

Two genetic loci for beta globin chain synthesis exist, one on each chromosome no. 11. Mutations of the beta globin genes result in either complete absence of (β0) or impaired production of (β+) beta chains. In either case, there is a relative excess of alpha chains. Excess alpha chains bind to the red-blood-cell membranes and cause membrane damage. The disease can be classified clinically into minor (carrier), intermedia and major sub-types, depending on the degree of reduction in beta-globin chain synthesis.

Beta thalassaemia trait (minor) – If only one beta globin allele carries a mutation (e.g., β0/β or β+/β), the affected individual is clinically asymptomatic. Mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV) are low, and the proportion of haemoglobin A2 is increased (3.5% or greater).

Beta thalassaemia major – If both beta globin alleles bear a mutation (e.g., β^0/β^+ or β^0/β^0), betal globin chain synthesis is severely restricted. Hypochromic microcystic anaemia results, starting from few months after birth and will require life-long transfusions. The fetus is unaffected

though, because fetal haemoglobin ($\alpha 2\gamma 2$) has no beta chains.

Beta thalassaemia intermedia – Mutations can sometimes occur in one or both alleles causing moderate impairment of beta chains production (e.g., $\beta+/\beta+$). The woman's clinical condition is intermediate between the major and minor forms. The woman can enjoy normal life, although blood transfusions may occasionally be required.

Diagnosis

A low mean cell volume (MCV), mean cell haemoglobin (MCH) and a normal mean cell haemoglobin concentration (MCHC) often in the absence of anaemia are suggestive of alpha or beta thalassaemia trait. The concentrations of HBA_2 and HBF are raised. However, the definitive diagnosis is made by globin chain synthesis studies and DNA analysis. The pattern of inheritance in both conditions is autosomal recessive and prenatal diagnosis by chorionic villus sampling and amniocentesis is possible and should be advised. Preimplantation testing is also possible in couples undergoing in-vitro fertilization (IVF).

Management

Women with β- and α-thalassaemia trait should be given oral iron and folate supplements, but parenteral iron should be avoided. Intramuscular folate can be given if the anaemia does not respond to oral iron and folate; blood transfusion may be required prior to delivery.

Most of the available research on the effect of thalassaemia syndromes on pregnancy outcome is confined to β-thalassaemia major and intermedia. In the UK about 800 adults of the reproductive age have α-thalassaemia major with 20–30 babies born per year with the condition.[19]

Women with α-thalassaemia trait are usually asymptomatic in pregnancy, but women with β-thalassaemia trait might become anaemic during pregnancy. A main clinical concern in β-thalassaemia major patients is iron overload, due to repeated transfusions. This can lead to organ damage caused by haemosiderosis, which results from the deposit of the excess iron from the breakdown of donor erythrocytes. Affected organs are the heart, thyroid, pituitary, liver and the islet cells of the pancreas. Myocardial haemosiderosis can cause cardiac dysfunction with ventricular pump failure and arrhythmias. The liver can be damaged by haemosiderosis leading to hepatic dysfunction and diabetes and hypothyroidism can be results of haemosiderin deposits in the thyroid and pancreas. Expansion of the bone marrow, especially in those who are not regularly transfused can cause bone deformities. Pregnancy is very rare in women with β-thalassaemia major but is more likely in those with less iron overload.

In the rare event of a pregnancy in a woman with β-thalassaemia major, iron chelation therapy should be stopped and folate supplementation given. As a number of patients with β-thalassaemia major will have undergone splenectomy, a prophylactic dose of penicillin should be maintained during pregnancy. Pneumococcal vaccination and boosters are advised prior to pregnancy. It is also important to check the endocrine and cardiac status, preferably prior to pregnancy. The aim during pregnancy is to avoid fluctuations in the haemoglobin concentration and the cardiac workload and this means to maintain the haemoglobin level above 10 g/dL. Hence transfusions are likely to be required at a 3-weekly interval. There is an increased incidence of venous thromboembolism however routine prophylaxis with heparin is not advised during pregnancy, but usually given for up to 6 weeks in the postnatal period. In absence of diabetes and growth restriction, plans for delivery should be made as for women without thalassaemia. Breastfeeding is not contraindicated and iron chelation therapy should be resumed as soon as possible after delivery.

Modern haematological care for such children is changing and now includes bone-marrow transplantation, better tolerated regimens of iron chelation therapy, which would reduce the possibility of organ damage from haemosiderosis.

PLATELET DISORDERS

Thrombocythaemia

Essential thrombocythaemia causes an isolated increase in platelets count and is rarely encountered in pregnant women. It is a myeloproliferative disorder and some patients carry a mutation. The high platelet count can cause a transient occlusion of the microcirculation and arterial or venous thromboses with mainly involvement of the cerebrovascular, coronary and peripheral circulations. It can also be associated with haemorrhagic manifestations. Diagnosis is based on a high platelet count and thrombocytosis on a blood film. Thrombocythaemia can also be caused by infection or as a response to surgery.

Adverse effects on pregnancy is mainly a very high miscarriage rate of up to 43%, an increased rate of intrauterine death, premature delivery (8%), fetal growth restriction (4%) and pre-eclampsia (4%), possibly due to placental infarction due to thrombosis.[20]

During pregnancy, the platelet count may stabilize and become normal without any interventions. With platelet counts $>600{,}000/mm^3$ low dose aspirin should be given. Interferon-α can safely be used in pregnancy and is commonly used for myelosuppression. Low-molecular weight heparin is used when there is a history of previous thrombosis.

Thrombocytopaenia

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 it is between 100,000 and 50,000/mm^3 and severe when it is less than 50,000/mm^3.

Gestational thrombocytopaenia, a benign common disorder, is the numeric platelet deficiency most commonly seen in obstetrics. Second in frequency is the thrombocytopaenia characteristic of HELLP syndrome. The third type of thrombocytopaenia, which is rarely seen in pregnancy, is immune thrombocytopenic purpura (ITP). Also relatively uncommon are platelet disorders, secondary to dense granules deficiency. Other causes of thrombocytopaenia include platelet clumping in the sample, pre-eclampsia, disseminated intravascular coagulation, sepsis, haemolytic uraemic syndrome, HIV and infections, drugs, bone marrow suppression, antiphospholipid syndrome and systemic lupus erythematosus.

Gestational Thrombocytopaenia

Gestational thrombocytopaenia is the correct diagnosis in 80% of all the cases of thrombocytopaenia in pregnancy. The cause of gestational thrombocytopaenia is unknown. It appears in about 8% of pregnancies. The platelet count falls progressively during pregnancy and 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 baby. The main problem associated with gestational thrombocytopaenia is the reluctance of anaesthetists to give epidural or spinal anaesthesia if the platelet count is $<$80,000/mm^3. Treatment with immunoglobulin, steroids or platelet transfusion is sometimes necessary to raise the platelet count to a level acceptable to the anaesthetist.

Immune Thrombocytopaenia

Chronic immune thrombocytopaenia (ITP) usually affects young women and has an incidence of 1–2 in 10,000 pregnancies. It is characterized by an autoantibody-mediated destruction of maternal platelets. The patients are usually asymptomatic but may complain of easy bruising and bleeding and frequently have petechiae, however severe haemorrhage is rare.

Thrombocytopaenia in the first half of pregnancy is suggestive of the possibility of ITP as a diagnosis. The diagnosis of ITP is based on exclusion and should only be made if other causes have been excluded. Laboratory evaluation reveals thrombocytopaenia, enlarged platelets with otherwise normal erythrocyte and leucocytes counts. Confirmation of the presence of elevated direct or indirect platelet associated IgG antibodies in the plasma is not always possible; also the absence of antibodies does not exclude ITP.

When ITP appears during pregnancy, both the mother and the fetus can be affected as antiplatelet IgG can cross the placenta and cause fetal thrombocytopaenia. It is difficult to predict which fetus will be affected. Five to ten per cent of the newborns will have platelets of less than 50,000/mm^3. The incidence of neonatal intracranial haemorrhage is small, with less than 1.5% and it cannot be prevented by caesarean section. The best predictor of severe neonatal thrombocytopaenia is a previously affected child.

In pregnant women with ITP, the platelet count should be monitored on a monthly basis and then fortnightly in the last trimester when thrombocytopaenia often gets worse. Treatment is only required in the first and third trimester if the woman is bleeding, the platelet count is less than 20,000/mm^3 or the count needs to be increased prior to a procedure such as amniocentesis. First-line therapy is corticosteroids and it is common to use low doses of prednisolone (20–30 mg/day) in pregnancy which is safe and effective.[4] The dose can be weaned to the lowest dose maintaining a satisfactory platelet level ($>$50,000). Intravenous immunoglobulins may be used in women requiring prolonged therapy or who are resistant to steroid therapy or require a high maintenance dose. The response is rapid and in most cases a single dose will raise levels to over 50,000/mm^3, but it is expensive and the effect lasts for only 1–3 weeks.

Other treatment options for women not responding to oral prednisolone and IgG are intravenous methylprednisolone, azathioprine or cyclosporine. Platelet transfusions are given as last resort for bleeding or prior to surgery. Women with ITP and platelet counts over 50,000/mm^3 must be managed conservatively during labour and delivery and a caesarean section is performed only for obstetrical indications. However invasive procedures such as fetal blood sampling and traumatic delivery should be avoided. Cord platelet counts is determined after delivery and the newborn of a mother with ITP will require frequent measurements of platelet counts because they will drop after delivery, reaching a nadir on day 2, when splenic circulation is established. Most haemorrhagic events in the newborn occur within the first 24–48 hours of life and IgG is the recommended treatment.

BLEEDING DISORDERS

Congenital bleeding disorders are rare in pregnancy. The most commonly seen inherited coagulopathy seen in women of reproductive age is von Willebrand disease (vWD) with an incidence of approximately 1%.

von Willebrand Disease

The von Willebrand factor (vWF) is a high-molecular-weight glycoprotein produced by endothelial cells, which is a major component of the factor VIII complex. A quantitative and qualitative deficiency of vWF results in vWD. VWF is necessary for the binding of glycoproteins to the subendothelial matrix at sites of vascular injury, the first

step of formation of a clot. The vWF is also a carrier protein for factor VIII and prolongs its half-life in the circulation.

There are three types of vWD:

- **Type 1**: It is the most common and affects about 75% of all patients with this condition. Its inheritance is autosomal dominant and the mutation causes the synthesis of an abnormal protein that forms dimmers that are trapped in the endoplasmic reticulum and cannot be secreted into 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.
- **Type 2**: It is characterized by functional abnormalities of the vWF.
- **Type 3**: It is very rare. Bleeding in these cases can be severe and factor VIII levels are markedly decreased.

The bleeding time is prolonged. This test has wide variability and has been replaced by the automated platelet function-100 assay (PFA-100). It measures platelet function which will be reduced in vWD. Activated partial thromboplastin time (APTT) may be prolonged and vWF and factor VIII may be reduced. The functional test (ristocetin cofactor activity) measures the percentage of normal vWF antigen present in plasma. More specialized tests are used to sub classify the type of vWD.

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 factor VIII and vWF should be measured to confirm the diagnosis.

The course of pregnancy in the majority of patients with vWD is benign. The most frequent complication is bleeding during labour, delivery or postpartum period. In general, vWF rises to 50% of the normal concentration by the third trimester (a three to four fold increase of vWF and factor VIII due to pregnancy) and the probability of bleeding is small with no need for therapy. But the levels fall rapidly in the postpartum period and there is an increased risk of primary and secondary postpartum haemorrhage, but severe problems are largely preventable.

Women with vWD should be managed jointly with haematologist with specialist interest in bleeding disorders. It is important to ascertain the subtype of vWD and whether they respond to desmopressin (DDAVP) or not. Desmopressin is the drug of choice for postpartum bleeding in women with Type 1 vWD. It is a vasopressin analogue which has been successfully used in vWD to promote the release of vWF. In some cases, DDAVP can be given prior to delivery, epidural or procedures to increase the levels of factor VIII and vWF. The effect normally lasts for 4–6 hours and is not recommended in the antepartum period as it can stimulate uterine contractions. Patients with resistance to DDAVP or those who have type 2 and 3 require therapy with FFP or plasma-derived factor concentrates containing vWF and factor VIII.

Haemophilia A and B

Factor VIII deficiency (haemophilia A) and factor IX deficiency (haemophilia B) are rare X-linked recessive disorders. Hence only male fetuses are affected. The sex of the fetus can be diagnosed with prenatal screening either by ultrasound diagnosis or from free fetal DNA in maternal blood, and CVS or amniocentesis can confirm an affected male fetus.

Haemophilia A accounts for 80–85% of haemophilia cases and affects 1:5000 live male births.

Factor VIII and IX levels should be checked at booking and again before delivery. Management of these cases should be by a team with relevant expertise; therefore, close liaison with the haemophilia centre is essential. Some female carriers may be symptomatic and may need DDVAP of factor VIII concentrates for haemophilia A and tranexamic acid or factor IX concentrate for haemophilia B. Caesarean section is indicated only for usual obstetric reasons, and its always best to avoid invasive procedures and traumatic deliveries, if required, forceps delivery is preferable to ventouse delivery.

RED CELL ALLOIMMUNIZATION

Introduction

Before the discovery of the Rh system by Landsteiner in 1940, little was known about the aetiology of erythroblastosis fetalis, a condition in which the fetus becomes oedematous and often dies in the uterus from severe anaemia and high output cardiac failure. After this discovery it was quickly known 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 way of measuring the severity of the fetal anaemia and by the realization that early delivery and intrauterine infusions (IUTs) could be lifesaving measures for the compromised fetus. Finally, it was discovered that the administration of D-immunoglobulin to mothers at risk is an extremely effectiv e way of preventing the initial immune response causing Rh alloimmunization. Advances in molecular biology have led to the successful determination of fetal blood group using free fetal DNA from maternal blood. A non-invasive method to detect fetal anaemia, the ultrasound-based measurement of the peak systolic velocity of the mid-cerebral artery has superseded the spectrophotometric analysis of amniotic

fluid. Despite these advances, the incidence of Rh alloimmunization remains constant at about six cases per 1000 births,[21] the 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 haemolyzed by maternal alloantibodies that have crossed the placenta. The resulting anaemia leads to fetal heart failure, massive oedema (hydrops fetalis) and intrauterine death. It may also cause varied degrees of neonatal hyperbilirubinaemia (haemolytic disease of the newborn). Approximately 97% of all cases of erythroblastosis fetalis are caused by maternal antibodies directed against the RhD antigen present in fetal red cells. The remaining cases are caused by immunization against other fetal antigenic groups such as C, c, E, e (Rh system, non D), K, k (Kell), Fya (Duffy), M (MNS) and Jka (Kidd).[22]

Maternal alloimmunization may also be the result of the transfusion of Rh-positive blood to a Rh-negative female. In response to this immunological stimulation, the mother develops antibodies, the latter being able to destroy the fetal red cells.

During normal pregnancy, fetal red cells cross the placenta in 5% of cases in the first trimester and 46% of cases by the end of the third trimester. However, in the majority of cases Rhesus sensitization is the consequence of feto-maternal bleeding taking place at the time of delivery. Passage of fetal blood into the maternal circulation at the time of parturition is almost universal, but only 10–15% of Rh negative mothers who have Rh positive fetuses get sensitized at delivery.[23] This happens because in most cases, the amount of fetal blood cells transferred to the mother is small and insufficient to produce a primary immune response. Other factors influencing the probability of primary alloimmunization are:

- **Size of the inoculum**: The greater the amount of fetal blood 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 blood cells;
- **Coexistence of ABO incompatibility between mother and fetus**: If the mother is group O and the father A,B or AB, the frequency of sensitisation is decreased by 50–75% because maternal anti-A or anti-B antibodies destroy 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 a Rh negative mother with a Rh positive fetus, the initial maternal response is the development of anti-Rhesus antibodies of IgM class, with a molecular weight too large to cross the placenta. This is followed by the synthesis of IgG antibodies that cross the placenta and adhere to fetal red cells accelerating their destruction. Timing between the bleed and the initiation of the mother's primary immune response is not exactly known and has some biological variation. Usually there is an interval of several weeks between the bleed and the appearance of anti-Rh antibodies in the maternal serum. This explains why the prophylactic administration of D-immunoglobulin to the mother shortly after delivery or eventual sensitizing events in pregnancy inhibits the immune response. Anti D-immunoglobulin should be given within the first 72 hours of delivery/sensitizing event but it can be protective if given up to 10 days after the event.

Depending on the severity of haemolysis of the fetal red cells after being exposed to anti-Rh antibodies from the mother, the clinical picture may include congestive heart failure, hepatomegaly, splenomegaly, peripheral oedema and placental hypertrophy. The marked hepatomegaly and splenomegaly present in hydropic stillborns results not only to the development of large foci of compensatory extramedullary haematopoiesis, but also to 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 in the brain) and jaundice are not components of fetal erythroblastosis during intrauterine life because accumulation of the pigment is prevented by the removal via the placental circulation and metabolism by the maternal liver. After birth, however, the newborn cannot effectively handle the large amount of pigments released due to the brisk haemolytic process and this leads to a rapid increase in serum bilirubin and eventual tissue deposition.

Genetics

The Rhesus factor is the largest and clinically the most important protein-based blood group system. So far, over 49 antigens have been described. This large number of Rhesus antigens is due to its complex genetic basis. The antigens are located on two Rhesus proteins, RhD and RhCE and are characterized by differences in their protein sequences. Both genes are in close proximity on the short arm of chromosome number 1.[24] 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 complete deletion of the RHD gene. Rh-positive individuals may have one copy (heterozygous) or two copies (homozygous) of the RHD gene. This means that if a Rh-positive homozygous father (DD) is mated with a Rh-negative mother, he will necessarily pass on the D gene to his offspring and, as a result, the offspring will be Rh-positive in 100% of the cases. If the father is heterozygous (D), the chances of the child receiving the 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 are rare. The C and E antigens usually cause immunization via blood transfusion, rather than as a consequence of a feto-maternal bleed. Other blood groups systems different from the Rh have antigens with potential to cause fetal haemolytic disease. The most common are the K (Kell), Fya (Duffy) and Jka (Kidd). Another antigen frequently found in antenatal testing is the Lewis group (Le-a and Le-b). The Lewis antigens do not cause fetal haemolytic disease and differ from all other red cell antigens in that they are not synthesized by the red cell membrane but are absorbed onto it. Other rare antigenic groups may also cause mild-to-severe erythroblastosis fetalis. 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 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. Some individuals of African and Asian ancestry have parts of non-functioning Rh genes that produce false positive Rh determinations with the polymerase chain reaction technology (PCR).

Diagnosis

Rhesus typing and an antibody screen should be performed at the first prenatal visit. The presence of D antibodies in the maternal serum is diagnostic of maternal Rh alloimmunization. The test most commonly used for diagnostic purposes is the indirect Coombs test. It determines antibodies in the maternal plasma and is the most accurate technique for determining antibodies. Maternal plasma is incubated with Rh-positive erythrocytes. Any anti-D antibody will adhere to the red blood cells. Those are then washed and suspended in Coombs serum. Red cells coated with maternal anti-D will be agglutinated by the antihuman Coombs globulin, which is referred to as a positive Coombs test.

The concentration of anti-D antibodies will be determined by a titration procedure in which double dilutions of maternal serum will progressively be incubated with group O Rh positive erythrocytes and the agglutination of the erythrocytes will be used as the end point of the reaction. For example, a titre of 32 indicates that the tube with the greatest dilution where agglutination was detected had a dilution of 1:32. As there are variations between the different laboratories, the obstetrician managing an immunized pregnancy should use the same laboratory for all antibody titre determinations of a given patient. For most laboratories, the critical anti-D value is between 8 and 32.

The gel micro column assay (GMa) card is a promising alternative to traditional tube agglutination tests for determining anti-D antibody titres. The main advantage is that it is less susceptible to inter and intra-laboratory sources of variability, furthermore, it yields clear objective results and takes less time and it is compatible with automation. However it may produce higher titres compared to tube tests and more data is needed to establish the correlation between GMA titre and the severity of fetal anaemia before this assay can be used to manage alloimmunization in pregnancy. The use of automated enzymatic methods for Rhesus antibody screening is not recommended as these techniques are less accurate.[25]

Management

Rh-negative women presenting for obstetrical care can be categorized in two different groups: (a) Rh-negative non-immunized women and (b) Rh-negative immunized women. The last group can be divided into two further subgroups: Rh-negative immunized women and Rh-positive women immunized against non-D Rhesus antigens or against other blood group systems. These two sets of patients are managed differently. In Rh-negative non-immunized women, the primary aim of care is the prevention of alloimmunization. In already immunized women, it is the early detection and adequate treatment of fetal anaemia.

All women should have their ABO blood group and rhesus types determined at their booking appointment in the first trimester, along with screening for atypical antibodies using the direct Coombs test. This should be repeated at 28 weeks.

Management of Rh-Negative Non-immunized Women

Rh-negative non-immunized women do not have detectable alloantibodies in the initial prenatal evaluation. Paternal Rhesus typing is not routinely offered in the UK. The complexities of paternal testing and the potential for misidentification of the father need to be acknowledged. If the father is known to be Rh-negative the baby will be Rh negative, the possibility of alloimmunization does not exist and the pregnancy should be managed like any other pregnancy without further testing or treatment related to the Rh factor. If the father is Rh-positive there is a 50% or 100% (father

heterozygous/father homozygous) chance that the fetus will inherit one copy of the RhD gene and therefore Rh alloimmunization may occur during pregnancy. 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 alloimmunization may occur before delivery is small (about 1%). To identify the few Rh-negative women who will develop antepartum sensitization antibody screening should be repeated at 28 weeks. 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 any evidence of alloimmunization, the patient should receive anti-D a t 28 weeks gestation and further antibody screenings will be unnecessary. Also the time of delivery will determine the mother's eligibility for a second dose of anti-D immune globulin.

The need for 4 weekly antibody screening in non-immunized 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 haemolytic disease.

Prevention of Rhesus Alloimmunization

Antenatal and Postnatal Prophylaxis

In 1969, a post-delivery immune-prophylaxis programme with anti-D immunoglobulin was introduced in the UK and led to a significant reduction in the frequency of maternal Rh alloimmunization and associated fetal and neonatal complications. However RhD alloimmunization still occurred and the antenatal anti-D prophylaxis (RAADP) was introduced in the UK in the 1990s, which led to an even bigger reduction of the incidence of alloimmunization from 18–20/1000 to 2/1000 patients compared to before the programmes were introduced. Alloimmunization still occurs especially in countries where prophylaxis is not easily available.

Late immunization during the third trimester of a first pregnancy is responsible for 18–27% of the cases. In a significant proportion (55–80%), there is no recognized sensitizing event, thus the sensitization is called 'silent'. Less than 10% of the cases occur before 28 weeks, the rationale of the prophylaxis programme is to protect against these unpredictable events.

Standard UK practice based on the recommendations of the National Institute for Health and Clinical Excellence routinely offers routine anti-D prophylaxis to all unsensitized Rh negative in the third trimester of pregnancy (28 and 34 weeks). The blood test for screening for other atypical antibodies at 28 week should be taken before the administration of anti-D globulin. There are three recommended regimes and there is no evidence to prove that anyone of these regimes is better than the other:

- Two doses of 500 IU of anti-D immune globulin at 28 and 34 weeks.
- A single dose of 1500IU at 28 weeks.
- Two doses of 1000-1650 IU at 28 and 34 weeks.

After the administration of anti-D immune globulin, the antibody screening will detect anti-D antibodies in the patient's serum, but the titre should not be greater than 4 at term. An anti-D titre greater than 4 at term most probably results from alloimmunization rather than from anti-D immunoglobulin administration. Anti-D prophylaxis for unsensitized women who are rhesus-D negative is also recommended after potentially sensitizing events presented in the Table 14.1.

The most common occasion for fetal red cells to enter the maternal circulation is at the time of birth. See the intrapartum events in Table 14.1 for events that can increase the risk of sensitization. It has been reported that without administration of anti-D immune globulin, a Rh negative woman has a 7.2% risk of developing rhesus antibodies within 6 months of giving birth. Routine postnatal prophylaxis should be given within 72 hours after birth as it has its maximal protective effect then. However there is evidence that administration of anti-D immune globulin several days to weeks after delivery still had a protective effect, although the efficiency of the protection is reduced.

In the UK, a Kleihauer test is performed from maternal blood within 2 hours of delivery to identify RhD negative women with a large feto-maternal haemorrhage who require additional anti-D immunoglobulin. Cord blood should be collected to identify the fetal blood group and anti-D

TABLE 14.1 Potential Sensitising Events

Antepartum	Intrapartum	Postpartum
Miscarriages/ERPC Ectopic pregnancy Obstetric procedures • Amniocentesis • Chorionic villus sampling • External cephalic version • Fetal blood sampling • In-utero blood transfusion Abdominal trauma Feto-maternal haemorrhage	Forceps deliveries Caesarean sections Still births Multiple pregnancies Hydrops fetalis Placental abruption Manual removal of placenta	Blood transfusion

should be administered as early as possible within 72 hours if the baby is Rhesus positive. It is not needed if the baby is Rhesus negative.

The routine dose of anti-D immunoglobulin for postnatal prophylaxis is 300 mcg, which is equivalent to 1500 IU of anti-D and is often enough to suppress 15 ml of Rhesus positive fetal blood cells (= 30 ml of fetal blood). Some European countries, with the exception of the UK, France and Ireland use a standard postnatal dose of 1000–1500 IU without performing a routine Kleihauer test. This policy does not take into account the fact that up to 0.3% of women have a feto-maternal haemorrhage (FMH) greater than 15 ml, which will not be covered by the given dose. This means that in the UK about 200 women would not receive the correct amount of anti-D immune globulin.

The Kleihauer–Bethke test is based on the fact that an acid solution elutes adult but not fetal haemoglobin from the red cells. It can detect as little as 0.2 ml of fetal blood diluted in 5 ml of maternal blood. It has a high false positive rate though. An alternative to quantify the size of FMH is flow cytometry. It has the advantage that the results are more accurate than those from the Kleihauer test. This is helpful in women with high levels of fetal haemoglobin and flow cytometry is most effectively employed in these cases where the Kleihauer implies a large FMH which requires accurate quantification. Another alternative is the rosetting technique for quantifying FMHs of over 4 ml.[26]

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. Maternal antibody titres are most useful in the first sensitised pregnancy.

Paternal Rh Phenotype and Genotype

When a clinically significant antibody capable of causing haemolytic disease of the fetus and newborn (HDFN), particularly anti-D, anti-c and anti-K, is present in a maternal sample, determination of the Rhesus phenotype of the baby's father is important as it provides useful information to predict the likelihood of a fetus carrying the relevant red cell antigen. A fetus can only be affected by maternal alloantibodies if its red cells express the antigen. If the father is Rh-negative, the fetus will be Rh-negative too and is therefore not at risk. If the father is homozygous the baby has a 100% chance of being Rh-positive and if he is heterozygous the chances are 50%. DNA testing has become available and techniques such as multiplex quantitative polymerase chain reaction (PCR) can reliably determine paternal zygosity.

Fetal Blood Group

If the father is heterozygous for the antigen in question, it becomes important to determine the fetal antigen status as soon as possible. This used to be done by invasive procedures, such as chorionic villous sampling (CVS), amniocentesis or fetal blood sampling. CVS had the advantage that it could be done early in pregnancy but it had the potential disadvantage of increasing the severity of alloimmunization if the fetus was Rh-positive. Amniocentesis seemed to be the safest and most reliable option and was the investigation of choice in most centres. It used to be carried out after 15 weeks gestation and amniocytes were used to obtain the fetal genotype using PCR. There was a false-positive rate of 1.5%. Fetal rhesus-D status can be determined reliably by PCR analysis of cell-free fetal DNA from maternal plasma or serum. A meta-analysis reported accurate fetal-D determination in 98.7–100% of fetuses in four studies, including at least 200 cases.[27] These techniques have superseded invasive testing for the assessment of fetal blood group. They are not only reliable but also enable women to avoid invasive procedures to determine fetal genotype.

First Affected Pregnancy

Maternal anti-Rh antibody titres are most useful in assessing the risk of fetal anaemia during a first affected pregnancy. This is because the correlation between antibody titres and transfer of fetal cells into the maternal circulation that exists in the first affected pregnancy is lost during subsequent gestations. In the majority of first immunized pregnancies, the anti-Rh antibody concentration is low and rarely exceeds the critical level for most laboratories. The critical level means that no death due to fetal haemolytic disease has occurred within 1 week of delivery when the antibody titre was at the level or lower. In Europe and the UK, the threshold for a critical titre is based on comparison with an international standard and invasive testing is recommended if the titres exceed 15 IU/l. The indirect antiglobulin (Coombs) test is used to detect the presence and the degree of alloimmunization. It should be regarded as a screening test. Positive anti-D titres mean that the mother is sensitized and that the rhesus-positive fetus is at risk of developing haemolytic disease but it does not mean that haemolytic disease has already occurred or necessarily will.

In a first affected pregnancy, fetal effects of alloimmunization tend to be less severe but they worsen with every subsequent pregnancy. Initially serial quantification of antibody titres is undertaken every 4 weeks until 28 weeks and then every 2 weeks. If levels cross the critical titre further assessment is necessary to exclude fetal anaemia. This normally means referral to the regional fetal medicine unit. There is some correlation between the antibody titres and the severity of the disease but overall the level of antibody

titre does not predict the severity of the disease. In subsequent pregnancies, the most powerful predictor of severity of the disease is the titre at which the fetus was affected previously. Women with a history of a previously affected pregnancy (hydrops, neonatal exchange transfusion, preterm delivery caused by fetal anaemia) are more likely to develop severe fetal anaemia at an earlier gestation in a subsequent pregnancy and assessment of fetal anaemia should be carried out 10 weeks prior to the gestational age at which the previous pregnancy was affected.

Ultrasound Assessment

High-resolution ultrasound is a valuable tool in the modern management of sensitized Rh-negative patients. The dating scan can establish an accurate estimation of the gestational age. This influences management decisions such as the interpretation of laboratory values and timing of delivery. Ultrasonography also allows early diagnosis of fetal hydrops which is a serious condition in the fetus characterized by an accumulation of fluid in at least two body areas of the fetus (Fig. 14.1).

It is due to fetal anaemia when the heart needs to pump a much greater volume of blood to deliver the same amount of oxygen. This increased demand for cardiac output leads to heart failure and subsequent oedema. On ultrasound features such as ascites, pleural and pericardial effusions can be seen.

Hydrops is normally not observed until the fetal haemoglobin deficit is at least 7 g/dl below the mean for the gestational age and its development often significantly affects the course of treatment.[28] Other ultrasound features for severe fetal anaemia are polyhydramnios, increased placental thickness (above 4 cm) and dilatation of the cardiac chambers, an increased umbilical vein diameter, enlargement of liver and spleen and visualization of both sides of the bowel wall. However, none of these have proven to be sufficiently reliable for clinical use.[29] Ultrasound is also important to determine fetal growth and well-being and for guiding invasive procedures such as amniocentesis, fetal blood sampling and intrauterine transfusions. It has improved the safety and success rates of invasive procedures.

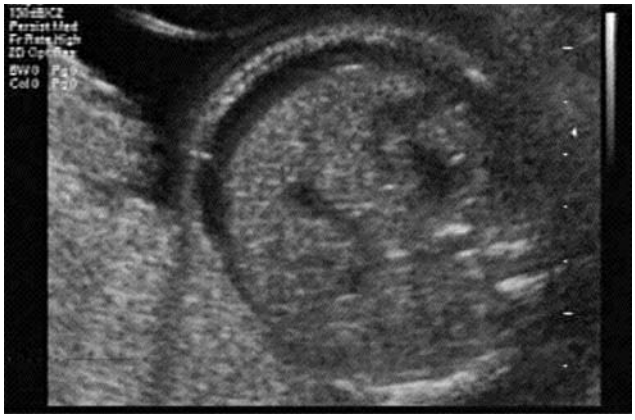

FIGURE 14.1 Ultrasound appearance of a fetus with hydrops fetalis. Note the presence of fluid in the fetal abdomen.

Middle Cerebral Artery-Peak Systolic Velocity (MCA-PSV)

Doppler assessment of the fetal middle cerebral artery (MCA)-peak systolic velocity (PSV) has superseded the invasive method of amniocentesis and then spectrophotometric analysis of the amniotic fluid to determine the concentration of bilirubin which used to be the traditional method for evaluating the severity of the fetal haemolytic process. Studies have shown that MCA-PSV is preferable to amniocentesis as it can safely be used for the timing of cordocentesis and due to its non-invasive nature it has led to a more than 70% reduction in the number of invasive testing, which carries a high risk of fetal death in the assessment of red cell alloimmunized pregnancies.[30] It is based on the principle that fetal anaemia leads to lowering of the viscosity of the blood. The increase in peak flow velocity of systolic blood flow in the MCA can be used to detect moderate and severe anaemia of non-hydropic fetuses (Fig. 14.2).

The interval between rescanning for MCA assessment is 1–2 weeks depending on the trend. It can be used reliably from 18 weeks onwards but after 35 weeks gestation the false-positive rate of MVA-PSV in predicting fetal anaemia rises considerably. It is therefore not recommended after 36 weeks.

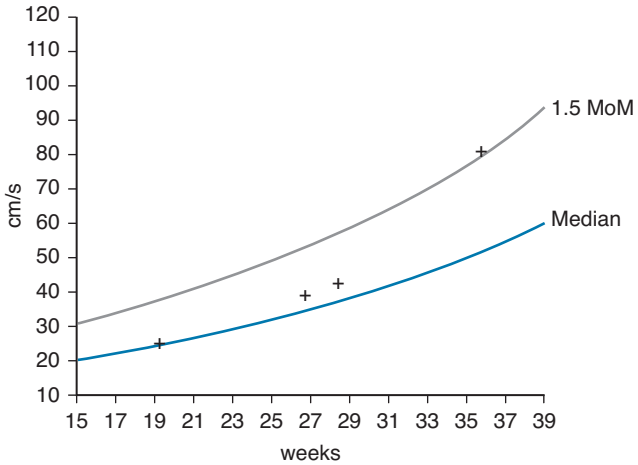

FIGURE 14.2 Serial MCA PSV recordings of a fetus at risk of developing anaemia. Fetal anaemia was suspected at 35–36 weeks. Delivery was advised and birth of a baby with moderate to severe anaemia was anticipated and confirmed at birth.

Fetal Blood Sampling (FBS) and Intrauterine Transfusion (IUT)

Fetal blood sampling is also called *cordocentesis* or *percutaneous umbilical sampling*. It was introduced by Daffos in 1983 and dramatically changed the management and therapy of Rh-sensitized patients.[31] It is the only definitive means of confirming fetal anaemia by giving a precise measurement of the fetal haematocrit and haemoglobin concentration to determine the need for intrauterine transfusion. During fetal blood sampling and in-utero transfusion, the placental insertion of the umbilical cord is found using high-resolution ultrasound and colour flow mapping. Then, still under ultrasound guidance, a needle is introduced into the umbilical vein and fetal blood is drawn to determine the fetal blood group, Rh status, haemoglobin and haematocrit. A haematocrit of less than 30% (=Hb 8 g/dl) is an indication for in-utero transfusion. Cordocentesis requires a degree of expertise and has the potential for serious complications, most commonly bleeding, which is normally transient but also feto-maternal haemorrhage, fetal loss (1–2% after 24 weeks gestation), placental abruption, thrombosis of the umbilical vessels, fetal distress and amnionitis. It also allows the adequate assessment before and after transfusion. Cordocentesis carries an increased risk of fetal death that may be as high as 5% if performed before 24 weeks. It can be performed as early as at 16–20 weeks.

In-utero transfusion has been performed since 1963 and intravenous in-utero transfusions have now largely replaced intraperitoneal transfusions because they are associated with less procedure-related morbidity and mortality. Most operators aim to transfuse to supranormal haemoglobin levels enabling long intervals of 2–4 weeks between transfusions. Some studies have shown that on an average three transfusions are required but sometimes more than 10 might be needed during pregnancy. These will be carried out until 34 weeks gestation. After 34 weeks, the risk of the procedure outweighs the benefits and delivery is preferable if severe anaemia is suspected. In a series of 254 fetuses treated with 740 in-utero transfusions, perinatal death was about 11% (7.4% fetal and 3.9% neonatal), highlighting the complications often associated with this procedure.[32] Once an invasive procedure has been carried out, use of antibody titre as a marker for disease severity is no longer valid, because the titres invariably rise after FBS.

Care at Delivery

Timing of the delivery depends on gestational age, severity of fetal anaemia and fetal maturity. If fetal surveillance is reassuring, labour can often be induced between 37 and 38 weeks. This has the advantage that a vaginal delivery can be allowed. However delivery by caesarean section is common when the fetal condition necessitates a delivery before 34 weeks. If delivery is anticipated before 36 weeks, the use of steroids for lung maturation is recommended. A direct agglutinin test is recommended on a sample of cord blood in alloimmune women.

Despite the huge improvement in neonatal care, the principles for the treatment of haemolytic disease of the newborn are the same. Early anaemia and hyperbilirubinaemia are treated with exchange or top-up infusions and milder cases with phototherapy. Neonates from severely affected pregnancies are less likely to show signs of haemolytic disease because they will have received in-utero transfusions and at the time of birth nearly all their blood volume consist of adult donor Rh-negative blood cells. Recombinant erythropoietin has shown to reduce the need for top-up infusions. The role of intravenous gamma globulin still remains unclear.

During delivery, these measures should be followed:

- Keep cross-matched blood ready before induction of labour;
- Clamp cord immediately;
- Keep cord long for possible catheterization;
- Collect cord blood for blood group, bilirubin and direct agglutinin test. Exchange transfusions may be needed soon after birth.

ALLOIMMUNIZATION TO NON-RHESUS-D ANTIGENS

Unfortunately no screening or immunoprophylaxis programme is available for non-rhesus-D and other atypical antigens. As a result, a significant number of new immunizations are due to these non-D red cell antigens. This is either due to blood transfusion or sensitization during pregnancy. Blood is routinely typed for ABO and Rhesus groups but no other blood group typing is being carried out before a routine blood transfusion. In the USA, two-third of women with Kell antibodies have a previous history of blood transfusion as the cause of their sensitisation.[33] This can be prevented by using Kell-negative blood for blood transfusions in girls and women of the reproductive age.

There are three antibodies commonly associated with severe haemolytic disease: anti-D, anti-c and anti-Kell. In terms of prevalence, the E and C antigen are the most frequent cause of alloimmunization after D and Kell. Anti-c antibodies are equivalent to anti-D antibodies in their need for neonatal exchange transfusions. The E antigen has traditionally been considered to be less immunogenic than D and causes less severe haemolytic disease of the newborn but in a study of 62 newborns with positive direct Coombs' test born to mothers sensitized against the E antigen it was shown that 42 had mild, 8 modest, 5 severe and 1 very severe haemolytic disease of the

newborn.[34] This study also found that there was no correlation between anti-E titres in the maternal serum and the severity of the fetal anaemia. Contrary to this, a study of 42 newborns showed that there was good correlation between anti-c titres and haemolytic disease.[35]

Currently in the UK, routine screening for atypical antibodies is carried out at booking. This is repeated at 28 weeks. Treatment is similar to Rh-D alloimmune women and involves monitoring of maternal antibody titres and fetal assessment for evidence of fetal anaemia using MCA-PSV and possible fetal blood sampling. With alloimmunization to the c, E and C antigens assessment with ultrasound should be performed early because fetal anaemia may occur at lower levels than with rhesus D autoantibodies. The regional reference laboratory should be consulted for advice in reading the critical titres for atypical antibodies. Alloimmunization caused by anti-Kell antibodies is managed in a similar way. It is widely believed that anti-Kell antibodies attack and destroy erythroid precursors leading to low haematocrit and fetal anaemia without any accompanying increase in bilirubin breakdown products. However, MCA-PSV can be reliably used to predict anaemia in these babies.[36]

FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPAENIA (FNAIT)

Fetal and neonatal alloimmune thrombocytopaenia (FNAIT) is a potentially devastating condition, which may lead to intracranial haemorrhage (ICH) in the fetus or newborn, and can result in death or major neurological damage. It is the result of maternal sensitization to fetal platelets antigens. Fetal platelets cross the placental barrier to initiate maternal production of specific anti-platelet antibodies against antigens expressed on fetal platelet glycoproteins inherited from the father. FNAIT is pathophysiologically similar to Rhesus disease, except that in FNAIT, the alloantibodies are directed against fetal platelets rather than fetal red cells. Unlike in Rhesus disease, fetuses in first pregnancies can be very severely affected.

The disorder affects about 1 in 1000–2000 live births with approximately 10–30% sustaining an ICH which takes place half of the times antenatally. The work of Bussel shows that platelet levels fall early in fetuses of allo-immunised women.[37] Levels of about half the fetuses of sensitized mothers showed the first platelet count of $\leq 20{,}000/mm^3$. There are different types of platelet antigens which vary with different races. At least in Caucasians, it is the HPA-1a antigen, which is responsible for approximately 85% of FNAIT. HPA-5b is the other commonly observed antigen responsible for FNAIT.

A Danish national screening program for HPA-A1 can be used to learn the natural history of the disease.[38] HPA1 typing was performed on 100,448 women out of whom 2111 (2.1%) women were HPA-1a negative and 1990 of these were examined for antibodies. Anti-HPA-1a antibodies were detected in 210 (10.6%). Out of 161 neonates who were HPA-1a positive and whose platelet counts were measured at birth, severe thrombocytopaenia (platelet count $<50 \times 10^9$/L) was found in 55 neonates, whereas 30 suffered from mild-to-moderate thrombocytopaenia (platelet count between 50×10^9/L and 150×10^9/L). The remaining 76 neonates had normal platelet counts.

Currently, there is no routine screening programme for HPA antibodies. Therefore, presentation of FNAIT is invariably unexpected. The diagnosis is usually made following investigations for a neonate with thrombocytopaenia, the finding of intracranial haemorrhage (ICH), or unexplained intrauterine death. Testing for anti-platelet antibodies is therefore advisable for any fetus or neonate with unexplained ICH and any neonate with thrombocytopaenia with or without bleeding symptoms.

Antenatal screening to identify women at risk of FNAIT has previously been considered, but the main limitations remain uncertainty about what intervention should be applied to women with anti-platelet antibodies, and the lack of reliable parameters to identify severely affected fetuses in need of antenatal intervention. A further limitation is the cost of HPA 1a typing in a screening programme given that only 0.3–4% of women are expected to be immunized. More recently however, low-cost HPA 1a typing by flow cytometry has become available.

In the absence of a routine screening programme, prenatal diagnosis and treatment are applicable to women with past history in subsequent pregnancies. This usually involves screening these women for maternal–fetal HPA incompatibility by paternal HPA typing. If the father is homozygous positive for the specific HPA antigen, the fetus is will also be, and therefore at risk. Amniocentesis may be considered to achieve fetal HPA typing, if the father is heterozygous positive. Recently, determination of fetal platelet antigen from free fetal DNA in maternal plasma has been reported. This will eliminate morbidity associated with invasive procedures for fetal platelet typing. A high maternal allo-antibody concentration (28 IU/mL or more) measured before 28 weeks of gestation and before any treatment is correlated with severe fetal thrombocytopaenia.[39] This threshold is associated with a high sensitivity (81.2%) and specificity (83.3%) for detection of severe thrombocytopaenia (platelet count $<50 \times 10^9$/L), with high positive and negative predictive values (86.7% and 76.9%, respectively).

The main aim of antenatal treatment is the prevention of severe thrombocytopaenia. The optimal antenatal treatment regimen however remains controversial. The past few years have seen a gradual shift from an exclusively invasive management protocol involving serial platelet transfusions to a less invasive management protocol and on to a completely non-invasive management approach.

Commonly used antenatal treatments include serial fetal platelets transfusions or transplacental medical treatments using immunoglobulins and/or corticosteroids. Serial platelet transfusions are very efficient in elevating platelet count, but are associated with increased fetal loss mainly from exsanguination in the presence of severe thrombocytopaenia. Two perinatal losses were reported in 12 affected pregnancies managed by 84 platelet transfusions (8.3% per pregnancy).[40] The optimum frequency of platelet transfusions remains questionable given the short half life (3 days) of transfused platelets. Additionally, every transplacental needling leads to boosting of maternal antibody levels.

There is now a much wider use of non-invasive options, which involves the use of intravenous immunoglobulins (IVIG) with and without corticosteroids. Van den Akker and coworkers reported their experience of 52 pregnancies complicated by HPA antibodies resulting in 53 neonates.[41] Five out of these 52 had a sibling with ICH. IVIG (1 g/kg of maternal body weight) was initiated at 16 weeks of gestation if the sibling did have an ICH and at 32 weeks of gestation if the sibling did not. Women were allowed to labour if there was no history of a sibling with ICH, and 31(65%) achieved a vaginal birth. Severe thrombocytopaenia was observed in 11/53 newborns following this therapy. Although addition of steroids to IVIG appears to improve newborn platelet counts,[39,42] maternal steroid administration (prednisolone 1 mg/Kg) is not without side effects and may be reserved for those at a particular high risk (Past history of ICH, high anti-platelet antibody levels).

IVIG is generally considered to be very safe and well-tolerated, even though it is expensive. Theoretical concerns remain about risks for viral and other infections because it is sourced from human blood donors. Other options used in conjunction with fetal therapy are near term delivery by induction of labour or caesarean section and delivery in a tertiary centre. In case of vaginal birth, it is advisable to avoid invasive procedures such as forceps, ventouse, scalp electrodes and fetal blood sampling. Termination of pregnancy is an option in cases with ultrasound evidence of severe fetal ICH.

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%.[43-45] The incidence of Rh sensitization during pregnancy is about 1.9% and the perinatal loss due to Rh alloimmunization has been reported to be between 1% and 2.5%.[45,46] Factors protecting against Rh sensitization include maternal–fetal blood group ABO incompatibility and immunological non-responder 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 non-existent. Lastly the benefits of protecting non-immune Rh-negative mothers from isoimmunization with the use of prophylactic injection anti-D immunoglobulin are either unknown or ignored because of cost considerations.

Fetomaternal hemorrhage (FMH), fetomaternal leak (FML), or transplacental leak (TPL) are the causes 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 haemorrhage, 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, caesarean 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 non-immunized patients the benefit of antenatal injection 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.

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.[45] 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.[47] Reports from several Indian centres containing the incidence of TPH (transplacental haemorrhage) 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

TABLE 14.2 Incidence of FML Following MTP (Indian Survey)

Author	Year	Incidence
Bakshi and Rosario-Pinto[a]	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.[b]	1985	First trimester – 6.0%
Ramanan et al.[c]	1980	First trimester – 15% MTP using D&C – 23.0%

a. Bakshi V, Rosario-Pinto Y. Feto-maternal leak after MTP. *J Obstet Gynaecol India*. 1978;28:346.

b. Ambiye A, Shanbag A, Vaidya PR. Fetomaternal hemorrhage following MTP. *J Obstet Gynaecol India*. 1985;35:162.

c. Ramanan S, Ganguli AG, Krishna UR. Incidence of feto-maternal leak after MTP. *J Obstet Gynaecol India*. 1980;30:48.

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.[48] Overall about 16% of Rh-negative women are at risk of isoimmunization, this risk is reduced to 1.5–2.0% if immunoprophylaxis with injection anti-D immunoglobulin 300 µg is started antenatally at 28 weeks of gestation. A repeat top-up dose of injection 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.[48] If the newborn is Rh-negative, there is no need to administer the anti-D immunoprophylaxis. Deka and coworkers from New Delhi advocated determination of fetal Rh group by PCR on amniotic fluid obtained by amniocentesis.[49] In case of Rh-negative pregnant women whose fetus is Rh-negative, the need for antenatal anti-D immunoprophylaxis is completely obviated.[49]

The basic pathology of Rh isoimmunization results from the haemolysis of fetal RBCs as a result of maternal serum antibodies crossing the placental barrier into the fetal circulation and causing progressive haemolysis over time leading to fetal anaemia and its grave consequences. A wide range of sonographic findings have been documented in response to fetal anaemia.[50] 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 (colour Doppler flow studies). On sonography there may be evidence of presence of fluid in serous cavities, subcutaneous oedema, 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 haematocrit of <40% is indicative of fetal anaemia. The lower the reading, the worse the prognosis. A haematocrit 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.[51]

Important Points

- Anaemia is the most common haematological disorder in pregnancy;
- Supplementation of iron and folate in pregnancy is the best way to prevent its deficiency, at least in women at high risk of developing anaemia;
- Women with sickle cell disease are at increased risk of crises, thrombosis and pre-eclampsia in pregnancy;
- High-dose folic acid (5 mg) should be given and education of patients on how to avoid triggers of crises (dehydration, infection) and where to seek help early is an important part of the antenatal care;
- Gestational thrombocytopaenia is common and does not normally require intervention unless counts are 50–80 $\times$ 10^9/L and warrant treatment before delivery in order to facilitate administration of regional anaesthesia;
- The diagnosis of immune thrombocytopaenia can only be made when other causes have been excluded;
- Effective prophylaxis programmes have significantly reduced the prevalence of Rhesus-D alloimmunization.
- New immunizations from non-Rhesus-D antigens and other atypical antibodies, however, remain a problem. This is due to an increase in blood transfusions especially in obstetrics;
- Sensitized women are best managed in specialized centres where advanced procedures including MCA-PSV, fetal blood sampling and intrauterine transfusions have shown to dramatically reduce perinatal morbidity and mortality.

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Chapter 15

Diabetes in Pregnancy

Gargee Pandit and Kaizad R. Damania

Chapter Outline

Diabetes occurs quite often during pregnancy even in unsuspected cases. There are a lot of conflicting guidelines and protocols for the screening, diagnosis and treatment of diabetes in pregnancy. Early diagnosis and treatment of diabetes in the present pregnancy can help to reduce the overall future prevalence of diabetes in the general population. This chapter aims to simplify the understanding of various problems associated with the condition and provide evidence-based easy algorithms for its diagnosis and treatment and important tips from the practical point of view.

INTRODUCTION

Diabetes mellitus is a disorder of carbohydrate metabolism. It is caused by a combination of hereditary and environmental factors, and is characterized by either inadequate secretion or inadequate action of insulin. Diabetes complicating pregnancy has become more common worldwide. However due to advances in the management of diabetes and its complications, there has been an overall improvement in the maternal and perinatal outcome. The world prevalence of diabetes among adults was around 6.4% in 2010 affecting 285 million adults and has been estimated to increase up to 7.7% and 439 million adults by 2030.[1] Abnormal maternal glucose regulation occurs in around 3–10% of pregnancies. The prevalence of gestational diabetes derived from a recent study using newer cut-offs and data correlating with adverse outcomes is around 18%.[2] The reasons for the rise in the prevalence of diabetes are mainly changes in lifestyle, dietary habits, older age at first conception, polycystic ovarian disease, obesity and moreso due to the increased awareness and changing methodology in testing for the condition. Gestational diabetes poses short term as well as long-term effects on the health of both the mother and the child. And hence an indepth knowledge of the disease and its management is a must for every obstetrician.

CLASSIFICATION OF DIABETES

From the obstetricians point of view it is important to classify diabetes as

- Pregestational or gestational
- Uncomplicated or complicated

The etiological classification refers to the underlying cause for the glucose intolerance.

It can be classified as follows:

- Insulin dependent or type 1 diabetes
- Insulin independent or type 2 diabetes
- Gestational diabetes mellitus (GDM)

- Other causes:
  - Abnormality in insulin receptor
  - Abnormality in insulin action
  - Disease of exocrine pancreas, e.g. Pancreatitis
  - Endocrine abnormality, e.g. Cushing's syndrome, acromegaly
  - Chromosomal abnormality, e.g. Trisomy 21

Another classification is the Whites[3] classification which takes into consideration the duration of the disease, age at onset of disease and the complications. It distinguishes between gestational diabetes (type A) and diabetes that existed prior to pregnancy (pregestational diabetes). These groups are further subdivided according to their associated risks and management.

The two subtypes of gestational diabetes are

- **Type A 1:** Abnormal oral glucose tolerance test, but normal fasting and postprandial (2 hours after meals) blood glucose levels. Dietary modifications are sufficient to control blood glucose levels.
- **Type A 2:** Abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals. Additional therapy with insulin or other medications is required.
- **Type B:** Onset at age 20 or older and duration of less than 10 years.
- **Type C:** Onset at age 10–19 or duration of 10–19 years
- **Type D:** Onset before age 10 or duration greater than 20 years
- **Type E:** Overt diabetes mellitus with calcified pelvic vessels
- **Type F:** Diabetic nephropathy
- **Type R:** Proliferative retinopathy
- **Type RF:** Retinopathy and nephropathy
- **Type H:** Ischemic heart disease
- **Type T:** Prior kidney transplant

CARBOHYDRATE METABOLISM IN PREGNANCY

Pregnancy is a unique physiological condition. It is a diabetogenic condition due to progressive increase in the insulin resistance. The diabetogenic effects of pregnancy are:

- **Insulin resistance:**
  - Production of human placental lactogen, cortisol, estriol and progesterone which all have anti-insulin action
  - Increased destruction of insulin by kidney and placenta (insulinase)
- **Increased lipolysis:** Mother utilizes fatty acids for her caloric needs sparing glucose for the fetus
- **Changes in gluconeogenesis:** Alanine and other amino acids which are a major gluconeogenic source in the mother is preferentially used by the fetus

In early pregnancy, there is an increased risk of hypoglycemia due to increased insulin sensitivity. Also the nausea and vomiting common in the first trimester contribute to reduced food intake which may cause hypoglycemia. The opposite occurs from the mid second and third trimester when the insulin resistance starts occurring to provide nutrition to the growing fetus. This explains why gestational diabetes is common after 26 weeks of pregnancy. It also explains the increased risk of ketoacidosis in pregnant women with type 1 diabetes.

COMPLICATIONS OF DIABETES MELLITUS

The complications of diabetes are common in those with uncontrolled and fluctuating blood sugar levels. Long standing uncontrolled hyperglycemia results in most complications. These complications may aggravate in pregnancy and hence the risk in pregestational diabetes.

The complications of diabetes could be classified as acute and chronic.

Acute complications are mainly due fluctuations in the blood glucose levels. There could either be severe hyperglycemia with ketoacidosis or hyperosmolar coma with a precipitating factor like infection, dehydration; or there could be mildly symptomatic to life threatening hypoglycemia.

Chronic complications occur due to long standing hyperglycemic state. This causes endothelial damage leading to small vessel or large vessel disease. These include the following:

- Microvascular angiopathy leading to
  - Neuropathy
  - Retinopathy
  - Nephropathy
- Macrovascular angiopathy leading to
  - Coronary artery disease and cardiomyopathy
  - Stroke
  - Peripheral vascular disease

GESTATIONAL DIABETES MELLITUS

The definition of gestational diabetes mellitus according to American College of Obstetrics and Gynaecology (ACOG) is 'any degree of glucose intolerance that either commences or is first diagnosed in pregnancy'.[4] This definition includes women whose glucose tolerance will return back to normal after pregnancy and also those who will persist with glucose intolerance and develop type 2 diabetes. The latter group may also include those women who had unrecognized type 2 diabetes prior to pregnancy.

The incidence of this condition is increasing, reflecting the increasing prevalence of obesity and metabolic

syndrome. The trend towards older maternal age, adoption of modern lifestyle, changing eating habits and reduced physical activity may all contribute towards an increased prevalence of GDM. Family history of diabetes, past history of gestational diabetes and ethnicity, such as non Caucasians, Asian, African Americans, Mexican Americans, American Indians, native Hawaiians, etc., are also high risk factors for GDM.

Risks associated with GDM are almost the same as those with pregestational diabetes. The one important difference is that since majority women diagnosed GDM have normoglycemia at the time of conception. Hence the risk of structural congenital anomalies in the fetus may not be seen with GDM.

The International Association of Diabetes and Pregnancy Study Group (IADPSG) in 2010 recommended new terminology and diagnostic cut-offs for GDM based on the hyperglycemia and pregnancy outcome (HAPO) study. In this large prospective observational study, around 25,000 pregnant women from 9 countries underwent a 75 g oral glucose tolerance test between 24 and 32 weeks gestation.[5] The primary outcomes were birth weight > 90th centile for that gestational age, primary caesarean section, clinically diagnosed neonatal hypoglycemia and cord blood c-peptide level > 90th centile.

According to these IADPSG guidelines, diabetes first recognized in pregnancy can be classified as 'gestational' or 'overt'. Thus, an increasing number of women have undiagnosed type 2 diabetes at the time of conception leading to congenital anomalies and other complications of diabetes.[2]

The criteria for diagnosis of overt diabetes include any one of the following:

- Fasting plasma glucose (FPG) >/= 126 mg/dl
- HbA1c >/= 6.5% (on standardized assay)
- Random plasma glucose (RPG) >200 mg/dl along with confirmation by fasting glucose or glycosylated haemoglobin levels.

The criteria for diagnosis of gestational diabetes were first established in the 1960s[6] and have subsequently undergone modifications.

SCREENING AND DIAGNOSIS OF GDM

A universal recommendation for the ideal approach for screening and diagnosis of GDM remains elusive. Important questions in screening of gestational diabetes are whether there should be selective or universal screening, when the screening be performed and how should it be done. There are different schools of thought. Opinions differ about optimal screening and diagnostic techniques due to differences in population risks, cost effectiveness and lack of an evidence base to support large national screening programmes. The most elaborate regimen includes either fasting or random blood glucose during the first visit, a screening glucose challenge test at 24–28 weeks, followed by a oral glucose tolerance test if the test results are outside normal limits. In case of high suspicion, testing may be done earlier.

In 2001, the ACOG recommended universal screening for GDM, whether by patient history, clinical risk factors or with a 50g one hour loading test at 24–28 weeks. They rely on the 100g 3 hour OGTT for diagnosis. This is referred to as the 'two step method'. The Fifth International Workshop Conference on GDM (November 2005) endorsed continuation of the use of classification criteria and strategies for detection and diagnosis of GDM that were recommended at the Fourth Workshop Conference. The risk factors for GDM should be assessed and according glucose testing be done. Pregnant women can be classified as low, moderate or high risk based on various factors (Adapted from the Fourth International Workshop Conference on GDM, August 1998):

Low risk: Blood glucose screening not routinely required in these:
- Age <25 years
- Member of an ethnic group with low prevalence of GDM
- No history of diabetes in first degree relative
- No history of abnormal glucose metabolism
- Weight normal before pregnancy
- Weight normal at birth

Moderate risk: One or more of the following:
- Age >25 years
- Member of an ethnic group with high prevalence of GDM
- Diabetes in first degree relative
- Overweight prior to pregnancy
- Weight high at birth
- In these women, blood glucose testing be done at 24–28 weeks (one or two step procedure)

High risk:
- Marked obesity
- Strong family history of type 2 DM
- Previous history of GDM or impaired glucose tolerance or glycosuria or macrosomic baby
- In these women, glucose testing should be done as soon as possible.

In the two step approach recommended by ACOG, initially a 50g glucose challenge test (O'Sullivan test) is performed, which if positive, is followed by an oral glucose tolerance test (OGTT).

The glucose challenge test is performed by administering 50g of anhydrous glucose orally irrespective of time of day and previous meal. Venous blood glucose is then measured 1 hour later. The cut-off used for diagnosis of the test determines its sensitivity. When 130 mg/dl is used as the upper limit, the sensitivity of the test is 90% which falls to 80% if the upper limit is increased to 140 mg/dl. Thus, a

larger number of the population gets an OGTT with a lower cut-off value. However, the number of false positives also increases with the 130 mg/dl threshold.

The OGTT should be done after an overnight fasting of between 8 and 14 hours. During the previous 3 days, there must be an unrestricted diet (with at least 150g carbohydrate per day) and unlimited physical activity. The patient must be seated throughout the test and not smoke. A solution containing 100g anhydrous glucose powder is given to the patient. Blood is then drawn at hourly intervals (3 samples). Two or more of the following values should be abnormal:

- **Carpenter and Coustan criteria (upper limits of normal):** F 95, 1 hr 180, 2 hr 155, 3 hr 140 mg/dl or
- **NDDG (National Diabetes Data Group) criteria:** F 105, 1 hr 190, 2 hr 165, 3 hr 145 mg/dl.

(The glucose used for OGTT is anhydrous 75g glucose. The commercially available glucose is a glucose monohydrate and hence 82.5g of which equals 75g of the anhydrous form)

The recent ACOG recommendations (Sept 2011)[4] suggest that universal screening (by patient history, clinical risk factors or with a 50g one hour loading test at 24–28 weeks) be done. Diagnosis of GDM be done on the basis of two or more positive values in the 100g 3 hour OGTT since there is evidence that treatment improves outcome. It also suggests that that the one-step screening and diagnostic test outlined in the IADPSG guidelines (subsequently explained) is not recommended since there is no evidence at present that diagnosis using these criteria leads to significant improvement in the maternal or fetal outcome and would lead to a significant increase in health care costs (18% of pregnant women would be diagnosed as having GDM).

The NICE guidelines of 2008[7] recommended that screening for GDM be done using risk factors in a healthy population. In women with any high risk factor like BMI > 30kg/sqm, previous baby >4.5kg, first degree relative with DM, ethnicity, the 2 hour 75g OGTT be used to test for gestational diabetes at 24–28 weeks. Diagnosis of GDM is made on the basis of criteria defined by the World Health Organization (fasting of >/=126mg/dl and 2 hour value of 140mg/dl). Women with previous gestational diabetes should be offered OGTT at 16–8 weeks and a further repeat testing at 24–28 weeks.

As against this, the American Diabetic Association (ADA) and the IADPSG recommend the one-step diagnostic 75g 2 hour OGTT. The cut-offs for this OGTT are as follows:

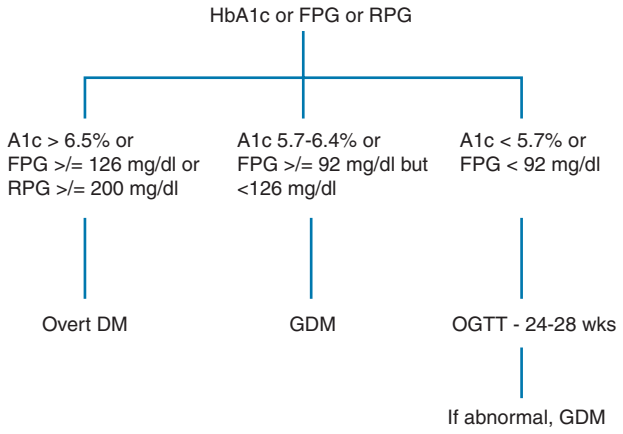
- Fasting blood glucose: ≥ 92mg/dl
- Post 1 hour: ≥ 180mg/dl
- Post 2 hours: ≥ 153mg/dl

These cut-offs are lower than the traditional values. These were considered after the results of the HAPO study which suggested increased complications even below the traditional cut-offs used for diagnosis of GDM.

The earlier mentioned cut-offs of Carpenter and Coustan criteria and the NDDG criteria was based on data that was derived mathematically as being two standard deviations above the mean, and were validated for their predictive value for future diabetes in the mother, rather than on pregnancy outcomes. This 75g OGTT (now recommended by ADA and IADPSG) threshold cut-offs were derived to give an odds ratio of 1.75 times the likelihood of adverse outcomes at mean glucose levels of the HAPO study.[8]

The following algorithm was suggested combining the recommendations of the ADA and IADPSG in 2011 for diabetes in pregnancy[9]:

- Testing of all women at the first antenatal visit <13 weeks – early detection reduces complications, OR
- Test women who have ANY risk factor:
  - Non-Caucasian
  - BMI >25 (at risk BMI may be lower in some ethnic groups)
  - History of GDM or prediabetes, unexplained stillbirth, malformed infant
  - Previous baby 4000 gm or more
  - First-degree relative with diabetes mellitus
  - Glucosuria
  - Medications that raise glucose (e.g. steroids, betamimetics, atypical antipsychotics)
  - Polycystic ovarian syndrome, cardiovascular disease, hypertension, hyperlipidemia



- If entry to care is between 13-24 weeks and risk factors are present, test with OGTT as soon as possible.

The IADPSG recommendations do not specify that the first phase of testing should necessarily be universal rather it recommends that the decision be made on the basis of the background rate of abnormal glucose tolerance in the local population, as well as the resources.

Seshiah et al[10] has debated that the ADA/IADPSG suggestions and cut-offs have certain disadvantages:

- The HAPO study was essentially conducted in the Caucasian population (except Bangkok, Hong kong). They hypothesize that ethnically Asians have higher insulin resistance in pregnancy which may result in higher blood glucose levels.
- Also, most pregnant women do not come fasting for the antenatal visit. Thus the dropout rate is very high when she is asked to come back for an OGTT, especially in developing countries where the number of antenatal visits are so few.
- Glycosylated Hb is not possible in low resource settings because of its cost and lack of technically qualified staff.

To overcome these problems in the developing countries, the Diabetes in Pregnancy Study Group India (DIPSI) recommended a 'single step' diagnostic procedure for all patients (universal screening). In the antenatal clinic, after preliminary examination, the pregnant woman is given 75g glucose load orally, irrespective of her fasting status or timing of previous meal. GDM is diagnosed if the post 2 hour blood glucose value is >/= 140 mg/dl. The rationale behind this test is that a normal glucose-tolerant woman would maintain euglycemia despite the glucose load. While in a GDM patient, the glycemic excursion exaggerates further.

This single step procedure has been approved by the Ministry of Health, Govt. of India and also recommended by the WHO.

Advantages of the DIPSI procedure are:

- Pregnant women need not be fasting and can be performed at the first visit itself, and can be best repeated again in the second and third trimester.
- Hardly affects the daily routine of the woman.
- Is both a screening as well as a diagnostic procedure.

EFFECTS OF DIABETES ON PREGNANCY

Both pregestational as well as gestational diabetes pose many risks to the mother and the fetus. The consequences of diabetes lead to increased maternal and fetal morbidity.

Maternal Effects

As previously mentioned, diabetes results in a number of macrovascular and microvascular complications. These are mainly seen in patients with longstanding pregestational diabetes. The severity of these complications varies with the duration and severity of abnormal glucose levels. In pregnancy, there may be acceleration of the end organ diseases like retinopathy and nephropathy. There may be risk of death due to diabetic cardiomyopathy.

One of the most severe complications of GDM is the increased risk of developing preeclampsia. Preeclampsia occurs in around 10% of patients with GDM. Studies have shown that the GDM patients who developed preeclampsia were younger, nulliparous, obese and gained significantly more weight during pregnancy. The problem arises especially in cases of known diabetes with nephropathy wherein proteinuria is already present. The risk of superadded preeclampsia is around 35–60% in women who have microalbuminuria in early pregnancy. Other complications of diabetes include preterm labour, chorioamnionitis, polyhydramnios, urinary tract infections and others. The steroids and tocolytics like beta2 agonists given in cases of preterm labour worsen hyperglycemia and can predispose to ketoacidosis. In case of uncontrolled diabetes prior to pregnancy, risk of recurrent pregnancy loss increases.

Conditions during the antepartum period like febrile illnesses, dehydration from hyperemesis or diarrhoeal disease can precipitate ketoacidosis which can be life threatening not only for the mother but may also cause sudden fetal death. Reports suggest around 4–15% maternal mortality rate from ketoacidosis in pregnancy. There is increased need for hospital admission to either initiate insulin therapy or during inter current illnesses or in cases of emergency situations like preterm labour and diabetic ketoacidosis. There are also chances of recurrent hypoglycemic episodes especially in first and early second trimester in patients with pregestational diabetes on insulin therapy.

In patients with pre-existing diabetes, there is added risk during pregnancy of worsening of end organ damage. Of particular importance are nephropathy, retinopathy and cardiovascular disease. Neuropathy may manifest just in the form of gastroparesis resulting in increased gastric emptying time.

Renal disease develops in around 25–30% women with insulin-dependent diabetes of a long duration, around 14–16 years, that is in class C and D of Whites classification or class F. Overt diabetic nephropathy becomes difficult to differentiate from preeclampsia, hence the importance of regular blood pressure monitoring in cases of diabetes in pregnancy. The stages of development of diabetic nephropathy are as follows:

Stage 1: microalbuminuria (albumin to creatinine ratio >/= 3.5mg/mmol or 24 hr urinary collection showing urine albumin excretion of 20–199 mcg/min or 30–299 mg/24 hr)

Stage 2: macroalbuminuria (albumin to creatinine ratio >/= 30mg/mmol or urinary albumin concentration of 200mg/L or more)

Stage 3: end stage renal disease

In the staging followed by the ADA for diabetic nephropathy, stage 1 and 2 may be silent and be present in the patients throughout their life without being symptomatic. In these stages, physical exercise may unmask the albuminuria. Further progression of renal damage may be prevented by optimal glycemic control and insulin therapy. Stage 3 is incipient diabetic nephropathy, where the albuminuria ranges between 15 and 300 microgram/min. Hypertension starts manifesting in this stage. Stage 4 is overt diabetic nephropathy with persistent proteinurea of >0.5g/24 hr. In this stage, long-term anti hypertensive treatment postpones uraemia considerably. The final stage is of end stage renal failure requiring dialysis or renal transplantation.

Hence assessment of renal function is important because nephropathy can increase potential risks of preeclampsia, fetal growth restriction, preterm birth and chronic hypertension and maternal morbidity.

However, studies have shown that though some women with moderate to severe nephropathy progress to end site renal failure, for most women pregnancy was not associated with increased incidence or progression of mild nephropathy. Treatment of nephropathy prior to conception and after delivery with ACE inhibitors or angiotensin II receptor blockers is recommended. Improvement in the glycemic control and treatment of hypertension have shown to reduce the risk or slow the progression of diabetic nephropathy. These drugs are contraindicated during pregnancy as they are associated with fetal proximal renal tubular dysgenesis and oligohydramnios. Hence, alternative drug therapy (like labetalol or alpha methyldopa) must be started as soon as pregnancy is diagnosed.

Similarly, background or mild nonproliferative retinopathy should be screened for and followed up during pregnancy by a dilated fundus examination in all cases of gestational or pregestational diabetes. In known diabetics, fundoscopy is recommended prior to conception, at first antenatal visit and again at 28 weeks if previous examinations are normal. In case of any pre-existing lesion, a repeat examination should be done at 16–20 weeks (2008 NICE guidelines). Nonproliferative stage of retinopathy can be managed by observing good glycemic control. In case of proliferative stage, pan retinal photo coagulation is done. Diabetic macular edema needs to be controlled by focal or grid laser.

Diabetic retinopathy is not a contraindication for vaginal delivery (NICE 2008, Royal College of Ophthalmologists 2012). But in cases of proliferative retinopathy which is untreated, labour may result in increased intraocular pressure, which could result in intravitreal haemorrhage due to rupture of the fragile vessels. Hence, such patients must be identified and treated and decision regarding mode of delivery for each patient be individualized. Ophthalmic follow up for at least 6 months after delivery is recommended in cases of preproliferative retinopathy.

Intrapartum, there may be increased need for intervention, chances of infection and need for operative delivery either instrumental or caesarean section. The need for caesarean section rises due to dysfunctional labour, macrosomic babies, prolonged labour, apart from other obstetric indications.

In the postpartum period, there is risk of postpartum haemorrhage, infection, puerperal sepsis. There is long-term risk of developing type 2 diabetes and other cardiovascular or renal disorders.

Fetal and Neonatal Effects

The main fetal risks are

- Growth abnormalities: macrosomia, growth restriction and malformations
- Chemical imbalances after birth
- Fetal oxygenation problems: Sudden fetal demise, chronic fetal hypoxia and respiratory distress syndrome
- Long-term sequelae

Growth Abnormalities

Disordered fetal growth is a problem of all types of maternal diabetes. Macrosomia, defined as fetal weight more than 90th centile for that gestational age or estimated fetal weight equal to or more than 4000g is the commoner abnormality. Macrosomia results from maternal hyperglycemia (Pedersen hypothesis) leading to excess transplacental glucose transfer which in turn causes fetal hyperinsulinemia. This effect is seen after 20 weeks of gestation when the fetal pancreatic islet cells are capable of secreting insulin in response to hyperglycemia. It is suggested that intrinsic fetal pancreatic beta cell hyperplasia assists in maternal glycemic control.[11] Insulin acting like a growth factor causes excessive fetal growth and deposition of subcutaneous fat in the baby. Some suggest that this results in a larger fat pad in the shoulder and trunk region causing shoulder dystocia and subsequent birth trauma to the fetus (like clavicular fracture and brachial plexus injury) as well as the mother. There also occurs fetal hepatomegaly, splenomegaly and cardiomegaly due to hyperinsulinemia. The positive predictive value for detection of macrosomia is greater than 90% when the abdominal circumference is more than 95th centile. ACOG suggests that if gestational diabetes remains undiagnosed or untreated, the risk of macrosomia is as high as 20%.[12]

In cases of pregestational diabetes of prolonged duration wherein there is evidence of systemic vasculopathy, there is a risk of development of uteroplacental insufficiency.

Uteroplacental insufficiency leads to intrauterine growth restriction. This vascular insufficiency is accompanied by maternal hypertension.

Before 20 weeks, fetal islet cells are not well developed. Thus, the main culprit is the high glucose levels. Exposure to high glucose levels at the time of organogenesis results in a number of fetal malformations in those with uncontrolled pregestational diabetes.[13] More than 50% of these anomalies affect the central nervous or cardiovascular system. Following anomalies are associated:

- **CNS:** neural tube defects including anencephaly, meningomyelocoele, encephalocoele
- **CVS:** transposition of great vessels, ventricular and atrial septal defects, hypoplastic left heart and others
- **Skeletal:** Caudal regression syndrome, spinal anomalies
- **Renal:** hydronephrosis, renal agenesis, cystic kidneys
- **Intestinal:** duodenal atresia, anorectal malformation

Maternal glycosylated haemoglobin levels in the first trimester may help to predict the risk of occurrence of congenital anomalies in the fetus in cases of pregestational diabetes. Studies[13] show that:

- HbA1c less than 7% – no greater risk for anomalies than nondiabetic mothers
- 7-8.5% – risk of 5% for anomalies
- >10% – risk of anomalies rises to 22%

Periconceptionally, the patient should be counselled regarding the risk of anomalies on the basis of her glycemic control. In cases of high HbA1c levels, the decision regarding continuation of pregnancy is at the patient's discretion. Screening for anomalies must be done by ultrasound.

Though most congenital anomalies occur early in gestation, a condition called the small left colon syndrome may be seen in second half of gestation especially in type 1 diabetes. In this, there is uniformly small diameter of the descending and sigmoid colon and the rectum. It may result from wide fluctuations in the maternal and fetal glycemic levels. Hyperglucagonemia occurs in response to decrease in fetal glucose levels causing intestinal hypomotility. Intestinal motility is a main factor for stimulating intestinal growth and differentiation.[14] A neonate with small left colon syndrome may present with intestinal obstruction and may mimic meconium plug syndrome.

Chemical Imbalances

Fetal hypoglycemia due to maternal hypoglycemia can result in sudden intrauterine fetal death. Neonatal hypoglycemia occurs due to hyper insulinemia in the fetus and removal of the exogenous glucose source (maternal) at the time of delivery.[13] Hence these babies be closely observed.

Other chemical imbalances seen in a neonate of a diabetic mother are hypocalcaemia and hypomagnesaemia which occur within 72 hours of birth. Hypocalcaemia occurs due to delayed postnatal parathyroid hormone regulation, pathophysiology of which is still unclear. This effect is independent of birth asphyxia. The cause of hypomagnesaemia is similar to that of calcium metabolism in the neonate. It could also occur due to long standing diabetic nephropathy in the mother leading to maternal renal magnesium losses and hence reduced availability of magnesium for the fetus.[13]

Risk of neonatal hyperbilirubinemia is increased due to preterm delivery, ineffective erythropoiesis, expanded red cell mass and relative immaturity of the hepatic bilirubin conjugation and excretion.

Studies have shown that around 65% infants of diabetic mothers have abnormalities of iron metabolism. Due to accelerated erythropoiesis, there is deficiency of iron at tissue level indicated by low serum ferritin levels. Iron deficiency increases the risk for neurodevelopmental and behavioural abnormalities.[15] However, these babies are not anaemic and spontaneous recovery of the iron status has been documented.

There is also risk of respiratory distress syndrome due to surfactant deficiency. Babies of diabetic mothers are prone to this complication due to increased risk of preterm delivery and also due to late maturation of type II alveolar cells.[16] Fetal hyperinsulinemia antagonizes the action of cortisol causing blunted production of surfactant.

Fetal Oxygenation Problems

Fetal hyperglycemia and hyperinsulinemia increase the rate of oxygen consumption by around 30% in a relatively oxygen limited environment.[17,18] Though the fetus increases substrate intake, there exists some degree of oxygen deficit. This is further accelerated by placental vasculopathy. Chronic hypoxia results in excessive erythropoietin secretion by fetal kidneys causing accelerated erythropoiesis. This results in neonatal polycythemia and hyper viscosity. This may cause neonatal stroke, seizures, necrotizing enterocolitis and sudden fetal death. The degree of maternal hyperglycemia correlates with the severity of polycythemia. Studies have shown the use of amniotic fluid or cord erythropoietin as a marker of fetal hypoxia. Neonatal hypoglycemia, hypertrophic cardiomyopathy and admission to intensive care unit occur in those with a higher amniotic fluid erythropoietin levels. In a study, the mean amniotic fluid erythropoietin levels at term was found to be 14mU/ml in diabetic pregnancies (range of 2–1975mU/ml), and 6.3mU/ml in controls (range 1.7–13.7mU/ml).[19]

Sudden intrauterine fetal death is associated with diabetic pregnancies which is difficult to predict by any kind of antenatal fetal surveillance. Umbilical artery Doppler can detect placental insufficiency which could be a cause. However in absence of vasculopathy, prediction of sudden fetal death is almost impossible. Though amniotic fluid erythropoietin level can indicate a hypoxic fetus, the feasibility of use of this parameter is still under study. Moreover, it may not predict when a fetus may succumb. Various explanations for sudden fetal demise have been proposed which include maternal hypoglycemia, ketoacidosis, chronic hypoxia, placental villus edema impairing nutrient transfer.

Long-Term Sequelae

Babies born to diabetic mothers have the risk of developing obesity, type 2 diabetes, cardiovascular disease and impaired cognitive and motor function. This can be due to a combination of factors including genetic inheritance, intrauterine or perinatal asphyxia, abnormal glucose, calcium, magnesium metabolisms and iron deficiency.

MANAGEMENT OPTIONS

Prepregnancy

Women in the reproductive age group with diabetes should undergo a complete health checkup and preconceptional counselling prior to planning pregnancy to achieve optimal glycaemic control. Till then appropriate method of contraception must be used so as to prevent unplanned and unwanted pregnancies.

Appropriate dietary measures, exercise, weight loss, drug therapy with oral hypoglycemic agents or insulin can help achieve optimal glycemic control. Renal, cardiovascular function and retinal assessment by digital imaging using mydriatic like tropicamide must be done to detect end organ damage and accordingly treated. Therapy must be targeted to achieve a prepregnancy HbA1c of less than 6.1% (NICE guidelines 2008). This would likely reduce the risk of congenital anomalies. Those with HbA1c >10% should be advised to avoid pregnancy.

All oral hypoglycemic agents except metformin should be stopped before pregnancy and insulin must be substituted. Rapid acting insulin (aspart and lispro) and intermediate acting insulin are safe in pregnancy. However, there is insufficient evidence on the use of long acting insulin in pregnancy. Metformin may be continued. Other drugs like ACE inhibitors, angiotensin receptor antagonists and statins must be discontinued.

In case pregnancy occurs before assessment of all these parameters, they must be done as soon as pregnancy is diagnosed.

Antenatal Management

Recent data provide evidence that early initiation of therapy for diabetics helps improve outcome and reduce adverse effects. There is also evidence that there occurs significant treatment benefit in even minor degree of impaired glucose tolerance. The ADA recommends[20]

- Fasting < 95mg/dl
- 1 hour post meal < 140mg/dl
- 2 hour post meal < 120mg/dl

In spite of these cut-offs, there could still be some risk of macrosomia. At the same time, too tight control may result in small for gestational age babies. Hence certain studies have utilized fetal ultrasound parameters (abdominal circumference >75th centile) to modify treatment strategies. In one such study, following upper limits were considered[21]:

- **If AC >75th centile:** fasting <80mg/dl and post prandial <100mg/dl
- **If AC<75th centile:** fasting <100mg/dl and post prandial <140mg/dl

Modification of treatment on the basis of these parameters did reduce the number of macrosomic and small for gestational infants.

Self-Monitoring of Blood Glucose (SMBG)

SMBG is required to identify those patients wherein intensification of treatment is needed. Initially SMBG may be required to be done as many as six to seven times a day which may then be reduced to three times. Usual practice is to perform fasting glucose and 2 hours after lunch and dinner or before meal on alternate days. Though fasting glucose alone does not predict need for initiating insulin therapy, the HAPO study had demonstrated an increase in adverse perinatal outcome with elevated fasting glucose level alone on OGTT.[5] A glucose level must also be done at 3am to document nocturnal hypoglycemia which may occur due to excess bed time insulin resulting in fasting hyperglycemia (Somogyi phenomenon). In case fasting hyperglycemia occurs without nocturnal hypoglycemia, it is called Dawn phenomenon, the cause of which is unknown. This requires an increase in the bed time long acting insulin. Taking into consideration target glycemic levels, depending on the degree of glucose intolerance, dietary modification with or without pharmacotherapy is instituted.

Medical Nutrition Therapy (MNT)

First line therapy for women with GDM is dietary modification. This must be done in consultation with a nutritionist, taking into account the dietary habits and cultural preferences. The total calorie intake varies according to the BMI of the woman.

- BMI < 25kg/sqm – 3000 cal/day
- Overweight (BMI 25–30kg/sqm) – 2500 cal/day
- Morbid obesity (BMI >40kg/sqm) – 1250 cal/day

The total calorie requirement should consist of <45% carbohydrate, 30% protein and 25% fat (mainly unsaturated fats).[22] Calories must be met through three major and three minor meals at equal intervals. Studies have shown that a diet rich in fibre and low in glycaemic index is able to avoid insulin therapy.[23] A close watch on the weight gained during pregnancy at each antenatal visit is important as both obesity and diabetes are associated with macrosomia. Similarly, excess weight gain and edema may be an early sign of developing preeclampsia.

Exercise

Around 30 minutes of mild to moderate exercise daily helps in improving glycemic control by improving insulin sensitivity at the skeletal muscle level (NICE guidelines). This reduces overall insulin requirement. Light exercise in the form of walking especially after a meal helps reduce postprandial glucose levels.[24]

Pharmacotherapy

Insulin

Insulin therapy has remained gold standard in the treatment of GDM and pregestational diabetes. Most associations recommend the use of short acting regular insulin (onset of action 30 minutes lasting for 6–8 hours) and intermediate acting NPH insulin (onset of action 1 hour, lasting for 10–14 hours). Recent research has added newer rapid acting insulin lispro and aspart whose action begins within 15 min. A study on the use of glargine (long acting insulin) observed that there was no increased adverse outcome as compared to NPH.[25] However, glargine (Lantus) has still not been recommended for use in pregnancy due to concern regarding its mitogenic action and causing increased fetal growth due to high affinity for the Insulin-like growth factor receptor-1.[26]

The requirement for insulin increases with gestational age, glycaemic control, obesity and other factors. Dose of insulin varies from 0.6–1U/kg/day in divided doses depending on the trimester of pregnancy. ACOG recommends insulin therapy for those who are not able to achieve the gylcemic targets mentioned previously with MNT. Commonly used formula for insulin therapy is:

Total daily insulin requirement = ⅔ in the morning + ⅓ at night such that

Morning dose = ⅔ NPH + ⅓ short acting;
Predinner dose = ½ NPH + ½ short acting

Patients need to be taught self-administration of insulin and be warned against hypoglycemia. In case of recurrent hypoglycemic episodes, insulin dose requires readjustment. Patient may be offered continuous subcutaneous insulin infusion pump therapy (NICE guidelines).[7] Insulin dose needs to be adjusted according to the glucose levels especially in emergency cases like ketoacidosis, in labour and postoperative period, during management of preterm labour due to hyperglycemic effect of beta mimetics and steroid.

Apart from hypoglycemia, administration of insulin may be associated with complications like infection and pain at injection site, lipodystrophy. Compliance is a problem with insulin therapy due to the daily multiple injections required. Hence, any patient on insulin must be strictly observed.

NICE guidelines also suggest daily testing of urine sugars and ketones by dipstick method for patients on therapy.[7]

Oral Hypoglycemic Agents (OHA)

Two OHAs have been used in pregnancy—Metformin (biguanide group) and glyburide (sulphonylurea group). In the past, there was concern regarding the teratogenecity of these drugs due to their transplacental transfer.[27] Though not recommended by most organizations, use of OHAs has become popular in clinical practice especially if it has been started preconceptionally for obesity or PCOS. NICE guidelines suggest use of metformin during pregnancy if the benefits outweigh the potential risks of using the drug.

The Metformin in Gestational diabetes (MIG) trial showed that use of metformin in GDM patients reduced the required dose of insulin and also reduced the total weight gain.[28] There was however no difference in the perinatal outcome. Patient acceptability was better.

Similarly, though evidence suggests that glyburide in the dose of 5–10 mg BD appears to be safe for the fetus, it did not have any added advantage over insulin in treatment of GDM.[29]

There have been hardly any studies to see the combined effect of metformin and glyburide for treating GDM.

Maternal antenatal management also involves early identification and treatment of anaemia, urinary tract infections or vaginal infections since asymptomatic bacteuria and candidiasis are very common in diabetics. The thyroid function should be evaluated.

Women with pregestational diabetes must be screened by various investigations for end organ damage—fundoscopy, serum creatinine, 24 hour urinary protein, USG KUB, ECG and echocardiography.

Frequent antenatal visits, monitoring weight and fundal height, recording blood pressure and asking patient for general well-being forms an integral part of antenatal care.

Fetal Surveillance in Diabetes

First Trimester

Early ultrasound for confirmation of viability and dating must be done. This helps in later confirmation of gestational age in preterm cases or for planning time of delivery. First trimester screening including maternal serum PAPP-A and βHCG with ultrasound evaluation for detecting chromosomal anomalies in the fetus must be offered between 11 and 14 weeks of gestation (NICE guidelines). Diabetes per se does not increase the risk of chromosomal abnormalities. However, many of these patients are elderly which may predispose chromosomal anomalies. Nuchal translucency (NT) >3.5mm is associated with cardiac anomalies in chromosomally normal fetuses. Cardiac anomalies are commonly associated with diabetes. Hence NT is an important marker. Also, an early scan at 11–12 weeks can detect neural tube defects which are seen in diabetes.

Second Trimester

A detailed scan for anomalies must be done between 18 and 20 weeks by an experienced sonologist. Maternal serum alpha protein levels are increased in neural tube defects. However, there is no added benefit if the anomaly scan is normal.

Fetal echocardiography at around 24 weeks as a routine in all diabetic patients may not be cost effective. Major cardiac anomalies can be detected (especially those of the conotruncal septum) by the 4 chamber and outflow tract view on ultrasound. Thus, fetal echocardiography may be justified in women with diabetes with increased nuchal translucency in the first trimester with a normal karyotype or when a cardiac anomaly is suspected in the anomaly scan or when the cardiac visibility is restricted on ultrasound due to maternal obesity or in pregestational diabetes mellitus with poor glycemic control in the first trimester.

In cases of diabetes complicated with hypertension or restricted fetal growth, an umbilical artery Doppler should be done for assessing uteroplacental insufficiency. In such cases, Doppler studies help to predict perinatal outcome and plan subsequent management. In the absence of risk factors, umbilical artery Doppler is ineffective in predicting adverse fetal outcome.

Third Trimester

The NICE guidelines suggest 4 weekly monitoring of fetal growth from 28–36 weeks. This would help to detect macrosomia and polyhydramnios. The ACOG suggests that accuracy of ultrasound biometry for suspected macrosomia is similar to clinical palpation by Leopold's manouvers.

Diabetic mothers must be explained the importance of daily fetal kick counts (DFKC) which is easy, inexpensive and noninvasive method for fetal well-being. Any reduced movements must be immediately reported and investigated further. Presence of polyhydramnios sometimes poses difficulty in perceiving fetal movements.

Biophysical profile takes into consideration fetal movement, breathing, tone, amniotic fluid largest vertical pocket and nonstress test. A good BPP score is reassuring. However, it cannot predict adverse perinatal outcome or sudden fetal death.

In women with well-controlled diabetes and no complications, the value of antenatal fetal well-being tests is questionable. In case of hypertension or vasculopathy, depending on the severity, the frequency of these tests will vary. If pregnancy goes beyond 38 weeks, then weekly or biweekly intense fetal monitoring with modified BPP does seem appropriate.

Timing and Mode of Delivery

Although most associations recommend delivery after 38 completed weeks of gestation in a diabetic patient, some state that uncomplicated cases of gestational diabetes (not pregestational) may be allowed to wait for spontaneous labour upto 40 weeks with adequate fetal surveillance. The main concern with vaginal delivery is the risk of shoulder dystocia due to macrosomia. However, it has been seen that 50% of cases with brachial plexus palsy occur in absence of shoulder dystocia. The ACOG and NICE guidelines suggest that vaginal delivery is not contraindicated for suspected macrosomia unless the estimated fetal weight is >4.5kg. In the Indian population, the average baby weight is less. Balaji et al in their study on the diagnosis of GDM in Indian women considered birth weight of 90th centile, which is 3.45kg, as macrosomia.[30] Vaginal delivery should be allowed after a proper assessment of pelvic adequacy. Depending on the bishops score, labour can be induced using mechanical methods, prostaglandins or oxytocin.

Suspected macrosomia is also not a contraindication for allowing vaginal birth after previous caesarean.

Management During Labour

- Consent be taken explaining high risk, need for instrumental delivery or caesarean, if required.
- Whole blood be cross matched and kept available.
- On the evening prior to induction (if indicated), insulin dose and meal are taken by the patient.
- Morning dose of insulin is omitted and fasting blood glucose done. Aim is to keep glucose level between 72 and 126 mg/dl.
- 2 I.V. lines must be secured.
- If blood glucose level is not maintained then dextrose-insulin neutralizing drip is started. 50 units of regular insulin in 50ml of normal saline is started. Dose is adjusted according to glucose level:
  - < 90mg/dl– 0.5U/hour
  - 90-126mg/dl– 1U/hour
  - 126-180mg/dl– 2U/hour
  - 180-240mg/dl-3U/hour
  - >240mg/dl– 4U/hour

- 10% dextrose drip at the rate of 125ml/hour is continuously given through the other line.
- It is important to monitor vitals and fluid intake and output, urinary ketones and blood glucose level 1–2 hourly.
- Fetal heart must be continuously monitored and partograph be charted in active labour.
- Labour analgesia can be offered.
- Care must be taken during second stage. Instrumental delivery must be undertaken with care.
- Both traumatic and atonic postpartum haemorrhage must be watched for.
- Baby should be evaluated by the neonatologist.

Precautions During Caesarean

Elective caesarean for macrosomia is recommended in a diabetic pregnancy if the estimated fetal weight is >4.5kg (ACOG).

- Anaesthetist must be consulted prior to elective surgery.
- After appropriate consent and blood availability, a light meal and night dose of insulin are given.
- Elective section of a diabetic patient should preferably be performed as the first case in the morning as the patient is fasting and also there is availability of all the necessary personnel.
- Morning insulin dose is omitted and fasting glucose level done.
- If required sliding scale of insulin can be started and continued in the postoperative period.
- Severely obese may require thromboprophylaxis.
- Special precautions while performing the section are adequate incision size to allow delivery of the big baby, use of forceps to deliver high floating head, to check for and suture extensions of the uterine incision which may take place especially while performing a second stage caesarean.
- Postoperative glucose monitoring must be continued and patient must be mobilized as early as possible.

Postpartum Management

In GDM, the need for insulin after delivery reduces. It can be stopped if the glucose levels are within normal limits. The pregestational diabetics must be continued on insulin for a while and then can resume their preconceptional medications. Once the patient resumes full diet by third day after delivery, a fasting and post lunch glucose level can be done and subsequent therapy decided.

Wound care is important as there are high chances of infection in diabetics. Prolonged antibiotic therapy must be given especially in cases of complicated caesarean or instrumental delivery.

ACOG recommends testing of all cases of GDM 6–12 weeks postpartum to identify women with glucose intolerance or diabetes. The 5th International Conference on GDM also recommends 75g OGTT for women with GDM in 6–12 weeks postpartum. If it is normal, 3 yearly assessments should be done. In case of diabetes or impaired tolerance, both MNT and pharmacotherapy are required depending on degree of intolerance.

Management of Diabetic Ketoacidosis

More commonly seen in cases of type 1 diabetes, ketoacidosis can precipitate in conditions of excessive stress, diarrhoea, infection, preterm labour and others.

This is a life-threatening condition for the mother as well as the fetus.

Diagnosis of diabetic ketoacidosis (DKA) is made when:

- Blood glucose >250mg/dl. It may occur at lower level also in pregnancy
- Ketone bodies in blood and urine
- Arterial pH < 7.3
- Serum bicarbonate level < 15meq/L

Figure 15.1 shows the pathophysiology of ketoacidosis.

Initial laboratory assessment should include: blood glucose, serum and urine ketones, blood gases, electrolytes, complete blood count, ECG and chest X-ray.

- Periodic monitoring of pulse, blood pressure, input and output, capillary blood glucose, urine ketones and blood gases and electrolytes.
- Fetal heart monitoring.
- Fluid replacement: severe dehydration may result in a large fluid deficit as much as 6–7 litres. The estimated fluid deficit must be replaced in around 12–24 hours.
- In the first hour, 1 litre of normal saline is infused, followed by 300–500ml/hr till pulse and BP are back to normal.
- Hypokalemia generally occurs with DKA. If <4meq/L 30meq/hrKCl must be given. When the level rises >4meq/L the amount of KCl can be reduced to 10–15meq/hr.
- Insulin therapy is started as soon as possible. 0.2U/kg intravenous bolus followed by 0.1U/kg/hr in normal saline. If the blood glucose does not fall by 30% in the first 3 hours, the drip rate is doubled. Once glucose level is between 200 and 250mg/dl, normal saline is changed to 5% dextrose.
- Bicarbonate administration is required if pH falls less than 6.8.
- Antibiotics are given.
- Treatment of the cause is important.

Prompt treatment can prevent maternal and fetal mortality.

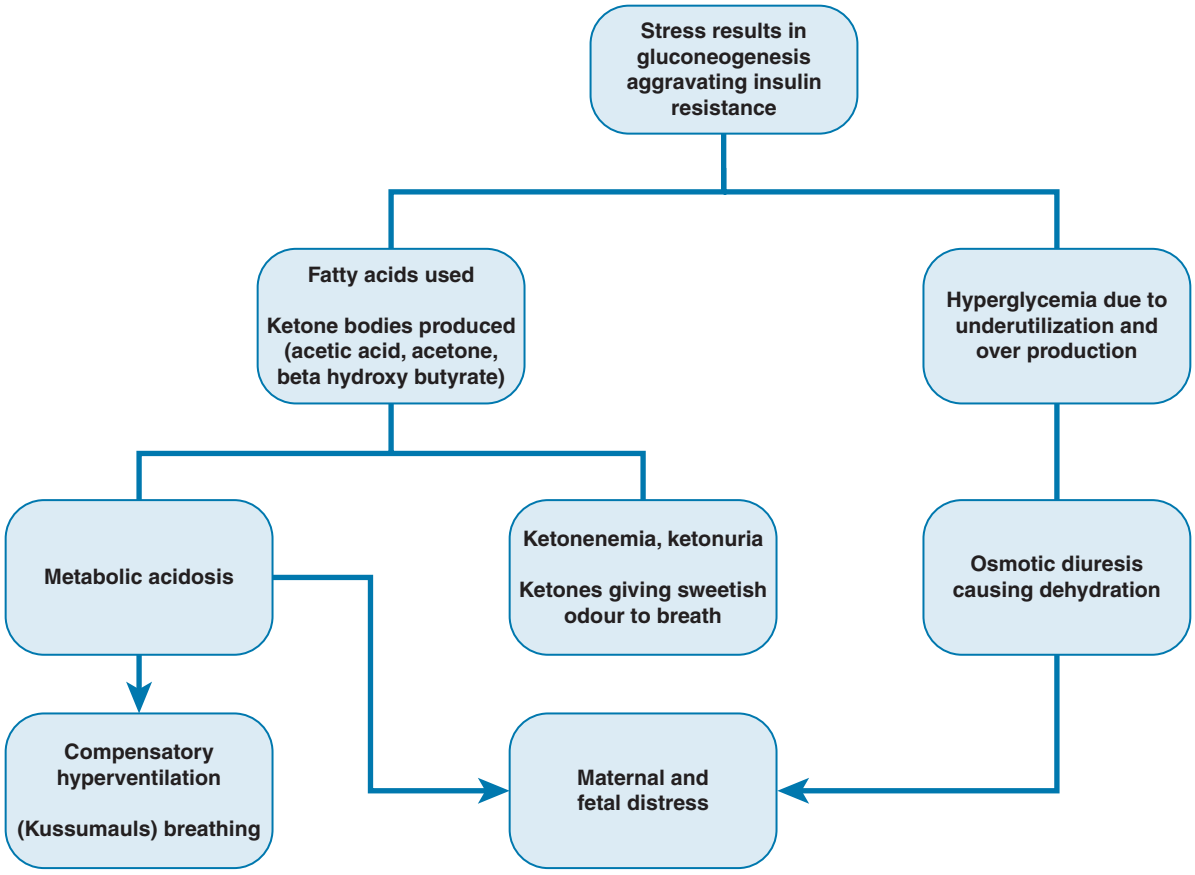


FIGURE 15.1 Pathophysiology of ketoacidosis.

CONTRACEPTIVE ADVICE

Patients must be counselled regarding contraception. Barrier methods are ideal. Progesterone only pills are also safe. Combined oral contraceptive pills may be best avoided, especially when diabetes mellitus is of a long duration. Intrauterine devices may predispose to infection. A diabetic patient may undergo tubal sterilization with precaution. Counselling the husband for vasectomy is also a good option.

Thus, diabetes management in pregnancy has evolved over the past years due to changing lifestyles and increase in maternal obesity and age at delivery. Due to this, a thorough knowledge regarding the best possible therapy for the patient is a must. Treatment has to be individualized. Though a lot has already been studied, there still remain newer techniques to explore and research.

GESTATIONAL DIABETES: INDIAN PERSPECTIVE

India has been called the diabetic capital of the world with more than 43 million diabetics in the country. A lot of these are women in the child-bearing age group. A survey reported the prevalence of impaired glucose tolerance between 12 and 15% in the age group of 20–40 years.[31] Various studies have found the prevalence of gestational diabetes as 5–18%. Due to this disease burden, various studies have been conducted showing the effects of diabetes in pregnancy.

- Considering the Indian population, DIPSI suggests guidelines for screening and diagnosis of gestational diabetes as explained previously.
- A significant increase in frequency of abortions [p = 0.017] and low birth weight babies [p = 0.029] was observed with increasing fructosamine levels in the mothers with pregestational diabetes.[32]
- In a study conducted by Jindal et al in 2001, it showed 32% incidence of macrosomia, 32% women with excessive weight gain, 48% pregnancy induced hypertension and 28% polyhydramnios among those with gestational diabetes.[33]
- Jindal et al also showed that the incidence of fetal malpresentations and caesarean delivery was higher in GDM.[33]
- Postpartum complications occurred more commonly and maternal mortality was 10 times more in GDM.[34]
- GDM is thus associated with increased maternal and fetal morbidity and mortality.

Important Points

- Diabetes is a health problem rising worldwide resulting in increased prevalence of pregnancies complicated with diabetes.
- Diabetes in pregnancy is associated with multiple maternal complications which may cause end organ failure, complicated labour and delivery and increased maternal morbidity and mortality.
- The fetus of a diabetic mother is also at risk for problems beginning in utero and extending into the neonatal period and adult life.
- Women with pregestational diabetes should undergo periconceptional counselling and have appropriate glycemic control before planning pregnancy.
- Most organizations recommend universal screening for GDM.
- Although an anomaly scan is necessary for all GDM patients, the role of various methods for fetal well-being in detecting adverse perinatal outcome in uncomplicated diabetes is doubtful.
- Insulin therapy being the gold standard, drugs like metformin and glyburide also are finding a way in the treatment of GDM.
- All GDM women must be screened postpartum for type 2 diabetes.
- Lifestyle modification, reduction in obesity and avoiding delay in first pregnancy can help reduce GDM.

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Chapter 16

Cardiac Disease and Pregnancy

Milind S. Phadke and Vinay R. Jaiswal

Chapter Outline

At present, cardiac disease complicates 0.2–4% of all pregnancies in Western countries.[1] In developing countries like India, cardiac diseases complicate 2% of pregnancies and contribute to about one-fifth of all maternal deaths.[2] In the Western world, 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 last 40 years is being compensated by an increase of pregnancy in women with congenital heart disease. Congenital heart disease is the most frequent cardiovascular disease present during pregnancy (75–82%) in the industrialized world, with shunt lesions being predominant (20–65%).[3] It represents just 9–19% outside Europe and North America. Rheumatic valvular heart disease is most common cause in developing countries, comprising 56–89% of all cardiovascular diseases in pregnancy.[2,3] Cardiomyopathy is uncommon, but represents severe cause of cardiovascular complications in pregnancy. Peripartum cardiomyopathy (PPCM) is the most frequent cause of severe complications.[4] Maternal heart disease is now the major cause of maternal death during pregnancy in developed countries.[5] Hypertensive disorders of pregnancy including chronic hypertension are the most frequent group of cardiac disorders complicating pregnancy.[6] In developing countries, the 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 birth. As a consequence, cardiologists and obstetricians are now facing an increasingly large group of pregnant women with surgically corrected congenital abnormalities.

Today, the management of cardiac disease in pregnancy is a team effort often controlled by cardiologists or internists. However, obstetricians are often the first to identify cardiac lesions as part of pre-pregnancy or antenatal care, and the ones who often face cardiac emergencies during pregnancy. Therefore, they should have adequate information about cardiac diseases during pregnancy so that they can function effectively as a member of the team that will be taking care of the patient. Moreover, they should be able to diagnose and in many cases initiate the management of some of the medical complications that may affect pregnant patients with heart disease. Finally, obstetricians 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.

PRECONCEPTIONAL COUNSELLING

Women with cardiac conditions who desire or anticipate pregnancy should be offered preconceptional counselling. Counselling sessions should typically include but not be limited to discussions regarding the optimum time to become pregnant, the effects of pregnancy on the heart condition, general characteristics of their care during pregnancy, neonatal/perinatal risks and the ways to optimize their cardiac conditions before pregnancy occurs. The ideal situation for counselling would be in early teenage years because sexual activity may often begin in adolescence and in many cases is unprotected.

The first step in the preconceptional counselling session is to obtain a thorough history, perform a physical examination, and have available information from recent electrocardiograms and echocardiograms. This information will make it possible to obtain a functional classification and to place the patient in a risk category. The functional classification universally used is that proposed by the New York Heart Association (NYHA), as described in Table 16.1. As shown in Table 16.2, risk categories are defined as low or minimal risk, intermediate or moderate risk, and high or major risk.[7] 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 counselled to deliver in tertiary centers.

Several risk scores have been developed to refine risk estimation based on the predictors that have been identified in large population-based studies, of which the CARPREG risk score (Table 16.3) is most widely known and used.[3]

The task force of European Society of Cardiology (ESC) recommends that maternal risk assessment be carried out according to the modified World Health Organization (WHO) risk classification.[8] This risk classification integrates all known maternal cardiovascular risk factors including the underlying heart disease and any other comorbidity. It includes contraindications for pregnancy that are not incorporated in other risk scores/predictors. It divides patients into risk categories based on specific cardiac conditions as shown in Tables 16.4 and 16.5. The practical application and the general principles are depicted in Tables 16.4 and 16.5.

TABLE 16.1 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 causes undue 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

TABLE 16.2 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 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 myocardial infarction
High risk	Pulmonary hypertension Marfan syndrome with aortic valve involvement & root dilatation Cardiomyopathy Complicated aortic coarctation

TABLE 16.3 Predictors of Maternal Cardiovascular Events and Risk Score from the CARPREG Study[3]

Prior cardiac event (heart failure, transient ischaemic attack, stroke before pregnancy or arrhythmia)
Baseline NYHA functional class >II or cyanosis
Left heart obstruction (mitral valve area <2 cm^2, aortic valve area<1.5 cm^2, peak LV outflow tract gradient >30 mmHg by echocardiography)
Reduced systemic ventricular systolic function (ejection fraction<40%)
CARPREG risk score: For each above-mentioned CARPREG predictor that is present, a point is assigned. Risk estimation of cardiovascular maternal complications 0 point 5% 1 point 27% >1 point 75%

NYHA: New York Heart Association
Source: ESC Guidelines on the management of cardiovascular diseases during pregnancy. *European Heart Journal* 2011;32:3147–3197.

TABLE 16.4 Modified WHO Classification of Maternal Cardiovascular Risk

WHO Risk Class I
Uncomplicated, small or mild • pulmonary stenosis • patent ductus arteriosus • MVP: mitral valve prolapse
Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductusarteriosus, anomalous pulmonary venous drainage) Isolated atrial or ventricular ectopic beats
WHO Risk Class II (if otherwise well and uncomplicated)
Unoperated atrial or ventricular septal defect
Repaired tetralogy of Fallot
Most arrhythmias
WHO risk class II–III (depending on individual)
Mild left ventricular systolic function impairment
Hypertrophic cardiomyopathy
Native or tissue valvular heart disease not considered WHO I or IV
Marfan syndrome without aortic dilatation
Aorta <45 mm in aortic disease associated with bicuspid aortic valve
Repaired coarctation
WHO Risk Class III
Mechanical valve
Systemic right ventricle
Fontan circulation
Cyanotic heart disease (unrepaired)
Other complex congenital heart disease
Aortic dilatation 40–45 mm in Marfan syndrome
Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
WHO Risk Class IV (pregnancy contraindicated)
Pulmonary arterial hypertension of any cause
Severe systemic ventricular dysfunction (LVEF <30%, NYHA III–IV)
Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
Severe mitral stenosis, severe symptomatic aortic stenosis
Marfan syndrome with aortic root dilatation> 45mm
Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve
Native severe coarctation

LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; WHO: World Health Organization
Source: ESC Guidelines on the management of cardiovascular diseases during pregnancy. *European Heart Journal* 2011;32:3147–3197.

TABLE 16.5 Modified WHO Classification of Maternal Cardiovascular Risk: Principles

Risk Class	Risk by Medical Condition
I	No detectable increased risk of maternal mortality and no/mild increase in morbidity
II	Small increased risk of maternal mortality or moderate increase in morbidity
III	Significantly increased risk of maternal mortality or severe morbidity. Expert counselling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and the puerperium
IV	Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III

WHO: World Health Organization
Source: ESC Guidelines on the management of cardiovascular diseases during pregnancy. *European Heart Journal* 2011;32:3147–3197.

The counselling sessions should include discussion of the clinical problems that women may develop during pregnancy. Heart failure, pulmonary edema, fatal arrhythmias, aortic dissection, any other complication 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 requiring critical care and central haemodynamic monitoring should be explained as well. The need for induction of labour, shortening of the second stage of labour, methods of anaesthesia used during labour and delivery, endocarditis prophylaxis and anticoagulation therapy should also be a part of the consultation. Patients with Eisenmenger syndrome, severe pulmonary hypertension, severe left-sided obstructive lesions, and women with Marfan syndrome and dilated aortic roots should be informed about the high risk of maternal mortality and be counselled to consider avoiding pregnancy and choose adoption or other methods to have a family.

HAEMODYNAMIC CHANGES DURING PREGNANCY

During Pregnancy

The haemodynamic changes begin early in the first trimester. The plasma volume starts increasing in the sixth week of pregnancy and approaches 50% above baseline till the end of second trimester (Fig. 16.1). It then tends to plateau until delivery. As compared to plasma volume there is slightly lesser rise in red cell mass, which results in the relative anaemia of pregnancy. The heart rate increases to reach a level about 20% above baseline to facilitate the

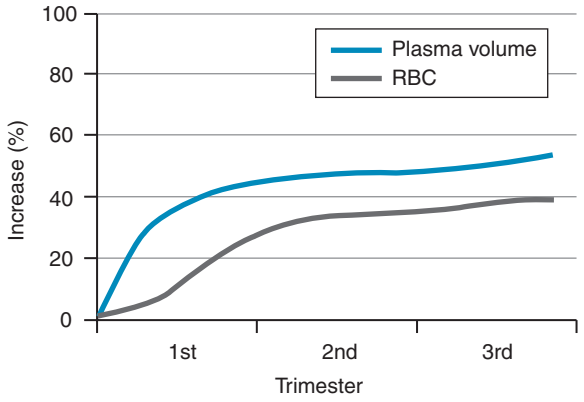

FIGURE 16.1 Plasma volume and red blood cell (RBC) increase during the trimesters of pregnancy. The plasma volume increases to approximately 50% above baseline by the second trimester and then virtually plateaus until delivery.

increase in cardiac output (Fig. 16.2). With placental growth, uterine blood flow increases and there is a fall in the peripheral resistance. This may result in a slight fall in blood pressure, which also begins in the first trimester. Most healthy women (about 80%) develop pedal edema as a result of increased venous pressure in the lower extremities. The haemodynamic changes of a normal pregnancy lead to an increase in cardiac output, which begins in the first trimester and approaches 30–50% above baseline by the end of the second trimester.

During Labour and Delivery

The haemodynamic changes during labour and delivery are sudden. Upto 500 mL of blood is released into the circulation with each uterine contraction, prompting a rapid increase in cardiac output and blood pressure. The cardiac output is often 50% above baseline during the second stage of labour and may be even higher at the time of delivery.

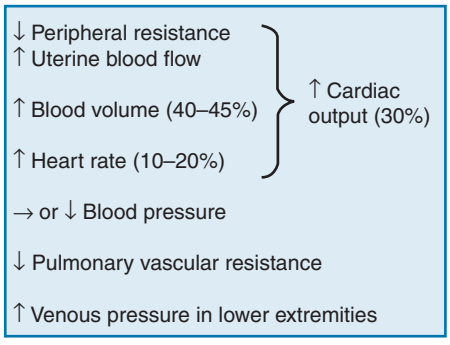

FIGURE 16.2 Haemodynamic changes during pregnancy relate to increased cardiac output and a fall in peripheral resistance. Blood pressure in most patients remains the same or falls slightly. Venous pressure in the legs increases, causing pedal edema in many patients. *(Source: Bonow RO, Mann DL, Zipes DP, et al.* Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. *9th Ed., pg. 1771.)*

Around 400 mL of blood is lost during a normal vaginal delivery. In cesarean section, about 800 mL of blood is often lost and may pose a more significant haemodynamic burden to the mother. There is an abrupt increase in venous return after delivery of the baby, in part because of auto-transfusion from the uterus, but also because the uterus no longer compresses the inferior vena cava. In addition, there continues to be auto-transfusion of blood in the 24–72 hours after delivery, and this is when pulmonary edema may occur.

All these abrupt changes mandate that for the high-risk patient with cardiac disease, a multidisciplinary approach during labour and delivery is essential. The cardiologist and obstetrician should work with the anesthesiologist to determine the safest mode of delivery.

EFFECTS OF MATERNAL CARDIAC DISEASE ON PREGNANCY

Pregnancy has profound effect on the patient with cardiac disease as it increases cardiac work and their combined effect may exceed the limited functional capacity of the diseased heart. This can precipitate congestive heart failure (CHF) and pulmonary edema, also sudden death may occur. Maternal mortality may be as high as 15% for all cardiac patients which varies with the severity of cardiac problem. During pregnancy, there are several periods when the danger of cardiac decompensation is especially great as mentioned next.

- The first one is between 12 and 16 weeks of gestation when the haemodynamic changes of pregnancy begin.
- Between 28 and 32 weeks of gestation, when the haemodynamic changes of pregnancy peak and cardiac demands are at a maximum. About 50% of the patients who develop CHF at this stage of pregnancy were in class II or III of the NYHA classification earlier on in their pregnancies.
- Another dangerous time for pregnant cardiac patients is during labour and delivery. During labour, every uterine contraction injects about 300–500 ml of blood from the uteroplacental circulation. Simultaneously, during the second stage of labour, 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 labour may turn to be critical for some women with underlying heart disease.
- Another dangerous time is soon after delivery of the baby and placenta, when there is sudden transfusion of blood from the lower extremities and the uteroplacental circulation to the systemic circulation as a result of loss of obstructive effect of uterus on the venous return. This large and abrupt increase in blood volume is more than what 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. Some patients with primary pulmonary hypertension, Eisenmenger syndrome, aortic stenosis, and cyanotic heart disease may be able to go through pregnancy, labour and delivery without major complications. However, sudden death in the early postpartum period is a known complication in these conditions. 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 THE FETUS

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, depending upon the specific condition, there is an increased incidence (4–6% vs 0.6% in the overall population) of fetal congenital cardiovascular anomalies. The poor fetal outcome associated with maternal cardiac disease has been drastically modified with adequate prenatal care, prolonged hospitalization and intensive care. However, fetal death still occurs in pregnant cardiac patients, mostly in mothers with cyanotic heart conditions. In these cases, 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 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 may be by their primary providers, following recommendations by their cardiologists, maternal-fetal medicine specialists, anesthesiologists, and neonatologists. Women with cardiac lesions that place them at high risk for death during pregnancy are listed in Table 16.6.

The cardiologist should see the patient on a regular basis and be available whenever the obstetrician believes that the woman is showing signs of cardiac compromise. Early in the pregnancy and particularly if the fetus is affected by congenital heart disease, the patient should see the fetal medicine specialist 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 syndrome and pulmonary hypertension should be advised to terminate their pregnancy and be counselled for permanent sterilization.

TABLE 16.6 Cardiac Lesions Causing High Risk of Death During Pregnancy

Pulmonary hypertension
Dilated cardiomyopathy, ejection fraction <40%
Symptomatic obstructive lesions
Aortic stenosis
Mitral stenosis
Pulmonary stenosis
Coarctation of aorta
Marfan syndrome with aortic root >40 mm
Cyanotic lesion
Mechanical prosthetic valves

Monitoring Cardiac Function during Pregnancy

Evaluation of the cardiac response of the patient with heart disease to the normal haemodynamic 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 pulmonary venous hypertension or left-ventricular failure. Weight gain, dependent edema, hepatomegaly, and increase 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 present with 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 pulmonary venous hypertension, 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 dyspnea of left heart failure is different, in that the patient

clearly limits her level of activity and often also complains of orthopnea or cough. Some patients with left-sided heart failure develop bronchospasm and wheezing after a few hours of sleep, that is '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. Signs of right heart failure include elevation in the jugular venous pressure, pedal edema, hepatomegaly and rarely ascites.

Evaluation of Patient

- **Chest radiography:** A chest radiograph is not obtained routinely in pregnant patient because of concern about radiation to the fetus, but should be considered in any patient when there are concerns about her cardiac status and new onset of dyspnea or failure. The chest radiograph in a normal healthy patient may show slight prominence of the pulmonary artery, and as pregnancy advances, elevation of the diaphragm may suggest an increase in the cardiothoracic ratio.
- **Transthoracic echocardiography:** It is used most frequently to determine the ventricular function, to assess the status of native and prosthetic valve disease, and to assess pulmonary artery pressure. For those patients with congenital heart disease, a detailed assessment of any shunt and complex anatomy may be made.
- **Transesophageal echocardiography:** Transesophageal echocardiography is seldom performed during pregnancy but may be necessary to provide more detailed imaging of valvular disease, the presence or absence of a shunt, or intracardiac thrombus, or in suspected infective endocarditis to facilitate the detection of a valvular vegetation or perivalvular abscess.
- **Fetal echocardiography:** Excellent imaging of the fetal heart can usually be obtained by 20 weeks' gestation.

Measures and Medications Frequently Used in Women with Heart Disease and Pregnancy

Antepartum

- The most important measure for reducing the impact of pregnancy upon a diseased heart is restricted activity depending upon the severity of disease. Restricted activity helps in avoiding tachycardia, improves renal perfusion, induces diuresis and promotes elimination of water. Also, since restricting activity reduces the metabolic needs of several organs, especially the skeletal muscles, the blood flow to these organs at rest decreases markedly, decreasing 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 degree of dietary sodium restriction (4–6 g daily)
- If moderate restriction in sodium intake is insufficient to limit the normal intravascular volume expansion that occurs during gestation, then diuretics should be given. Most commonly used is the loop diuretic, furosemide (FDA category C). This drug acts by inhibiting sodium reabsorption in the loop of Henle. For the most part, loop diuretics are benign drugs. Their most common side effect is hypokalaemia, which can be avoided by increasing the dietary ingestion of potassium or administration of a potassium retaining agent. Diuretics must be used judiciously and cautiously as they may compromise the placental perfusion and fetal growth by decreasing the plasma volume. There is evidence indicating that a decrease in intravascular 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 intravascular volume depletion. Unfortunately, one cannot accurately measure the intravascular volume reduction 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.
- Digoxin is used in patients with heart failure symptoms despite optimal medications. It acts by improving the contractility of the heart and relieving symptoms such as easy fatigability, orthopnea and weakness. Digoxin is also used to control ventricular rate in atrial arrhythmias.
- 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 Labour and Delivery

In general, vaginal delivery is a better option than cesarean section for women with heart disease. The risk of bleeding, infection and thrombotic complications is less and vaginal delivery is not associated with the acute shift in blood volume that happens during cesarean section. However, a long labour and a difficult vaginal delivery are much more morbid and a cesarean delivery may be preferable in certain conditions (Marfan syndrome, anticoagulated patients, severe aortic stenosis or severe pulmonary hypertension). During labour, 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:

- The pregnant cardiac patient should always labour and even opt to deliver in the lateral supine position in order

to avoid the haemodynamic problems caused by the dorsal decubitus position.

- The patient should have effective pain relief during labour. Pain control reduces tachycardia, myocardial work and cardiac output. It has been calculated that pain during labour increases the cardiac output 50% above what is normally seen during the second stage of labour. During early labour, intramuscular/intravenous labour analgesia may be used. Later, if the patient is not on anticoagulation, the analgesia/anaesthesia of choice is epidural blockade which should preferably be administered by an anesthesiologist experienced in obstetrics. Many pregnant cardiac patients will benefit from epidural anaesthesia technique. It limits the extent of the sympathetic blockade and its effect on intravascular volume pooling and blood pressure. It is preferable to administer an epidural narcotic (e.g. fentanyl) than epidural anesthetics. Epidural narcotics may be given in situations where epidural administration of local anesthetics is a relative contraindication, such as in patients with aortic stenosis, mitral stenosis, aortic coarctation, Marfan syndrome with dilated aortic root, or hypertrophic obstructive cardiomyopathy.
- Intravenous fluids should be administered in a controlled manner, restricted to not more than 75 ml/hr. This should keep the patient on the "dry" side.
- Cardiac patients in labour should be continuously monitored with pulse oximetry. Mild degrees of desaturation may be corrected by oxygen administration via nasal prongs rebreathing mask. Desaturation during labour that is not corrected by oxygen may be indicative of pulmonary edema.
- Patients with complex congenital heart lesions and with artificial valve prostheses may be given antibiotic prophylaxis at the time of delivery in order to avoid subacute bacterial endocarditis. Although recent European Society of Cardiology (ESSC) and ACC/AHA guidelines do not recommend any antibiotic prophylaxis for heart disease in pregnancy, it is a common practice in developing countries to use IV antibiotics routinely during labour and if any procedure is contemplated.
- 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 for thromboembolic complications is approximately 2% for patients with rheumatic heart disease. To prevent these, it is necessary to initiate ambulation shortly after delivery, use compression bandages for the lower extremities, and administer prophylactic low-dose heparin during labour, delivery, and the immediate postpartum period in certain conditions as discussed subsequently.
- There is sudden transfusion of blood from the lower extremities and the uteroplacental circulation to the systemic circulation as a result of loss of obstructive effect of uterus on the venous return immediately after the delivery. This physiologic phenomenon increases the blood volume to a point where it may exceed the pumping ability of the heart, resulting in acute pulmonary edema. Patients with a fixed cardiac output and mitral stenosis are especially at risk for this problem. To decrease the risk of postpartum pulmonary edema, these patients should be placed in the sitting position following delivery as it allows more gradual adaptation to the postpartum haemodynamic changes by increasing venous pooling in the lower extremities and thereby reducing the venous return to the heart. Also, if the patient is under epidural anaesthesia, the anesthesiologist may raise the level of anaesthesia and sympathetic blockade.
- At the time of delivery, oxytocin is given to make the uterus contract and to avoid intrapartum and postpartum bleeding. In cardiac patients, intravenous bolus of oxytocin should not be administered as it may cause a fall in systemic vascular resistance and subsequent hypotension which may be difficult to tolerate for some patients. Also, ergot alkaloids for prophylaxis of uterine atony should not be used in cardiac patients as these agents cause significant vasoconstriction and elevation of blood pressure, which can be deleterious as well.

TREATMENT OF ACUTE CHF DURING PREGNANCY

Irrespective of the previous knowledge about their heart condition, all pregnant women presenting in CHF should be to investigated for the presence of factors contributing to or aggravating the occurrence of heart failure. Anaemia, infections, arrhythmias, noncompliance with medications or salt restriction, excessive physical activity, and administration of salt-retaining medications are 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:

- Reducing the cardiac work with bed rest
- Decreasing the preload with diuretics
- Improving cardiac contractility with digitalis or other agents (Dopamine, dobutamine)
- Reducing the afterload with vasodilators

Unfortunately, venous thromboembolism and pulmonary embolism are the most common harmful effects of bed rest. These occur more frequently in pregnant than in nonpregnant patients due to 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. Diuretic therapy should be monitored with daily weight checks, as well as serial measurements of hematocrit, electrolytes, and creatinine. A rise in hematocrit results from rapid constriction of the intravascular volume that may be hazardous. The appearance of a low potassium value or a rise in serum creatinine also indicates the need for therapeutic adjustment.
- Digitalis therapy is an important component of the 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 is relatively safe. It is usually started with a loading dose of 0.5 mg in a 24-hour period. Maintenance dosage is 0.25 mg daily (0.125–0.375mg). 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 intravascular 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 an antiarrhythmic medications, and correction of hypokalaemia 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 systemic vascular resistance (SVR). 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 adverse fetal side effects (including fetal growth retardation and fetal renal abnormalities). Hydralazine, in oral or intravenous forms, has been used for many years in patients with preeclampsia and eclampsia. Hydralazine acts primarily as 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, nitroglycerine is the vasodilator of choice for pregnant women since nitroprusside in animal studies showed that it readily crosses the placenta and an infusion of nitroprusside 25 mcg per kg per min for one hour to pregnant ewes resulted in death in all fetuses. In cardiac emergencies, dopamine and dobutamine can be used since maternal benefit would outweigh any potential fetal risks. Nitrates reduce both preload and after load, 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.

ACUTE PULMONARY EDEMA DURING PREGNANCY

Pregnant women are more likely to develop pulmonary edema during pregnancy than during nonpregnant state. Treatment of acute pulmonary edema during pregnancy should preferably take place in an intensive care unit. Invasive haemodynamic monitoring using Swan–Ganz catheterization may be necessary to adequately assess the haemodynamic parameters and the response to therapy. 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 aggravated by the decrease in plasma colloid oncotic pressure that normally occurs during pregnancy (due to physiological hypoalbuminemia) explains the propensity to develop pulmonary edema in pregnancy. However, it still requires an initiating agent or event to tip the balance to move fluid into the interstitial space. The majority of cases of pulmonary edema during pregnancy are due to chorioamniotic infection, fluid

overload and administration of beta-adrenergic agents; pre-eclampsia and eclampsia; pulmonary embolism; amniotic fluid embolism and cardiogenic causes. 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 labour. This typically occurs in patients having a combination of chorioamniotic infection, beta-agonist and glucocorticoid treatment and large continuous intravenous infusion of crystalloid solutions. Patients with exaggerated intravascular volume expansion, such as those with multifetal pregnancies, or those with chorioamnionitis, are 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 labour respond to the following treatment:

- Discontinuation of labor-inhibiting drugs
- 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)
- 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 SVR and fluid overload are contributory factors. Treatment of preeclamptic patient with pulmonary edema is difficult and the outcome may be poor despite the use of invasive haemodynamic monitoring. The main problem is our inability to modify with therapy the endothelial cell injury and capillary permeability problems. In this subset of patients, early delivery is generally a preferred mode of treatment.

Differentiating the above noncardiogenic causes from cardiogenic pulmonary edema caused by peripartum cardiomyomathy, ischemic heart disease or occult valvular heart disease begins with a detailed history, cardiac examination and an ECG. When in doubt, an echocardiogram can help exclude or confirm a cardiac cause.

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 intravascular 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 especially aortic stenosis are unable to increase their cardiac output in response to stress and 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 after-load 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. 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 ones 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 intravascular 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 these together increases 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 which results in pulmonary edema. This occurs in approximately 20–25% 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 haemodynamic 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.[10]

Restricted activity, diuretics and rate control are three plain elements for successful management of patients with mitral stenosis with meticulous application of measures earlier indicated in management of cardiac patients during pregnancy. If cardiac decompensation and pulmonary edema occur, the patient should be managed as mentioned in "Pulmonary edema during pregnancy". During labour, the essentials of management include adequate pain relief, labouring 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 intervention. The intervention of choice in most cases is percutaneous balloon mitral valvotomy (BMV). BMV is recommended for symptomatic patients with moderate to severe MS (i.e. a mitral valve area $< 1\ cm^2/m^2$ body surface area [BSA] or $<1.5\ cm^2$ in normal-sized adults) and with favourable valve morphology, no or mild MR, and no evidence of left atrial thrombus.[11,12] 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. Haemodynamically, these patients have fixed stroke volumes (due to the stenotic lesion) 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 mean gradient across the valve. In mild aortic stenosis, the mean gradient is < 25 mmHg in moderate cases between 25 and 40 mmHg, and in severe cases is > 40 mmHg. Cardiac complications during pregnancy occur almost exclusively in patients with severe stenosis.[10] 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 labour, epidural anaesthesia should be avoided because it will cause a decrease in SVR 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 be hydrated adequately to prevent decrease in systemic vascular resistance.

Pulmonic Stenosis (PS)

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 systolic gradient is greater than 50 mmHg in cases of valvular PS, consideration should be given to balloon valuloplasty before pregnancy or after the second trimester of pregnancy. The presence of right ventricular dysfunction necessitates institution of measures for CHF-like fluid restriction, cautious use of diuretics and digitalization.

Mitral Regurgitation

Mitral regurgitation during pregnancy is usually the consequence rheumatic heart disease in developing countries like India. In Western countries, mitral valve prolapse (MVP) is the most common cause of severe mitral regurgitation. Regurgitant lesions are usually well tolerated in pregnancy as peripheral vasodilatation leads to decrease in regurgitant volume. Rarely patients develop pulmonary congestion that usually responds well to diuretics. Severe mitral regurgitation causes left atrial dilatation with an 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 syndrome. The condition is well tolerated during pregnancy and symptomatic patients usually respond well to diuretic therapy.

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. Patients with mechanical prosthetic valves are at an increased risk of thromboembolic complications during pregnancy and need anticoagulation. Choices of anticoagulation include oral anticoagulation therapy with Coumadin analogues (warfarin, acenocoumarol), unfractionated heparin (UFH) and low-molecular weight heparin (LMWH). The two most commonly used regimens are oral anticoagulation throughout pregnancy versus oral anticoagulants in the first trimester followed by UFH. The latter regimen

carries a three to four fold increase in the risk of thrombotic complications and maternal mortality. Therefore, the European Society of Cardiology (ESC) guidelines recommend that the best anticoagulation regimen in pregnant patients with prosthetic heart valves is the use of low dose of oral anticoagulation throughout pregnancy with strict weekly INR monitoring. Although there are concerns about warfarin embryopathy, this is quite rare in patients requiring less than 5 mg/day warfarin. In individuals who need a higher dose, unfractionated heparin (UFH) may be substituted between the 6th and 12th weeks. If UFH is used, the activated partial thromboplastin time (aPTT) should be monitored, with a target value of 2.5 times the normal value 4 hours after administration of the dose. UFH given throughout pregnancy carries the risk of development of thrombocytopenia and osteoporosis. If LMWH is used, anti-Xa levels should be monitored (recommended levels of 0.8–1.2U/l 4 hours after the administration of the dose). LMWH should be discontinued at least 24 hours before delivery if epidural analgesia is to be used due to its long duration of action and the consequent risk of developing spinal hematomas. Unfractionated heparin can be substituted peridelivery because it can be started and stopped rapidly. With all strategies, anticoagulants should be resumed as soon as possible after delivery. At the time of labour and delivery, oral anticoagulants must be reversed. The patient on unfractionated heparin will have normal clotting 4–6 hours after discontinuing the medication. The patients on oral anticoagulants should be switched to heparin several weeks before the anticipated delivery time. Planned vaginal delivery is usually preferred. If labour occurs while the patient is on oral anticoagulant (OAC), caesarean section may preferably be performed after counselling, due to the risk of intracranial haemorrhage in the baby during vaginal delivery.[13]

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 Defect

The outcome of pregnancy in women with atrial septal defects (ASD) is usually benign. This defect is usually found in association with MVP, and complications associated with this defect are rare in the women younger than 40 years.

Ventricular Septal Defect

VSDs 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. Small or moderate size VSDs are usually tolerated well. Large VSDs are usually associated with significant pulmonary hypertension and Eisenmenger syndrome and have poor prognosis.

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.

Cyanotic Congenital Heart Diseases: Right to Left Shunts

These 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.[14] 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 anamoly, double-outlet right ventricle, single ventricle and tricuspid atresia. The outcome of pregnancy in women with uncorrected right to left shunts is not good.[15] 92% 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 haemoglobin concentration. Women with oxygen saturation less than or equal to 85% had a live birth rate of 12% as compared with 92% for those with oxygen saturation equal to or greater than 90%. Women with prepregnancy haemoglobin concentration of at least 20 g/dL have an 8% rate of live births.[15] 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.[16] Systemic ventricular function (i.e. morphological RV) may deteriorate during pregnancy with resulting CHF. As a general rule, an ejection fraction equal or larger than

40% in the right ventricle is associated with good outcome. Women with corrected tetralogy of Fallot do quite well during pregnancy as long as the ventricular function is good and there is no significant right outflow obstruction with severe pulmonic regurgitation and right ventricular dysfunction.[17] Women with surgically corrected transposition of the great vessels usually have a 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 (univentricular physiology). 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%.

Infective Endocarditis

The estimated overall incidence of infective endocarditis during pregnancy is 0.006% (1 per 100,000 pregnancies) and of 0.5% in patients with known valvular or congenital heart disease. The incidence of infective endocarditis is higher in IV drug addicts. Patients with a prosthetic valve or prosthetic material used for cardiac valve repair or history of previous infective endocarditis and some patients with complex congenital heart disease have the highest risk for infective endocarditis.

Prophylaxis for Infective Endocarditis

Now, prophylaxis for infective endocarditis is only recommended for patients at highest risk of acquiring endocarditis during high risk procedures, e.g. dental procedures. Given the lack of convincing evidence that infective endocarditis is related to either vaginal or caesarean delivery, antibiotic prophylaxis is no more recommended during vaginal or caesarean delivery. Although the ESC and ACC/AHA (American College of Cardiology/American Heart Association) recommend that antibiotic prophylaxis is not required in any cardiac condition during vaginal or caesarean delivery. This has not been widely accepted in the Indian scenario and prohylaxis for infective endocarditis is still a common practice especiallyfor those with a prosthetic valve, a history of infective endocarditis, cyanotic congenital heart disease and cardiac transplant recipients with valvulopathy. Antibiotics are also used in rheumatic valvular conditions, though there is insufficient evidence for benefit. Penicillins, cephalosporins and macrolides are common choices.

Myocardial Conditions

The myocardial conditions most commonly seen during pregnancy are peripartum cardiomyopathy (PPCM) and ischemic heart disease. In the majority of these cases, the maternal and fetal prognosis is guarded.

Peripartum Cardiomyopathy

Obstetricians should be familiar with this form of heart failure, which is intimately related to pregnancy. This disease occurs in 1:300 to 1:4000 pregnancies.[18,19] 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 upto 5 months after delivery, and hence the name ‘peripartum cardiomyopathy’ is being used more frequently. Peripartum cardiomyopathy is responsible for an increased proportion of maternal deaths, particularly in black women.[20] 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 haemodynamic 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.[21] This hypothesis is supported by investigations demonstrating evidence of myocarditis in heart biopsies of a high number of patients with PPCM.

The diagnostic criteria for postpartum cardiomyopathy are as follows[22]:

- Development of heart failure in the last month of pregnancy or up to 5 months postpartum.
- Absence of an identifiable cause for the cardiac failure.
- No recognizable heart disease before the last month of pregnancy.
- Left ventricular systolic dysfunction shown by echocardiographic criteria.

The majority of patients with PPCM are 20–35-year olds 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 tales, 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 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 myocardial biopsy indicates myocarditis and there is no improvement after 2 weeks of standard therapy, but is currently not recommended.[23] The prognosis for these patients is guarded and is especially poor in those with low left ventricular ejection fraction. Patients who have dilated heart 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 the 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.[24] 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.[25] 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 counselling about pregnancy in women with apparent recovery of left ventricular function.

Ischemic Heart Disease

Acute coronary syndromes (ACS) including unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction, (STEMI) are a group of conditions characterized by severe myocardial ischemia due to a demand-supply mismatch. In nonpregnant individuals, the most common underlying pathophysiology is rupture of a vulnerable atherosclerotic plaque with platelet adhesion, aggregation and total or sub-total occlusion of a major epicardial coronary artery. The occurrence of ACS during pregnancy is rare—with an incidence of approximately 3–6 per 100,000 deliveries. Today, women often opt for pregnancy at a later age and have associated risk factors for coronary artery disease (CAD) including hypertension, diabetes mellitus, hyperlipidemia, older age, smoking and positive family history. Therefore, it is important for obstetrician to be aware of the possibility of occurrence of ACS during pregnancy. Other conditions that contribute to ACS risk are preeclampsia, thrombophilia, postpartum infections, and severe postpartum haemorrhage. Pregnancy-related ACS can occur during all stages of gestation. Unlike nonpregnant patients, the commonest cause of STEMI during pregnancy is spontaneous coronary artery dissection. This is mostly reported around delivery or in the early postpartum period.[26-29] High progesterone levels may lead to structural changes in the collagen of the vessel wall causing dissection. Ergometrin may lead to coronary vasospasm and ischaemia. Coronary artery dissections and thrombi occur more frequently in the peripartum period. Acute MI carries a substantial risk for mother and fetus[30] with a reported maternal mortality of 35%. A more recent large series[27] reported 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 detection of elevated serum levels of markers of myocardial necrosis (troponins and others). Most of the cases occur in the third trimester when the risk of death is high, rather than in the second or first trimesters. Death occurs more frequently immediately following the MI or within the first 2 weeks following the event. 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. Coronary angiography with the possibility of percutaneous coronary intervention (PCI), that is intention to treat is preferred over fibronolytic therapy, as it will also diagnose coronary artery dissection. Potential damage can occur to fetus especially in the first trimester. Thrombolytic therapy may induce bleeding complications like subplacental bleeding, hence it should be reserved for those patients of STEMI with no access to PCI.[31]

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.[32] 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 coarctation. 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 labour. It is possible that vaginal delivery under epidural anaesthesia has equal results.[32,33] Management during pregnancy consists of frequent monitoring to detect the development of hypertension and delivery when this diagnosis is confirmed.

Eisenmenger Syndrome

Patients with Eisenmenger 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 syndrome is very poor. Maternal mortality is approximately 20–50% and total fetal wastage is also high.[15] Despite the best medical and obstetrical care, these patients often die in the postpartum period from irreversible cardiovascular collapse.

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 syndrome. Epidural narcotics can be used for pain relief during labour. To maintain SVR 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 in hospital for bed rest and monitoring, 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 anaesthesia may be used for pain control during labour.

Marfan Syndrome

Patients with Marfan syndrome have mutations in the Fibrillin-1 gene that encodes major constituent proteins of microfibrils which form a significant component of the extracellular matrix. This abnormality is manifested in 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 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 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 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 syndrome contemplating pregnancy should have a preconceptional echocardiogram to determine the diameter of the aortic root. If it is greater than 40–45 mm, she is at significant risk for aortic dissection and she should be offered surgery.[34] 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 favourable 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 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 left pleural effusion. Cardiac MRI is an excellent modality for diagnosis—it gives all the necessary anatomic information while obviating the need for radiation which are inherent in CT scanning or aortography.

Patients with aortic dissection should be treated and stabilized in an intensive care unit before having corrective surgery. Pharmacologic treatment is directed towards 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 haemodynamic changes of pregnancy.

One of the arrhythmias that the obstetricians occasionally observe is paroxysmal supraventricular tachycardia (PSVT). PSVT 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 ECG will show narrow QRS complexes. In 90% of the cases, the etiology of the PSVT is atrioventricular node re-entry. To convert a haemodynamically stable patient with PSVT to a normal sinus rhythm, the first treatment is carotid sinus massage. The right carotid sinus should be massaged first for about 10 seconds. If there is no response, it should be attempted on the left side for another 10 seconds. The two sinuses should never be massaged simultaneously. The patient may attempt a Valsalva manoeuvre 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, one can give 12 mg IV after 1–2 minutes. The 12 mg dose may be repeated if necessary. Intravenous metoprolol or calcium channel blockers like diltiazem or verapamil are recommended if adenosine fails to terminate the tachycardia. Antiarrhythmic drug therapy should be used only if symptoms are intolerable or if the tachycardia causes haemodynamic compromise. Cardioversion is necessary if there is evidence of haemodynamic instability.

Atrial fibrillation and atrial flutter may often occur in pregnant patients with mitral valve disease. Antithrombotic therapy is recommended for all pregnant women with atrial fibrillation. The type of therapy should be chosen with regard to the stage of pregnancy. Unless atrial fibrillation is known to be of new onset, most patients are candidates for ventricular rate control with digoxin, calcium channel antagonist or beta blocker. Direct current (DC) can be performed without fetal damage in women who become haemodynamically unstable because of atrial fibrillation. Administration of quinidine or procainamide may be used for cardioversion in pregnant women with atrial fibrillation who are haemodynamically stable (ACC/AHA recommendation Class IIbC).[35]

Ventricular tachycardia is rare but may be a consequence of ischemic heart disease or cardiomyopathy. The treatment depends on the rate of tachycardia and the haemodynamic status of the mother. Electrical cardioversion should be performed if there is haemodynamic compromise.

INDIAN PERSPECTIVE

After hypertensive disorders, valvular heart diseases are the commonest group of cardiac diseases complicating pregnancy. In a large study by Sawhney et al, maternal and perinatal outcome was reviewed in 486 pregnant patients with rheumatic heart disease; out of which 304 patients (63.3%) had single valve involvement and mitral stenosis was the most predominant lesion (89.2%), 171 patients (38.6%) had undergone surgical correction before pregnancy, 113 patients (22.6%) were identified as NYHA class III–IV. Forty eight patients underwent percutaneous balloon mitral valvotomy. There were 12% preterm birth and 18.2% small for gestational age newborns in above patient subgroup. Mortality occurred in 10 patients, of which 8 patients were NYHA III and IV.[36]

Although the incidence of acute rheumatic fever is on the decline, we still have a large pool of women with established rheumatic valvular heart disease in the child-bearing age group. Early diagnosis, preferably before planning pregnancy, is crucial in helping minimize further complications and morbidity. It is especially vital to diagnose mitral stenosis—the commonest rheumatic valvular lesion. Severe mitral stenosis with symptoms or with significant pulmonary arterial hypertension can be relieved with percutaneous balloon mitral

TABLE 16.7 Outcome of BMV in Pregnant Patients[38-41]

Author	Year	Number of Patients	Fluoroscopy Time (min)	Average Increase in MVA (cm^2)	Success No. (%)
Karla et al	1994	27	5.6	-	26 (96.2)
Kore et al	1996	20	3.6	0.9	20 (100)
Mishra et al	2001	85	3.6	1.25	80 (94)
Khadse et al	2002	53	2.9	0.7	49 (92)
Algotkar et al	2004	52	4.2	0.8	50 (96)
Pratibha et al	2009	25	-	0.9	25 (100)

valvotomy (PBMV) during the second trimester. When performed on patients with suitable valve morphology, PBMV is a very safe and effective procedure, as seen from the studies summarized in Table 16.7. PBMV is performed in the catheterization laboratory with shielding of the mother's abdomen. Studies have shown that there are no significant deleterious effects on the fetus with this procedure (Table 16.7).

There is scant data regarding the outcomes of pregnant patients with congenital heart disease (CHD) from the Indian subcontinent. A retrospective analysis of 196 pregnant patients with CHD was undertaken by Agarwal et al. They compared maternal and perinatal outcome of pregnancy in cyanotic and acyanotic congenital heart disease cases and between surgically corrected and uncorrected cases. It was concluded that maternal and perinatal outcome was better in the acyanotic group; maternal complications included a higher incidence of cardiac complications in the cyanotic group (33.3% vs 3.4% in the acyanotic group, P = 0.001), abruption (12.5% vs nil) and pregnancy-induced hypertension (16.6% vs 5.2%). Fetal complications, which included rate of prematurity (25% vs 11.6%), intrauterine growth retardation (50% vs 15.1%, P = 0.003) and abortion (4.1% vs 2.1%) were higher in cyanotic group. Corrected group showed better mean gestational age than the uncorrected group (37.3 vs 34.93 weeks, respectively). Infective endocarditis was not found in any of the patients. Maternal mortality was seen in four cases in the cyanotic group, two of which were in women with Eisenmenger syndrome. In acyanotic heart disease, one case died undelivered and one died on first postoperative day.[37]

The management of individual valvular lesions has been discussed separately. Additional issues in managing cardiac disease in pregnancy in the Indian context include lack of access to specialized cardiac care, noncompliance with medication, difficulties in monitoring patients and the occurrence of pregnancy in complex uncorrected congenital heart diseases. Careful history taking and clinical examination remains the key to diagnosing heart disease early. A multispeciality team approach in institutions experienced in caring for such patients should help considerably in reducing the impact of cardiac disease on the mother and fetus.

Important Points

- In normal pregnancy, circulation is hyperdynamic. There is a high cardiac output and decreased peripheral and pulmonary vascular resistance.
- The increase in intravascular 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.
- The haemodynamic changes that occur during normal pregnancy increase the cardiac work. This effect may exceed the functional capacity of an ailing heart.
- The danger of cardiac decompensation during pregnancy is greater between 28 and 32 weeks, when the haemodynamic changes of pregnancy peak, but is also increased during labour and delivery and in the postpartum period.
- 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.
- The pregnant cardiac patient should have effective pain relief during labour and should labour in the lateral supine position. In the majority of cases, the anaesthesia of choice is epidural blockade administered by an experienced obstetric anesthesiologist.
- The most frequent fetal complications in patients with heart disease are preterm birth and growth restriction.
- Almost all cardiac patients in labour should be kept dry and their IV fluids restricted to be not more than 75 cc/hour. An exception to this rule is the patient with aortic stenosis.
- The principal measures in the management of the pregnant patient in CHF are (a) decreased the cardiac work with bed rest, (b) decrease the preload with diuretics, (c) improve the cardiac contractility with digitalis and (d) reduce the after load with vasodilators.

- 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.
- Patients with Marfan 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.
- 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 ventricle 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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Chapter 17

Other Medical Disorders in Pregnancy

Ameya C. Purandare and Kaizad R. Damania

Chapter Outline

DERMATOLOGICAL DISORDERS IN PREGNANCY

Dermatological disorders in pregnancy can be classified as follows:

- Physiologic skin changes in pregnancy
- Pre-existing skin diseases affected by pregnancy
- Pruritus in pregnancy
- Dermatoses in pregnancy

Correct diagnosis is therefore essential for appropriate treatment.

Physiologic Skin Changes in Pregnancy

Endocrine and metabolic changes during pregnancy result in various skin changes. These include pigmentary changes like hyperpigmentation and melasma, vascular changes like spider angiomas, palmar erythema, nonpitting edema, varicosities and stretch marks (striae gravidarum). These changes are not associated with any maternal or fetal risk and resolve postpartum.

Most common hyperpigmentation is darkening of the lineaalba called lineanigra. Melasma (cholasma or mask of pregnancy) is seen in about 70% of pregnant women.[1] The malar pattern is usually common; however, usually the central face is affected called centrifacial pattern. It occurs due to melanin deposition and worsens with exposure to visible and UV light. It may recur in subsequent pregnancies or with use of oral contraceptive pills. The epidermal form of melasma is more responsive to treatment as compared to the dermal form. Mild cases can be treated with azelaic acid. Persistent melasma can be treated postpartum with topical hydroquinone (2–4%) and a broad-spectrum sunscreen, with or without a topical retinoid and mild topical steroid.[2] About 30% of the

cases are resistant to treatment. Chemical peels and laser treatment has been useful in some cases of postpartum.

Pre-existing Skin Diseases Affected by Pregnancy

Pre-existing skin diseases usually aggravate during pregnancy, however some improve in pregnancy. Those which may improve include acne, atopic dermatitis, autoimmune progesterone dermatitis, chronic plaque psoriasis, hidradenitis suppurativa, rheumatoid arthritis and sarcoidosis.

Eczema (Atopic Dermatitis)

Eczema is the most common dermatosis seen in pregnancy. It usually persists, but remission has been noted in about 25% of cases. There is usually a personal or family history present. Smoking can be a causal factor.[3] There are no adverse fetal effects noted. It is usually treated with moisturizers and low- to midpotency topical steroids. In severe cases, oral steroids may be required. In the presence of infection, erythromycin or penicillin are to be given. In cases with severe pruritus, systemic antihistaminics may have to be started. UVB light is a safe adjunct in chronic cases.[4] Nipple eczema may be associated with painful fissures and bacterial infection.

Acne Vulgaris

Pregnancy has an unpredictable effect on acne. Some patients may develop acne first time during pregnancy, while some may show both worsening and improvement during pregnancy. Comedonal acne is treated with benzoyl peroxide, while inflammatory acne is treated with azelaic acid, topical erythromycin or clindamycin or oral erythromycin. All these medications are safe during pregnancy.[4]

Psoriasis

Chronic plaque psoriasis is the most common type of psoriasis in pregnancy. It usually improves during pregnancy but worsens postpartum. Localized psoriasis is treated with topical steroids and topical tacrolimus. In nonresponding cases, UVB is the safest treatment. A short course of cyclosporine may be used in those not responding to UVB.[5]

Generalized pustular psoriasis (impetigo herpetiformis) is a rare variant seen in pregnancy. It is usually associated with low serum calcium and vitamin D levels.[6] It is usually noted in the third trimester and persists for long periods after delivery. It usually occurs as a group of discrete sterile pustules at the periphery of erythematous patches. These lesions are noted all over the body sparing the face, hands and feet. They may become crusted or vegetative.[7]

Histopathology shows features of pustular psoriasis, and direct immunofluorescence is negative. Leucocytosis, elevated ESR, hypocalcaemia and lowered vitamin D levels are detected.

It is treated with systemic steroids like prednisone (maximum dose: 60 mg/day). Calcium and Vitamin D replacement helps in remission. UVB and cyclosporine are to be used as second line therapies.[8] Systemic antibiotics should be started in the presence of super infection.

Maternal risks include tetany, seizures, delirium, renal failure and cardiac failure. Fetal risks include still birth and IUGR probably because of the chronic inflammatory state. Maternal monitoring of BP, cardiac and renal function should be strictly done. Fetal surveillance for IUGR should be instituted.

Only in those patients not responding to the earlier mentioned treatments, termination of pregnancy may be resorted to as the eruption resolves promptly afterward. Generally, the lesions resolve postpartum, but recur earlier and in more severe forms in subsequent pregnancies.

Malignant Melanomas

Melanomas that develop during pregnancy are thicker and may be due to delayed diagnosis. Prompt staging and excision should be performed for definitive management. Chemotherapy may be used after the first trimester with low risk of fetal anomaly. The placenta should be biopsied for occasional metastasis.[9] The major prognostic determinants of survival are tumour thickness (Breslow scale) and ulceration status.[10] The waiting period to become pregnant after diagnosis of melanoma is to be individualized. Specialized opinion should be obtained and a multidisciplinary team approach is recommended.

Pruritus in Pregnancy

Pruritus has been noted in about 20% of pregnancies. Since it is associated with a variety of conditions, a clinical and laboratory workup is helpful in reaching a diagnosis and starting the appropriate treatment. The various causes of pruritus in pregnancy and the management options are enumerated in Table 17.1 and Table 17.2, respectively.

Specific Dermatoses of Pregnancy

These are defined as those dermatoses that are predominantly encountered during gestation or in puerperium and result directly from the state of gestation or the products of conception.

Pemphigoid (Herpes) Gestationis

It is a rare autoimmune bullous disease of pregnancy and puerperium. It usually develops after midpregnancy; initially, the lesions are severally pruritic and abdominal in location. This is followed by a rapid generalized bullous eruption. Usually, these lesions flare at the time of delivery.

TABLE 17.1 Causes of Pruritus in Pregnancy

Intrahepatic cholestasis of pregnancy
Pre-existing skin diseases
Specified dermatoses of pregnancy
Systemic diseases with skin involvement
Allergic reactions
Drug eruptions
Pruritus associated with striae gravidarum
Viral hepatitis
Hyperemesis gravidarum

The disease resolves spontaneously in the postpartum period but it may take a long duration for the same. Recurrence in subsequent pregnancies is frequent and occurs earlier and in more severe forms.[11]

Histopathology of the lesions shows a spongiotic epidermis, marked papillary edema and many eosinophils. Immunofluorescence shows presence of C3 and IgG.[12] Genetic factors predisposing the occurrence of this condition is justified with the association with HLA-DR3 and HLA-DR4.[13] There may strangely be a paternal role in its occurrence.

Graves' disease may be associated with this condition. Neonatal vesiculo bullous lesion may be noted in 10% of cases due to transplacental transfer of antibodies. These eruptions are mild and resolve spontaneously in a few weeks without any treatment.

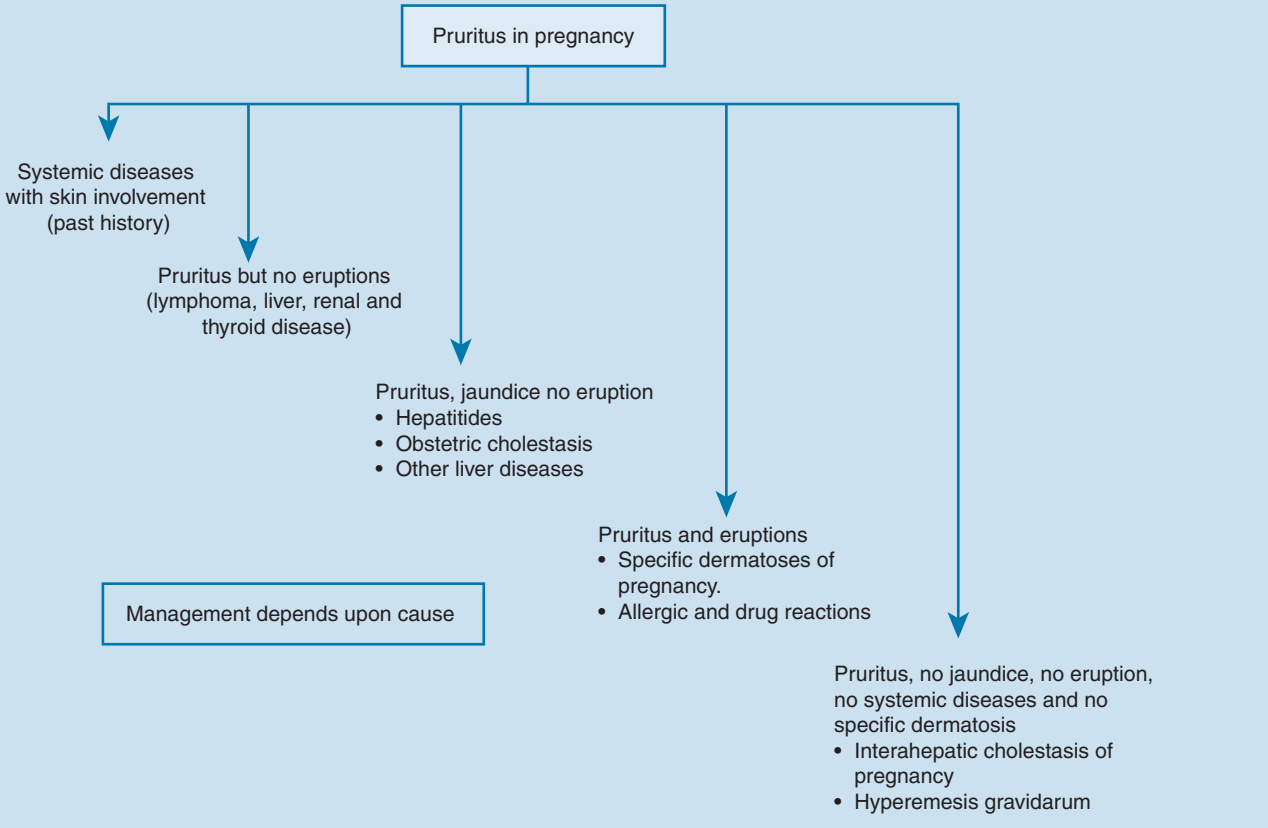
Early urticarial lesions are treated with topical steroids with or without oral antihistaminics. However, most cases will require and respond to oral steroids. If oral steroids fail, then plasmapheresis may be needed. Cyclosporine and IVIG may be beneficial.[14] Immunosuppressants can be an option in postpartum nonlactating mothers.

IUGR may occur in a few cases and fetal surveillance should be initiated and continued. After birth, the neonate should be assessed for neonatal lesions.

Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP)

PUPPP is the most common specific dermatoses of pregnancy. Incidence is about 1 in 240 pregnancies. It occurs frequently in primigravidas in the third trimester. PUPPP

TABLE 17.2 Pruritus in Pregnancy



occurs mainly in male fetuses. Recurrence in subsequent pregnancies is uncommon.[15]

The lesions usually begin in the abdominal striae with umbilical sparing. The lesions are polymorphous. At times, they are urticarial, vesicular and purpuric. Lesion then spread over the trunk and extremities but spare the palms and soles. Resolution is usually accompanied by hyperpigmentation.

PUPPP is primarily a clinical diagnosis, as specific laboratory or histopathological features are absent. The precise etiopathogenesis is unknown. One hypothesis is that it is due to the rapid abdominal wall distention that causes an inflammatory process, resulting in a delayed hypersensitivity reaction. PUPPP is about 10 times more common in multiple gestations. Usually PUPPP is not associated with any maternal or fetal risks.[16]

Mild cases of PUPPP are treated symptomatically with topical antipruritic medications and topical steroids. Oral histaminics may be added. Refractory cases may require oral steroids. Recent studies have shown resolution with cesarean section, probably this may be discussed with patients with severe and refractory lesions.[17]

Prurigo of Pregnancy

Prurigo of pregnancy affects between 1 and 300 pregnant females. It begins usually around 30 weeks of gestation. It is usually located on the extensor surfaces of the extremities as groups of excoriated or crusted papules. It usually resolves immediately after delivery and is then seen as hyperpigmented lesions. Sometimes, nodular lesions are seen.[18]

No consistent maternal or fetal risks are confirmed. It is usually closely associated with obstetric cholestasis and family history of atopic dermatitis.[18]

Symptomatic treatment is usually given in the form of moderately potent topical steroids and oral antihistaminics.

Pruritic Folliculitis of Pregnancy

This is a rare but specific dermatoses of pregnancy. It usually develops as pruritic follicular erythematous papules and pustules that are mainly distributed over the trunk. The condition develops in the last two months of pregnancy and resolves immediately after delivery. It is associated with low-birth weight, but no maternal risks.

The exact etiology is unknown and culture and special stains should be performed to rule infectious folliculitis. Topical benzoyl peroxide, low or mild topical steroids and UVB can be tried.[19]

AUTOIMMUNE DISEASES IN PREGNANCY

Autoimmune diseases are most common in women of reproductive age, hence they are commonly encountered during pregnancy.[20] Therefore, the obstetrician should know about their effects on pregnancy and vice-versa and the therapeutic options available for optimizing maternal and fetal outcome.

Systemic Lupus Erythematosus (SLE) in Pregnancy

SLE is an idiopathic, chronic inflammatory disease that affects the skin, joints, kidneys, lungs, serous membranes, liver, CNS and other systems of the body. Its course is characterized by phases of remission and relapse. It is almost 10 times more common in women than men.[20] SLE is known to have a familial predisposition and has been linked to alterations in the HLA system.

The clinical features in SLE are multisystemic and range from fatigue, fever, arthralgia, myalgia, weight loss, skin rashes, lymphadenopathy, nephropathy, effusions (pleural and pericardial), seizures and psychosis.

Diagnosis

SLE is suspected by clinical features and confirmed by serological markers indicating the presence of autoantibodies. The American College of Rheumatology devised criteria for SLE, which was last revised in 1997 as enumerated in Table 17.3.[21] To be classified as SLE, patients must have at least 4–11 clinical and laboratory criteria at one time or seriously. However, many patients may have less than four features of SLE, hence do not meet the criteria and are said to have lupus-like disease.

SLE and Pregnancy

SLE Exacerbation (SLE Flare)

Whether pregnancy results in increasing frequency of SLE flares is debatable. This is because preeclampsia may mimic SLE flares. The rate of flares during pregnancy or postpartum varies between 15% and 60%. Increase risk of flare is noted in women with active prepregnancy disease and in those who discontinue medication during pregnancy.[23]

Lupus Nephritis in Pregnancy

Women with lupus nephropathy may worsen during pregnancy. This in turn may increase risk of maternal and fetal complications. There may be increased proteinuria in patients with chronic renal failure. Pregnancy is favourable if the disease is well controlled prior to pregnancy and renal function is preserved. Overall, about one-third of women with lupus nephritis experience SLE exacerbation during pregnancy and 20% experience some form of renal deterioration. Permanent deterioration is noted in about 7% of patients. Pregnancy should be avoided in patients with active lupus nephropathy, nephrotic syndrome and severe hypertension. Presence of renal failure is an absolute

TABLE 17.3 Revised American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring possible in order lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion.
6. Serositis	a. Pleuritis - convincing history of pleuritic pain or rubbing heard by a physician, or evidence of pleural effusion b. Pericarditis - documented by ECG or rub or evidence of effusion
7. Renal	a. Persistent proteinuria > 0.5 g/day or > 3+ if quantitation not performed b. Cellular casts - red cell, haemoglobin, granular, tubular or mixed. Cellular casts-red cell, haemoglobin, granular, tubular or mixed.
8. Neurologic	a. Seizures in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis or electrolyte imbalance) b. Psychosis in the absence of drugs or metabolic derangements
9. Hematologic	a. Hemolytic anaemia with reticulocytosis b. Leucopenia <4,000/μL on two or more occasions
10. Immunologic	a. Anti-DNA - antibody to native DNA in abnormal titer b. Anti-Sm - presence of antibody to Sm nuclear antigen c. Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method or (3) a false-positive serologic test for syphilis for 6 mo
11. ANA	An abnormal ANA titer by immunofluorescence or an equivalent assay at any time in the absence of drugs known to be associated with 'drug-induced lupus' syndrome

*SLE can be said to be present if four or more of the criteria are present simultaneously or serially.
ANA, antinuclear antibody; ECG, electrocardiogram; Ig, immunoglobulin
From Tan EM, Cohen AS, Fries JF, et al: The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271–77; and Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.[22]

contraindication to pregnancy.[24] Differentiating factors between preeclampsia and SLE are described in Table 17.4.

Obstetric Complications of SLE in Pregnancy[25]

Preeclampsia

The exact incidence of preeclampsia in SLE is not known. Approximately, 20–30% of women with SLE develop either gestational hypertension or preeclampsia sometime during pregnancy. Important predisposing factors include lupus nephritis, chronic hypertension, APLA syndrome and chronic steroid use.

Pregnancy Loss

The rate of pregnancy loss is about 20% in women with SLE. Pregnancy loss is more likely if SLE is present in the index pregnancy and there is pre-existing as well as active renal disease. The presence of antiphospholipid antibodies is the strongest predictor of subsequent pregnancy loss in pregnancies with SLE. Stringent prepregnancy control and aggressive antepartum fetal surveillance helps in reducing pregnancy loss.

Preterm Birth

Preterm birth is common in pregnancies with SLE. The presence of aPLs, chronic hypertension and disease activity increase the risk of preterm birth in women with SLE. Common causes of preterm birth are pregnancy terminations due to preeclampsia, fetal distress and rarely PROM.

IUGR

IUGR occurs in SLE due to development of uteroplacental insufficiency. SLE patients receiving prophylactic glucocorticoids during pregnancy are more likely to develop IUGR. Other factors that lead to IUGR are real failure and hypertension.

Neonatal Lupus[26-28]

It is a rare condition, occurring in about 20,000 of all live births and in less than 5% of all women with SLE.

TABLE 17.4 Differentiating Preeclampsia and Systemic Lupus Erythematosus/Lupus Nephropathy Flare

Test	Preeclampsia	SLE
Serologic		
Decreased complement	++	+++
Elevated Ba or Bb fragments with low	±	++
CH50	−	+++
Elevated anti-ds DNA	++	+
Antithrombin III deficiency		
Hematologic		
Microangiopathic hemolytic anemia	++	−
Coombs' positive hemolytic anaemia	−	++
Thrombocytopenia	+	++
Leukopenia	+	+++
Renal		
Hematuria	—	+++
Cellular casts	±	++
Elevated serum creatinine	+	++
Elevated ratio of serum blood urea nitrogen/creatinine	±	++
Hypocalciuria	++	±
Liver transaminases	++	+

Lupus dermatitis is a most common feature and is seen on the face or scalp. Lesions appear in the first few days of life and may resolve after 6 months. Hematologic neonatal lupus is rare and may result in autoimmune hemolytic anaemia, leucopenia, thrombocytopenia and hepatosplenomegaly.

Cardiac lesions in neonatal lupus include congenital complete heart block and rarely endocardial fibroelastosis. It is due to disruption of the electro conductive system in the region of the AV node. Diagnosis is made when persistent fetal bradycardia (FHR: 60–80 bpm) with complete AV dissociation in a structurally normal heart is noted on fetal 2D Echo. This occurs due to the presence of anti-RO/SS-A and anti-LA/SS-B antibodies that cross the placenta and cause damage to the myocardium and conduction system of the fetal heart. Fetal mortality rate is about 20% and is due to cardiac failure and hydrops. In mild cases, neonatal pacemaker insertion may be needed for survival.

Management of SLE

SLE should be controlled prior to pregnancy by adjusting the dose of the maintenance medications. Azathioprine and cyclophosphamide should be preferably stopped if possible. Methotrexate should be avoided. Hydroxychloroquine can be continued.[29] Laboratory investigations should be performed to look for anaemia, thrombocytopenia, renal dysfunction and antiphospholipid antibodies. Patient should be informed about the risk of flares, preeclampsia and fetal compromise.

A multidisciplinary team should manage SLE during pregnancy. Antenatal care should begin early. Frequent antenatal visits every fortnight in the first and second trimester and weekly in the third trimester should be advised. Early dating USG should be performed. Strict monitoring aimed at SLE flares, preeclampsia and IUGR should be continued throughout pregnancy. For lupus nephritis patients, baseline 24 hrs urine creatinine clearance and total proteins should be assessed and repeated as required.

Hydroxychloroquine is effective and safe for treating SLE in pregnancy. It is found to be more beneficial than steroids as maintenance therapy. Its use is known to reduce the SLE disease activity to a greater extent than steroids. No birth or developmental defects have been noted.[29]

Glucocorticoids are most commonly administered to SLE patients in pregnancy. They are used for maintenance therapy and 'in bursts' to treat suspected SLE flares. The dosages remain the same as those used in nonpregnant states, but can be reduced in cases of remission. They should be used in patients with active disease. Usually, prednisolone or methyl prednisolone is used. Maternal side effects of steroid therapy are weight gain, striae, ache, hirsuitism, immunosuppression, GI ulcers and osteoporosis. Additionally, adverse obstetric outcomes encountered are preeclampsia, placental insufficiency, IUGR and glucose intolerance.

NSAIDs readily cross the placenta and aspirin can cause intracranial bleeds in preterm infants. Indomethacin is safe for short-term use, but if used after 32 weeks can lead to premature closure of fetal ductus arteriosus, oligohydramnios and neonatal renal failure. Hence aspirin and other NSAIDS should not be used chronically in pregnancy. Acctoaminophen may be an acceptable analgesic in pregnancy.[30]

Azathioprine and cyclophosphamide are only to be used if steroids are ineffective. Methotrexate should be avoided. Fetal growth and well-being should be assessed using USG every 3 weeks till delivery; 18–20 weeks scan to rule out malformations in the fetus is imperative.

Fetal surveillance should be generally initiated at 30–32 weeks. However, it may be advised earlier in patients with worsening disease or previous fetal loss.

SLE patients should be delivered at term. Postdatism should be avoided. Throughout labour fetal monitoring should be continuous. IV glucocorticoids should be given in patients receiving maintenance therapy or 'steroid busts' during pregnancy.

Postpartum SLE flares should be looked for. Maintenance therapy is to be restarted as before. Neonatal lupus should also be looked for. Maternally administered dexamethasone (4 mg) daily or IVIG may be useful in fetal heart blocks.

Management of SLE Flare in Pregnancy

Starting glucocorticoids or increasing their dosage treats mild to moderate SLE flares without renal or CNS involvement.[31] Prednisolone (15–30 mg/day) results in improvement. For severe exacerbations without renal or CNS involvement,

prednisolone 1–1.5 mg/kg/day in divided doses should be started and continued for about 10 days to achieve optimal response. After this, the steroids may be tapered gradually.

Severe exacerbations involving CNS or kidneys are to be treated aggressively. Initially, a daily IV dose of methylprednisolone 10–30 mg/kg for 5 days should be administered. Thereafter, the patient is to be treated with 1–1.5 mg/kg/day of prednisone in divided doses and rapidly tapered over 1 month. Most patients respond favourably to this regimen.

In nonpregnant patients, azathioprine and cyclophosphamide is effective severe cases of SLE. However, they are not to be used in pregnancy due to their adverse effects and proven teratogenicity. Plasmapheresis and IVIG are only reserved to treat severe cases of SLE flare refractory to standard therapy.[32]

Antiphospholipid Antibody Syndrome in Pregnancy

APS is syndrome characterized by thrombosis or fetal loss in association with presence of lupus anticoagulant (LA) or anti cardiolipin antibodies. Important obstetric criteria include recurrent pregnancy loss, fetal death, severe preeclampsia or placental insufficiency requiring delivery prior to 34 weeks gestation.

Antiphospholipid Antibodies[33]

The primary clinically relevant epitope for aPLs is on β2-glycoprotein I. This glycoprotein has regulatory roles in coagulation and fibrinolysis. The clinical assayed antibodies are summarized in the following Table 17.5.

TABLE 17.5 Types of Anti-Phospholipid Antibodies

Lupus anticoagulant
Screening with two phospholipid dependent, in vitro clotting assays using patient's platelet-poor plasma. The assays most commonly used are the activated Partial Thromboplastin Time (aPTT, which tests the intrinsic coagulation pathway) and the diluted Russel Viper Venom Time (dRVVT, which tests the final common pathway)
If either of the above is prolonged, the test is repeated with a mix (usually 1:1) of patient and normal platelet-poor plasma. If mixing studies do not correct the prolonged clotting time(s), lupus anticoagulant is suspected.
Lupus anticoagulant is confirmed by demonstrating marked shortening or correction of the prolonged clotting time after addition of excess phospholipids. If the confirmatory test is negative or equivocal, additional tests may be done to investigate other possible coagulopathies or specific factor inhibitors.
Anticardiolipin antibodies
ELISA for IgG and IgM antibodies. The assay used should employ available international calibrators, and results should be reported in GPL and MPL units.
Anti-β_2-glycoprotein I antibodies
ELISA for IgG and IgM antibodies.

Pathogenesis of APS

Pregnancy complications due to APS are due to abnormal placental function. This results in narrowing of the spiral arterioles, intimal thickening, acute atherosis and fibrinoid necrosis.

Additionally, extensive necrosis, infarction and thrombosis are seen in the placenta. aPLs cause endothelial cell activation leading to increased production of adhesion molecules, cytokines and arachidonic acid metabolites.[34] aPLs are also known to produce oxidant-mediated injury of the vascular endothelium. C3 activation and TNF-α release are a part of the signaling pathways resulting aPLs causing fetal loss.[35]

Diagnostic Criteria for APS

Sapporo revised the 1999 International Consensus Statement in 2006 to provide simplified criteria for the diagnosis of APS as enumerated in Table 17.6.[36]

APS in Pregnancy

Thrombotic Complications

Deep vein thrombosis (DVT) and pulmonary embolism have been associated with APLS. Transient ishemic attack (TIA) and cerebrovascular attack (CVA) are the most common arterial events associated with APS. However, venous thrombotic events are more common.[37] APLS should be kept in mind in cases of unexplained thrombosis. The rates of stroke and thrombosis are increased in APS patients especially during pregnancy.

Obstetric Complications

Preeclampsia

Gestational hypertension/preeclampsia occurs in about 30% of APS pregnancies. Preeclampsia usually develops earlier than usual. No therapeutic modality is useful in reducing the rate of preeclampsia. Preeclampsia is usually more severe in APS pregnancies.[38]

IUGR and Preterm Birth

aPLs frequently cause IUGR in almost one in three pregnancies with APS. APS pregnancies are also associated with nonreassuring FHR patterns during antepartum testing and abnormal fetal surveillance tests. Preterm birth rates are high, ranging from 30 to 60% in APS pregnancies.[39]

Pregnancy Loss

APS-related pregnancy loss could be an early recurrent pregnancy loss. Usually it is an embryonic fetal loss. In patients of RPL, about 10–20% have positive aPLs. Prognostically those with prior fetal death and thromboembolism are known to fare worse than those with early recurrent pregnancy loss.[40]

TABLE 17.6 Revised Sapporo Criteria for the Diagnosis of Definite Antiphospholipid Syndrome

APS is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

Clinical Criteria

1. Vascular thrombosis
   One or more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
   a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe preeclampsia defined according to standard definitions or (ii) recognized features of placental insufficiency, or
   c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory Criteria

1. LA present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on Las/phospholipids-dependent antibodies)
2. aCL antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. > 40 GPL or MPL, or >99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-β_2-glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >99th percentile) present on two or more occasions, at least 12 weeks apart, measured by standardized ELISA, according to recommended procedures.

Modified from Miyakis S, Lockshin MD, Atsumi T, et al: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS), J. Thromb Haemost 2006;4:295–306.

Catastrophic APS

It is rare but devastating in pregnancy, characterized by multiple simultaneously vascular occlusions in the body that finally lead to death. The diagnosis is usually confirmed with multiorgan involvement (more than three) showing acute thrombotic microangiopathy of the microcirculation. Renal affection is most common, about 80% with 30% requiring dialysis. Hypertension is usually present.[41]

Other common clinical manifestations include ARDS, DIC, myocardial microthrombi, CNS microthrombi and skin lesions.

Multiorgan failure usually results in death in half of the patients. The precipitating factors identified include infection, surgery, discontinuation of anticoagulant therapy and use of OCPs.

Early and aggressive treatment in a critical care unit is essential. Hypertension should be controlled. Combination of heparin and steroids plus either IVIG or plasmaphresis has been successful in some patients. Those with acute vascular thrombosis should be treated with streptokinase or urokinase. Early delivery is advised in patients with catastrophic APS.[41]

Treatment of APS in Pregnancy

The primary goals of treatment of APS in pregnancy are as follows:

- Optimizing perinatal outcome by reducing the risk of pregnancy loss, placental insufficiency, preterm delivery and preeclampsia.
- To reduce the risk of thrombosis in the pregnant lady.

Women with recurrent miscarriage and APS should be treated with heparin 5000 U S.C. twice daily and low dose aspirin as per the 2005 Cochrane Systematic Review.[42] Favourable pregnancy outcome is accomplished when heparin is started on noting cardiac activity in the fetal pole on USG in the early first trimester as favourable results were seen in the HepASA Trial.

The various heparin regimens are listed in the following Table 17.7.

APS pregnancies with thrombosis or those with prior preeclampsia should be given thromboprophylaxis in the postpartum period for at least 6 weeks by starting warfarin.

Other medications used are corticosteroids and IVIG. Usually, prednisone and low dose aspirin have been used in combination and 70% success rate achieved in affected pregnancies. IVIG alone or in combination with heparin has been tried. However, an increased of pregnancy loss and preterm delivery has been reported with IVIG, hence IVIG is not recommended in the treatment of APS in pregnancy.[42]

Management Strategies in Women with APS

In women with APS, prepregnancy levels of aPL should be estimated. The various maternal, obstetric and risks of heparin therapy should be explained to the patient.

The various risks that can be encountered in an APS pregnancy are summarized in Table 17.8.

TABLE 17.7 Suggested Subcutaneous Heparin Regimens for the Treatment of Antiphospholipid Syndrome in Pregnancy

Antiphospholipid Syndrome without Prior Thrombosis

- Recurrent early (preembryonic or embryonic) miscarriage
  - Unfractionated heparin
    - 5000–7500 U subcutaneously q12h
  - Low-molecular-weight heparin
    - Enoxaparin 40 mg, or Dalteparin 5000 U, subcutaneously once daily, or
    - Enaxaparin 30 mg, or Dalteparin 5000 U, subcutaneously q12h
- Fetal death (>10 wk' gestation) or prior early delivery (<34 wk' gestation) due to severe preeclampsia or placental insufficiency
  - Unfractionated heparin
    - 7500–10,000 U SC q12h in the first trimester; 10,000 U SVC q12h in the second and third trimesters, or
    - Q8–12h adjusted to maintain the midinterval aPTT 1.5 times the control mean
  - Low-molecular-weight heparin
    - Enoxaparin 30 mg, or dalteparin 5000 U, SC q12h

Antiphospholipid Syndrome with Thrombosis

- Unfractionated heparin
  - q8–12h adjusted to maintain the mid interval aPTT or heparin level (anti-Xa activity) in the therapeutic range
- Low-molecular weight heparin
  - Weight adjusted, e.g. enoxaparin 1 mg or Dalteparin 200 U/kg, subcutaneously q12h with monitoring of anti-Xa activity

TABLE 17.8 Risks in an APS Pregnancy

- Thrombosis
- Pregnancy loss
- Preterm delivery
- Preeclampsia
- Uteroplacental insufficiency/ IUGR
- Heparin-induced osteoporosis and thrombocytopenia

Women with APS should immediately report if they miss their periods. An early TVS should be done to confirm and date the intrauterine pregnancy. Anticoagulation should be started as soon as cardiac activity is noted. Calcium should be supplemented and daily exercise should be encouraged.

Visits to the antenatal care clinic should be at least every 2 weeks till 24 weeks and then weekly. Specifically monitoring for preeclampsia, thrombosis and fetal well-being should be performed at every visit. Serial USGs every 3 weeks must be performed assessing fetal growth and looking for IUGR and obligohydramnios.

Antenatal fetal surveillance in the form of daily fetal movement counts, weekly NSTs and AFI measurement should be initiated at 30–32 weeks or earlier.

During labour and delivery, APS patients should be considered as high risk for preeclampsia and uteroplacental insufficiency and hence continuous electronic fetal monitoring is recommended throughout labour.

Anticoagulants dosing should be altered in order to minimize the risk of bleeding during delivery as well as not increasing the risk of thromboembolism. Patients on thromboprophylaxis with heparin should not be given heparin following the onset of labour. In those where labour is to be induced or in cases of planned CS the last dose should not be given 24 hours prior to the procedure. In patients who are fully anticoagulated and if aPTT is prolonged, protamine sulfate should be given to reduce the risk of bleeding.

The American Society of Regional Anaesthesia (ASRA) recommends that needle placement should be withheld until 24 hours after the last injection in women on full anticoagulation with LMWH or adjusted dose of anticoagulation with UFH. However, in those patients on low dose thromboprophylaxis, ASRA has recommended that needle placement be delayed until 12 hours after the last dose.[43]

Anticoagulation should be resumed 6 hours after vaginal delivery and 12 hours after CS. Warfarin should be used for anticoagulation prophylaxis and continued for at least 6 weeks postpartum. Warfarin and heparin are safe during lactation. OCPs containing estrogen are contraindicated.[44]

NEUROLOGIC COMPLICATIONS IN PREGNANCY

Epilepsy in Pregnancy

Epilepsy is the most common neurological complication encountered in pregnancy. The incidence of seizures during pregnancy ranges from 0.15% to 10%. Effect of pregnancy on seizure frequency is a matter of controversy. Overall about one in every three epileptic pregnant patients will show an increase in frequency, while the remainder will show a decrease or no change. However, if epilepsy is under control prior to pregnancy, then there is reduced risk of worsening in pregnancy. Also, the levels of most antiepileptic drug (AED) concentrations are reduced during pregnancy and this may increase seizure frequency.[45]

This alteration is as a result of decreased absorption in the gastrointestinal tract and increased clearance (both renal and hepatic). Albumin levels fall in pregnancy leading to lower total drug levels.[46] These changes reverse back in the postpartum period.

Additionally, the commonly used AEDs (carbamazepine, phenobarb, phenytoin and valproic acid) are known to cross the placenta and hence can affect the fetus. The

rate of congenital malformations in patients taking AEDs is two to three folds greater than in nonepileptic women.[47] Combination therapy is known to increase malformation rates further. Frequently encountered anomalies include mild facial dysmorphology, stubby distal phalanges and hypoplastic fingernails. This is named fetal antiepileptic syndrome. Genetic predisposition may have a role to play in these teratopathies.

Specific AEDs are associated with specific anomalies:

AED	Specific fetal anomaly
Phenytoin	Coagulopathies
Phenobarb	Cleft lip and palate CVS defects Urogenital defects
Valproic acid	Spina bifida Cognitive impairment

Management

Control of seizure and serum AED levels should be monitored regularly. The dose of AEDs should be titrated to achieve seizure control. The serum levels of AED should be noted with the control dose. Toxic doses should be avoided. Folic acid supplementation should be stated preconceptionally.[45]

Detailed fetal anomaly scan should be done between 18 and 20 weeks. If seizures recur, a short acting benzodiazepine should be given. Vitamin K can be given to the mother in the last 4 weeks to minimize the risk of fetal coagulopathy.

AEDs should be continued during labour. Seizures during labour can cause fetal hypoxia. Cesarean section may be needed in refractory status epilepticus.

The newborn should be thoroughly examined for any abnormality. Injection of Vitamin K 1mg should be given to the neonate after birth to prevent coagulapathy. Breastfeeding is not contraindicated. Since all AEDs can cross into breast milk, any signs of neonatal sedation should be looked for.

Combined OCPs, POPs, vaginal ring should be avoided as contraceptives due to their interaction with the AEDs will make both less effective. WHO clearly states that IUCDs or DMPA can be used.

Status Epilepticus (SE)

Seizure activity that is ongoing and lasts for more than 30 min or recurrent seizure without full recovery of consciousness between episodes is defined as status epileptious. First aid measures aimed to avoid injury, maintain airway, administer oxygen should be started immediately. Anticonvulsant drugs like IV Phenytoin or IV Benzodiazepine should be administered immediately to control convulsions. Ventilation and pentothal sodium may be necessary if anticonvulsants fail to control convulsions.[48]

Preterm labour, PROM, abruption placenta, fetal distress and fetal death have been known to occur.

Cerebral Venous Thrombosis

Cerebral venous thrombosis is more likely to occur postpartum (during second and third week in puerperium). It is usually associated with infection and dehydration. Other associated conditions include anaemia, haemoglobinopathies, leukaemia, collagen vascular diseases, AVB, hypercoagulable states and antiphospholipid antibody syndrome.[49]

Presenting clinical features include severe headache, papilledema, seizures, visual disturbances, lethargy, focal neurological deficits and coma. Superior sagittal venous sinus is more commonly involved.

Diagnosis usually requires a high index of suspicion. Imaging study like MRI with venography can identify the thrombus.

Treatment involves adequate hydration, control of seizures and anticoagulant therapy.

Migraine in Pregnancy

Migraines are of two types: with or without an aura. Presence of transient neurologic features before, during or after headache is called an aura. Nausea, vomiting and photophobia accompany the headache. Migraines decrease in occurrence in the third trimester but may worsen postpartum.

Treatment involves avoiding precipitating factors. Nonpharmacological options like bed rest, avoiding light, adequate sleep, ice and massage are highly beneficial. Simple analgesics (e.g. acetaminophen) should be used as first line therapy in the first two trimesters but not third. Narcotics (like morphine) are to be used only in severe cases. Short course of adjuvant glucocorticoids should be used for refractory cases. Ergot preparations and benzodiazepines should be avoided for their adverse fetal effects. In cases of nausea, antiemetics should be given to provide symptomatic relief. Prophylactic therapy includes the use of propanolol and tricyclic antidepressants.[50]

There are no adverse fetal outcomes reported due to migraines in pregnancy.

Besides migraine, the other causes of headache in pregnancy are enumerated in Table 17.9.

RESPIRATORY DISORDERS IN PREGNANCY

Several physiological adaptations occur in the maternal respiratory system during normal pregnancy, which are well tolerated with minimal symptoms.

Mild breathlessness is common during normal pregnancy and hence does not always indicate cardiorespiratory disease. Some level of dyspnea is encountered by almost

TABLE 17.9 Causes of Headache in Pregnancy

Migraine
Preeclampsia
Meningitis, encephalitis
Cerebral haemorrhage
Subarachnoid haemorrhage
Cerebral venous sinus thrombosis
Embolic stroke
Pituitary tumors
Tension type headache
Postdural puncture headache

70% of pregnant women. This is generally described as 'air hunger'.[51] This is usually noticed between 28 and 32 weeks of gestation. This is usually a progesterone-mediated event along with fall in $PaCO_2$.

Asthma in Pregnancy

Asthma is the most common life-threatening chronic medical disease encountered in pregnant women. Prevalence of asthma during pregnancy is increasing and averages about 8% of all pregnant women.[52]

There are conflicting reports about the frequency of asthmatic symptoms during pregnancy, with contrary view of increasing and decreasing frequency of symptoms in pregnancy. However, most reports indicate the prepregnancy severity of asthma predicts its course during pregnancy.

The various risk factors which can cause worsening of asthma during pregnancy are listed in Table 17.10.

Asthma seems to worsen in pregnancy due to the frequent misconception that the treatment of asthma in pregnancy is detrimental to the fetus which affects the patient's compliance of taking medication.

Asthma can adversely affect the ongoing pregnancy several ways as listed in Table 17.11.

However, IUGR does not seem to be caused by maternal asthma. These complications are more likely in severe or poorly controlled asthma. Hence every effort should be made to achieve optimal control of asthma prior to planning a pregnancy.

TABLE 17.10 Risk Factors for Worsening of Asthma during Pregnancy

- Young age
- Unmarried
- Low socioeconomic status
- Poorly controlled/severe asthma prior to pregnancy
- Gastroesphageal reflux disease

TABLE 17.11 Adverse Effects of Asthma on Pregnancy

- Increased risk of preterm delivery
- Increased risk of preeclampsia
- Increased risk of hyperemesis gravidarum
- Increased risk of vaginal bleeding
- Increased risk of complicated labours
- Increased risk of congenital malformations
- Increased risk of asthma in the offspring

Management of Asthma in Pregnancy[53]

Pregnancy

The goal of treatment for asthma in pregnancy is to provide optimal therapy to maintain asthma control, defined as minimal or no chronic symptoms, day or night, minimal or no exacerbations, no limitation of activity, maintenance of normal pulmonary function, minimal use of short acting inhaled B_2 agonists, and minimal or no adverse effects from the treatment provided.

Maintenance medication should be adjusted to optimize respiratory function. Patients need to be educated with respect to use of spacers and PFFR meters. Patient education about continuation of medications during pregnancy is vital. Same drugs to be used as outside pregnancy, that is steroids and β2-agonists. If theophylline is used, increased dose may be required. Peak flow should be monitored and doses adjusted to control symptoms. Inhalation route to be preferred over oral route. Ensure maternal oxygen saturations >95% so as to ensure optimal fetal oxygenation. Chest physician and anesthesiologist to be consulted as required.

Labour and Delivery

Regional anaesthesia is preferable to general anaesthesia. Ensure maternal oxygen saturation is >95%. Avoid PGF2α and methylergometrine. Parenteral 'Stress dose' of steroids to be given in chronic asthmatics.

Postnatal

Continue maintenance drug therapy. Encourage breastfeeding. Advise chest physiotherapy.

Asthma Medications

Asthma medications are classified as either rescue agents or maintenance agents.

Rescue agents are those medications used to treat acute bronchospasm and provide symptomatic relief but do not treat the underlying inflammation. Rescue agents include all the inhaled β2 agonists and ipratropiums.

Maintenance agents are those medications that help to control airway hyperreactivity and generally treat the underlying inflammation of the airway. The inhaled steroids are the keystones of asthma maintenance. Other maintenance agents include systemic steroids, leukotriene antagonists and cromolyn.

The several asthma medications that can be used in pregnancy are tabulated in Table 17.12.

Asthma has to be managed using a stepwise approach in pregnancy as detailed in Table 17.13.

Tuberculosis in Pregnancy

Globally, TB infection continues to be a daunting problem. One-third of the world's population is TB infected with 8 million new cases and 2 million deaths per year due to TB, as per estimates.[55]

Effect of TB on Pregnancy

Incidence and transmission of TB is not altered by pregnancy. Main concerns of management include fetal infection and drug safety. Pregnancy does not alter the clinical course of TB. Fetal risks are mainly related to fetal infection, tetratogenesis with AKT drugs and fetal risks in severe cases of TB. Disseminated TB is associated with adverse outcomes like low-birth weight, preterm delivery and increased perinatal mortality.[56]

Mycobacterium TB rarely crosses the placenta. Therefore, true congenital infection is extremely uncommon. The criteria conclusive of congenital TB are listed in Table 17.14.

The newborn is at high risk of acquiring infection if the mother has a case of 'open Koch's' at the time of delivery.

Management

At risk population should be screened using a tuberculin skin test. If positive, treat appropriately and delay pregnancy until completion of AKT. The potential teratogenic effect of AKT drugs should be informed to the patient.

Tuberculin skin test (TST) should be performed on all 'high risk' women. However, in regions of high prevalence like India the TST may be of less benefit. However, when it strongly positive then it should be interpreted as a likely positive case. HIV testing should be performed in all women with positive TST. INH prophylaxis is to be administered during pregnancy to TST positive women (without active TB) if they are HIV positive, have a known recent TB exposure, or are new TST converters. Sputum cultures with antibiotic sensitivity testing should be done in women with active TB and AKT drug regimen should be started. Pyridoxine 25–50 mg/day should be given when INH is being taken. LFTs should be checked monthly to look for any hepatic dysfunction due to AKT drugs.[57]

TABLE 17.12 Asthmatic Medications in Pregnancy[54]

Class	Agent	Comments
Short acting inhaled β_2-agonist	Salbutamol, Terbutaline	Do not increase risk of congenital anomalies
Long acting inhaled β_2-agonist	Salmeterol	Probably safe in humans if given as inhalation
Inhaled anticholinergic agent	Ipratropium	Reassuring animal studies, no human studies. Effective in acute asthmatic attack justifiable
Inhaled corticosteroids	Low potency: beclomethasone Medium potency: triamcinolone High potency: Fluticasone, Budesonide	Most important in maintaining asthma control during pregnant and nonpregnant state. Budesonide should be considered preferred inhaled steroid in pregnancy.
Mast cell stabilizers	Cromolyn	Nonteratogenic, useful in mild cases
Leukotrine antagonists	Zafirlukast, Montelukast	Animal data indicate safety. Human data lacking. They are to be used only if prepregnancy control was achieved and during pregnancy no other agent is useful
Sustained release methylxanthines	Theophylline Ammophylline	Safe in pregnancy. To be used as second or third line agents
Systemic steroids	Oral: Prednisone IV: Methylprednisolone hydrocortisone	Systemic steroid no risk. However, first trimester use is associated with oral clefts, nevertheless in severe exacerbation its use is life saving and hence justified
Immunotherapy	Allergen extract used in increasing doses	Data limited. Avoided generally as may precipitate worsening

TABLE 17.13 Stepwise Management of Asthma in Pregnancy[54]

Category	Criteria	Step Therapy
Mild intermittent	• Symptoms up to twice a week and/or • Night-time symptoms up to twice a month • PEFR >80% predicted and day-to-day variability < 20%	No daily treatment necessary Inhaled β_2-adrenergic agonists as needed
Mild persistent	Symptoms more than twice a week but not daily and/or Night-time symptoms more than twice a month PEFR >80% predicted but day-to-day variability 20–30%	Inhaled β_2-adrenergic agonists as needed and Daily treatment with inhaled low-dose corticosteroid (preferably budesonide) Alternatives include daily cromolyn, a leukotriene receptor antagonist or a theophylline preparation
Moderate persistent	• Daily symptoms and/or • Night-time symptoms more than once a week • PEFR 60%–80% with day-to-day variability >30%	Inhaled β_2-adrenergic agonists as needed and Daily treatment with inhaled low-dose corticosteroid and treatment with salmeterol or Daily treatment with inhaled medium-dose corticosteroid If needed, combine treatment with daily medium-dose corticosteroid and daily salmeterol Alternative: daily low-medium dose inhaled corticosteroid, either theophylline or a leukotriene receptor antagonist
Severe persistent	• Continual symptoms that limit activity • Frequent night-time symptoms and acute exacerbations • PEFR < 60% predicted and day-to-day variability >30%	Inhaled β_2-adrenegic agonists as needed and Daily treatment with inhaled high-dose corticosteroid Daily treatment with salmeterol and, if needed Daily treatment with systemic corticosteroids

Source: James DK, Gonik B, Steer PJ, Weiner CP. High Risk Pregnancy: Management Options. 4th ed., pg. 662.

TABLE 17.14 Criteria for Congenital TB

(1) Confirmed diagnosis of TB in the newborn
(2) Primary granulomatous complexes in the neonatal liver
(3) In the absence of neonatal liver lesions, the diagnosis of TB made in the newborn in few days of birth (to differentiate congenital TB from postpartum infection)

During labour and delivery, there are no specific recommendations except infection precautions to be taken with active disease.

In the postnatal period, the baby must be separated from the mother at birth only if the mother has infectious TB and continued until the mother is no longer infectious, that is 10 days after starting therapy. Breastfeeding is to be encouraged. In all other cases, BCG vaccine and INH should be given to the neonate if the mother is infectious at birth. This will prevent acquiring neonatal infection.

The dosage and adverse effects of the various anti tubercular drugs in pregnancy are outline in Table 17.15.

Pneumonia in Pregnancy

The incidence of pneumonia in pregnancy is between 0.8 and 2.7 cases per 1000 deliveries. Respiratory failure occurs in up to 10% of pregnant women with pneumonia.

Risk factors for developing pneumonia in pregnancy are HIV infection, asthma, cystic fibrosis, smoking, anaemia, cocaine use, alcoholic abuse, tocolytic therapy and steroid use for fetal lung maturity.[58]

Clinical features are abrupt onset of fever with chills, productive cough, tachypnea, tachycardia, chest pain and localized harsh sounds on inspiration. Pneumonias can be more severe in pregnancy due to the immune suppression.

Effect of Pneumonia on Pregnancy

Maternal condition generally improves on timely initiation of antibiotic therapy. However, varicella and influenza pneumonia can be fatal. Women with HIV are at additional risk of pneumocystis carinii pneumonia that requires close monitoring.

Management

Vaccinate for influenza during flu season. Women with splenectomy or immunodeficiency should undergo pneumococcal vaccination. PCP prophylaxis should be continued in pregnancy in women with HIV and low CD4 counts.

Chest X-ray should be performed to confirm diagnosis. Evidence of pulmonary infiltrate is the gold standard for diagnosis. Abdominal shielding should be done while performing X-ray of the chest in order to reduce fetal radiation exposure. Differentiate pneumonia from pulmonary embolism and ARDS. Sputum and blood cultures should be sent

TABLE 17.15 Anti Tubercular Drugs in Pregnancy[54]

Drug and Dosage	Adverse Effects	Use in Pregnancy	Remarks
Isoniazid (INH) 5 mg/kg up to a maximum of 300 mg daily	Hepatitis Peripheral neuropathy Drug interaction with many agents, especially anticonvulsants Cutaneous hypersensitivity	FDA class C High lipid solubility; easily passes into fetal circulation Fair data to suggest this agent is safe in human pregnancy and any risk is outweighed by potential benefit However, concerns about potential increase in INH hepatotoxicity in pregnancy make its routine use for prophylaxis in pregnancy in low risk cases not advisable.	• Always administer with 25–50 mg/day of pyridoxine (vitamin B_6) to decrease the risk of neurotoxicity in the mother • Give vitamin K to mother near birth (10 mg PO daily from 36 week onwards) and infant at birth to decrease risk of postpartum haemorrhage and haemorrhagic disease of the newborn. • Check transaminases monthly while on the medication.
Rifampin 10 mg/kg, up to a maximum of 600 mg daily	Fever • Nausea • Hepatitis • Purpura • Flu-like symptoms • Orange secretions	FDA class C • Limited data suggest no adverse fetal effects	Give vitamin K to mother near birth (10 mg PO daily from 36 week onwards) and infant at birth to decrease risk of postpartum haemorrhage and haemorrhagic disease of the newborn
Ethambutol 15–25 mg/kg up to a maximum of 2500 mg daily	Retrobulbar neuritis in 1% patients Peripheral neuropathy	FDA class B • Limited data suggest no adverse fetal effects	At each monthly visit, patients should be questioned regarding possible visual disturbances, including blurred vision or scotomata; monthly testing of visual acuity and colour discrimination is recommended for patients receiving the drug for longer than 2 months
Pyrazinamide 15–30 mg/kg PO daily, up to a maximum of 3000 mg daily	Thrombocytopenia Hepatotoxicity Interstitial nephritis Nephrotoxicity	FDA class C • Human data extremely limited	Use in pregnancy supported by international recommendations Essential for multidrug resistant TB and HI-positive patients
Streptomycin Dose varies	• Ototoxicity	FDA class D • Reports of fetal ototoxicity	• Avoid use in pregnancy

Source: James DK, Gonik B, Steer PJ, Weiner CP. High Risk Pregnancy: Management Options. 4th ed.

in a serious patient. Appropriate antibiotic treatment should be started and continued for 10–14 days as described in Table 17.16. Tetracyclines and fluroquinolones should be avoided in pregnancy. Varicella pneumonia should be treated with acyclovir. Oxygen therapy should be given to maintain saturation above >94%.[59]

Pulmonary Edema and Acute Respiratory Distress Syndrome

The physiologic changes of pregnancy predispose pregnant women to the development of pulmonary edema. The overall incidence of pulmonary edema in pregnancy is 80 in 100,000 pregnancies and occurs more often than in nonpregnant state. Normal physiologic changes of pregnancy that predispose to or may exacerbate pulmonary edema are 20% decrease in colloid osmotic pressure, 50% increase in blood volume and cardiac output and decreased functional residual

TABLE 17.16 Antibiotic Regimens for the Treatment of Pneumonia in Pregnancy[60]

For uncomplicated pneumonia in patients who **do not require hospitalization:**

Standard: Azithromycin 500 mg PO on day 1 followed by 250 mg daily for 4 days

Alternate: Erythromycin 250 mg qid PO for 10–14 days

For uncomplicated pneumonia in patients **requiring hospitalization**

Ceftriaxone 2 g IV once daily with azithromycin 500 mg IV daily (or erythromycin 500 mg IV q6h).

Once patient is afebrile and stable switch to azithromycin 500 mg PO daily × 7–10 days (or erythromycin 250–500 mg PO qid × 10–14 days) with cefuroxime axetil 500 mg PO bid for 10–14 days

Source: James DK, Gonik B, Steer PJ, Weiner CP. High Risk Pregnancy: Management Options. 4th ed., pg. 674.

capacity (FRC) in pregnancy.[61] The causes of noncardiogenic pulmonary edema in pregnancy are listed in Table 17.17.

The criteria diagnostic of Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS) are listed in Table 17.18.

Management

Patients should be managed in an intensive care unit. Propped up position should be given. Supplemental oxygen should be given to maintain PaO_2 >65 mm Hg and oxygen saturation >95%. If the blood pressure is well maintained and there is no placental hypoperfusion, IV furosemide (10 mg) should be given. ECG should be done to rule out cardiogenic causes of pulmonary edema. Fluid balance should be strictly monitored. Fluid overload should be avoided by restricting IV fluids. Underlying cause should be treated, like discontinuing tocolytics, controlling preeclampsia and considering active efforts towards fetal delivery. Pyelonephritis should be treated with appropriate antibiotics. Airway should be protected if aspiration has occurred and coagulation studies should be done if amniotic fluid embolism is suspected. If oxygenation is not maintained then positive pressure nasal ventilation or semielective intubation should be used. CVP line should be inserted if the patient is unresponsive to diuretics, cardiac cause is suspected, poor urine output and hypotension is present. Inotropic and vasoactive agents should be used to maximize cardiac output in the presence of haemodynamic instability.[63]

TABLE 17.17 Causes of Noncardiogenic Pulmonary Edema in Pregnancy

Unique to Pregnancy
Tocolytic therapy
Preeclampsia/eclampsia/HELLP syndrome
Amniotic fluid embolism
Neurogenic pulmonary edema after eclamptic seizure
Sepsis: chorioamnionitis, endometritis, septic abortion
Incidental to Pregnancy
Sepsis: appendicitis, bacterial pneumonia
Chemical pneumonitis
Venous air embolism
Exacerbated or Facilitated by Pregnancy
Aspiration (Mendelson syndrome)
Sepsis: pyelonephritis, viral pneumonia, listeriosis
Severe haemorrhage

Source: James DK, Gonik B, Steer PJ, Weiner CP. High Risk Pregnancy: Management Options. 4th ed., pg. 676.

TABLE 17.18 Diagnostic Criteria for ALI/ARDS[62]

Acute onset
Bilateral chest radiographic infiltrates
A pulmonary artery occlusion pressure <18mm Hg or no evidence of left atrial hypertension
Impaired oxygenation manifested by a PaO_2/FiO_2 of 200–300 mm Hg for ALI and ≤200 mm Hg for ARDS

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FiO_2, fractional concentration of oxygen in inspired gas; PaO_2, arterial oxygen pressure.
Source: James DK, Gonik B, Steer PJ, Weiner CP. High Risk Pregnancy: Management Options. 4th ed., pg. 677.

RENAL DISORDERS IN PREGNANCY

Renal disorders are uncommon during pregnancy. However, maternal and fetal outcomes are dependent on the degree of pre-existing renal dysfunction and the degree of renal involvement during pregnancy.

The various renal changes during pregnancy are summarized as follows[64]:

- Renal vasodilation and RPF increase of 50–80% above nonpregnant level
- Renal hyperperfusion and hyperfiltration causing increased urine output, frequency and nocturia
- Increased GFR (by 25–55%) causing increase in proteinuria and creatinine clearance with decline in serum creatinine and BUN. The normal serum creatinine levels in pregnancy are usually between 0.4 and 0.9 mg/dl
- Reduced tubular glucose reabsorption causing glycosuria (in 70% of nondiabetic mothers)
- Hypercalciuria
- Increased renal size pelvicaliceal, ureteral, bladder, and urethral morphologic changes contributing to uninary stasis and vesico-ureteral reflux (VUR)
- Symptoms mimicking cystitis

Urinary Tract Infection in Pregnancy

UTI in women occurs because of an initial colonization of the vagina and periurethral tissues. This is followed by an upward (retrograde) ascent of the bacteria into the bladder via the short female urethra.

The most common causative microorganisms are E.coli and gram positive bacteria.

Asymptomatic bacteriuria (ASB) is defined as the growth of 10^5 or more CFU/mL of a single uropathogen from the first void midstream clean-catch specimen in women with no urinary symptoms. ASB is noted in 2–7% of pregnant women.

Significant bacteriuria is defined as 10^2 CFU/mL of a single organism. Changes in the urinary tract during

pregnancy favour the progress of ASB to lower UTI (cystitis) and eventually acute pyelonephritis. Acute cystitis occurs in 1–2% of pregnancies. The clinical features include pyuria, proteinuria, hematuria dysuria, increased frequency and urgency during urination.

Diagnosis of UTI is confirmed by urine microscopy and culture of freshly voided midstream urine sample. The presence of at least one bacterium per oil immersion field on gram stain indicates a positive urine culture.

UTI is defined as more than 10^5 CFU/ml of a single uropathogen in symptomatic women. However, some women with lower counts may also have acute symptoms.

Pyuria is defined as the presence of more than 10 leucocytes per high power field in an unspun urine sample or more than 50 leucocytes per high-power field in a spun urine specimen.

Positive nitrate dip stick test and leucocyte esterase (LE) test are also indicative of UTI. However, these are not as sensitive as urine culture in screening for ASB.

Screening for ASB must be done in all pregnant women as in the absence of treatment up to 30% will develop acute pyelonephritis. Treatment of ASB with antibiotics significantly reduces this progression to only 1%. However, about 30% of cases will have a relapse and hence these pregnant women should be screened every 4– 6 weeks throughout pregnancy.[65]

ASB is also known to be associated with increased risk of preterm delivery and low birth weight. Treatment of ASB reduced the incidence of preterm delivery and low birth weight.[65]

ASB or the first episode cystitis should be treated by the appropriate antibiotic depending upon the prevalent resistance. Generally, penicillins are not used because of significant resistance. Sulfa drugs are also to be avoided due to resistance and adverse fetal effects. Quinolones are known to cause arthropathy and hence are not to be used.

In an international double blinded, placebo controlled randomized trial conducted by WHO, a 7 day oral regimen of nitrafurantion (100 mg twice daily) was found to be most effective in cases of ASB.[66] Nitrofurantion should be avoided in patients of G6PD deficiency owing to the risk of hemolytic anaemia.

Urine culture should be obtained 2 weeks after completion of treatment to document cure. Cystitis is known to recur in 33% patients and should be treated with a second line agent based on antibiotic sensitivity for 10 days.[67] USG should be performed to exclude calculi or structural abnormalities of the urinary tract in cases of relapse or persistence. In cases of repeated reinfection, continued low dose nightly antibiotic suppression with nitrofurantion 100 mg orally or cephalexin 250 mg orally daily or the depending upon antibiotic sensitivities can be continued till 4 weeks postpartum.[68]

Acute Pyelonephritis

Acute pyelonephritis involves the upper urinary tract. Clinical features include lumbar pain, fever, chills, nausea, vomiting costovertebral angle tenderness, myalgia, headache, malaise and confusion. The costovertebral angle tenderness is more on the right side as the right kidney is more often affected. It occurs more often in the second and third trimester of pregnancy. Acute pyelonephritis can lead to several complications in pregnancy as listed in Table 17.19.

Acute pyelonephritis patients should be admitted to hospital. The following investigations should be performed, that is CBC, S.creatinine, BUN, LDH, S.electrolytes and urine analysis. Urine culture and blood culture IV antibiotic therapy should be started empirically until cultures results are known. The usual regimen includes cefoxitin 2 g every 6–8 hourly, or ceftriaxone 1 gm daily, 95% response rate is seen.[69]

IV crystalloids should be also given to restore the contracted blood volume.

Chest X-ray and arterial blood gases should be performed in the presence of respiratory distress. The respiratory symptoms usually respond to oxygenation by mask. ARDS will require tracheal intubation with mechanical ventilation and positive end expiratory pressure. Endotoxic shock mandates strict invasive haemodynamic monitoring. Fetal monitoring to rule out fetal distress should be performed.

IV antibiotics should be continued until the patient becomes afebrile and asymptomatic for at least 48 hours. Appropriate oral antibiotics should then be started and continued for 14 days.

If there is no improvement of the patient's condition within 96 hours, then an imaging study should be performed to visualize collecting system abnormalities. If obstruction is noted, then placement of double J-stent, percutaneous nephrostomy or surgical removal of the calculi should be performed.[69]

Urine culture should be repeated 2 weeks after completion of antibiotic therapy and then repeated monthly. Risk of recurrent pyelonephritis can be reduced from 20% to 8% with suppressive therapy with nitrofurantion 100 mg orally at night until 6 weeks postpartum. Suppressive therapy is especially important in the presence of urinary tract abnormalities and calculi.

TABLE 17.19 Complications in Acute Pyelonephritis

Hemolytic anaemia
Thrombocytopenia
Deceased GFR
Acute respiratory distress syndrome
Uterine contractions
Endotoxic shock
Hypothalamic instability

Acute Renal Failure During Pregnancy

Acute renal failure (ARF) is a rare complication of pregnancy. It is defined as a urine output of less than 400ml in 24 hours.

The various conditions that lead to ARF in pregnancy are enlisted in Table 17.20.

Haemorrhage, dehydration or septic shock lead to a prerenal insult that causes transient ATN if not adequately treated. In preeclampsia due to volumic constriction and endothelial dysfunction, ATN may progress to bilateral renal cortical necrosis (BRCN).

Urinary sodium levels less than 20 mEq/l are usually noted in prerenal azotemia without intrinsic renal damage, while a value greater than 25 mEq/l indicates the development of ATN. Also in ATN, the urinary sediment will show cellular debris and granular casts.

About 20% of patients of ARF in pregnancy progress to BRCN as a result of thrombosis in the renal microvasculature. If there is prolonged anuria, usually more than 1 week, BRCN should be suspected. These patients will require dialysis, without it survival may be only for less than month. Usually, BRCN in pregnancy is patchy and recovery occurs though slowly, taking up to a year. However, long-term renal function is known to progressively decline.[70]

ARF in Preeclampsia

Renal impairment is usually noted in cases of preeclampsia. Fortunately, timely and appropriate management results in complete recovery. On histology, glomerular endotheliosis and mesangiosis are usually noted. Proteinuria is present and there is elevation of urinary sodium, but there is a decline in urinary calcium due to reabsorption by renal tubules.

Serum creatinine values are an important indicator for decision making. A value less than 1.3 mg/dl is an indication for delivery as renal impairment although present is minimal. When the serum creatinine increases by 1 mg/dl/day, ATN usually will occur. Fortunately even in these cases delivery will result in reversal in a majority of such cases. However, pre-existing renal dysfunction will worsen the prognosis. Doubling of serum creatinine in 48 hours is associated with progression to BRCN and the need for dialysis. However, this is usually not seen in preeclampsia, but in other obstetric complications.[71]

Oliguria occurs in severe preeclampsia secondary to renal vasospasm, with 25% reduction in GFR. Transient oliguria may be common in labour and for a day postpartum and a fluid challenge of 500 ml over 30 min may be used to correct the intravascular volume depletion. However, one must be watchful for pulmonary edema.

In women with severe preeclamsia and serum creatinine greater than 1.36 mg/dL, fluid replacement must be judiciously monitored depending upon the pulmonary artery catheter findings. Monitoring with a CVP line may be at times inaccurate due to the increased systemic vascular resistance, seen in preeclampsia.

The appropriate treatment based on invasive haemodynamic monitoring is outlined as follows[72]:

Haemodynamic Parameter	Management
Low PCWP and high SVR	Fluid therapy at the rate of 250 ml/hr until PCWP is 10–12 mm Hg.
Normal/Elevated PCWP and Normal SVR	IV hydralazine or low-dose dopamine infusion (2.5 mg/kg/min.)
Marked elevated PCWP and high SVR	Aggressive reduction of afterload with diuretics (furosemide infusion 5 mg/ hr) and fluid restriction.

PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

Once the patient becomes euvolemic, IV fluids should be transfused equal to the previous hours urine output plus insensible losses. If the fluids can be taken orally, the IV fluids should be reduced. Invasive haemodynamic monitoring should be continued until the diuretic phase in the postpartum.

Fluid replacement should include blood to replace any blood losses and the isotonic sodium chloride or Ringer's lactate solution. Dextrose solutions are hypotonic and lead to maternal hypotension while colloid solutions (albumin) can increase PCWP markedly and should be avoided in patients with severe preeclampsia.

Dialysis may be needed rarely and the indications for the same are listed in Table 17.21.

TABLE 17.20 Etiological Causes of Acute Renal Failure in Pregnancy

Most Common Causes
Haemorrhage
Severe preeclampsia
Rare Causes
Septic shock
Hyperemesis gravidrum
Nephrotoxic drugs
Amniotic fluid embolism
HUS/TTP
Acute fatty liver of pregnancy
Obstructive uropathy
Postoperative oliguira
Idiopathic postpartum acute renal failure

TABLE 17.21 Indications of Dialysis in Pregnancy

Electrolyte abnormalities refractory to medical treatment
Volume overload with congestive heart failure and pulmonary edema refractory to standard therapy
Severe metabolic acidosis
Uremia (BUN > 39 mg/dL or SCr > 5.65 mg/dL)

The other causes of ARF in pregnancy and their management are outlined in Table 17.22.

Chronic Renal Failure in Pregnancy

Prepregnancy renal function and the presence of hypertension prognosticate the outcome during pregnancy. A linear relationship exists between the preconceptual creatinine levels and the risk of further renal damage during pregnancy. Creatinine clearance is a more accurate marker than serum creatinine. When the serum creatinine is above 2 mg/dl prior to pregnancy, then two-thirds of pregnant women will exhibit deterioration of renal function during pregnancy with 20% ending up in end stage renal disease (ESRD) within 6 months after delivery.[77]

Hypertension present at conception increases the perinatal mortality rate. Hence, pregnancy outcome is improved when blood pressure is well controlled prior to pregnancy and maintained at this level throughout pregnancy.

Changes in serum creatinine or creatinine clearance of at least 25% may justify delivery or termination of pregnancy. If the gestational age is between 24 and 31 weeks, with a normally grown fetus and hypertension well controlled, management should be expectant with dialysis as and when indicated.[78]

In pregnant women with severe edema in nephrotic syndrome, a low sodium diet (containing about 1.5 gms), bed rest in lateral position in order to improve GFR and a small dose of a loop diuretic should be administered intermittently and cautiously.

Antenatal visits should be scheduled every 2 weeks and weekly after 32 weeks. Fetal growth and well-being should be assessed by USG and umbilical artery Doppler studies. Biophysical profile is to be performed weekly from 28 weeks onwards especially in cases of worsening renal failure, hypertension, proteinuria and placental insufficiency.

Delivery should be attempted at term in the absence of maternal and fetal deterioration. Cesarean delivery should be reserved for obstetric indications only.

Specific renal diseases, their course and management in pregnancy are summarized in Table 17.23.

Chronic Dialysis in Pregnancy

Overall women having ESRD are less likely to conceive but with use of especially hemolysis, spontaneous conception is a possibility.[84]

In pregnancy the same criteria should be used when considering the modality of dialysis to be used. However, in peritoneal dialysis during pregnancy the catheter should be

TABLE 17.22 Causes of ARF in Pregnancy and Management

Cause of ARF	Management
Postoperative Oliguria	• Obstructive uropathy and the use of nephrotoxi drugs (NSAIDs) should be excluded. • Adequate volume and electrolyte replacement should be carried out.
Thrombotic Thrombocytopenic Purpura (TTP)[74]	• TTP should be differentiated from preclampsia using blood biochemistry tests. • Mild cases usually respond to plasma infusion. • In severe cases, plasmapheresis is to be used and is extremely effective. • Antiplatelet therapy using aspirin should be used as adjuvant to plasmapheresis. • Immunosuppresive therapy using prednisone or cyclophosphamide and splenectomy may be needed in nonresponders. • Delivery should be considered at 34 weeks.
Hemolytic Uremic Syndrome (HUS)[75]	• Dialysis is required usually. • If there is severe anaemia, it should be corrected by RBC transfusion (packed cells). • Plasma exchange and prednisone to be continued even postpartum for 1 month. • Delivery is advisable once diagnosis is confirmed as risk of maternal complications is high.
Acute Fatty Liver of Pregnancy[76]	• ICU case is indicated with invasive haemodynamic monitoring. • Clotting disorders, hypoglycaemia and fluid in balance should be corrected first. • Once mother stabilizes, delivery should be attempted. • Temporary dialysis may be needed in a few patients.
Urinary Tract Obstruction	• Ureteric stents should be placed and kept till 1 month postpartum. • Temporary nephrostomy may be indicated if stenting fails.

TABLE 17.23 Renal Diseases in Pregnancy

Renal Disease	Maternal-Fetal Risks	Management
Primary Glomerulonephritis[79]	• IgA Glomerulonephritis is the most common primary nephropathy noted in pregnant women. • The overall fetal loss rate is 20%, with the worst outcome in focal glomerulosclerosis. • About 20% of patients experience worsening or new onset hypertension in pregnancy.	• Changes in preconceptual immunosuppressive dosage are not recommended in pregnancy. • Chlorambucil must be avoided and cyclophosphamide must be not given in the first trimester.
Autosomal Dominant Polycystic Kidney Disease (ADPKD)[80]	• Frequently associated with chronic hypertension and preeclampsia • Associated with cerebral & aortic aneurysms, which are at an increased risk for rupture if patient is bearing down in labour.	• MRI angiography should be done to look for cerebral aneurysms. • Cesarean delivery is recommended for aneurysms. • Requires genetic counseling, as there is 50% chance of affection in the fetus.
Reflux Nephropathy[81]	• Common in childbearing women and associated with renal scanning and reduced GFR, especially in those with corrected VUR in childhood. • Pregnancy can lead to irreversible renal damage due to tubulointerstitial disease and gestational over distention.	• Close monitoring if there is flank pain, persistent infections, decreased urine output and hypertension, in order to look for hydroureter and hydronephrosis • Baseline renal USG at 12 weeks and in presence of symptoms is essential. • Urine cultures are to be performed every 4–6 weeks to look for asymptomatic bacteria. • If there are persistent bacteria, then low dose prophylactic antibiotics should be started. • Renal function deterioration may warrant temporary urinary drainage. • Fetus and neonate should be screened at birth with renal USG and those positive for VUR should undergo DMSA scan at 3 months. • Prophylactic antibiotics should be given to the neonate.
Diabetic Nephropathy[82]	• Even though 5–10% of pregnant women with pregestational DM have diabetic nephropathy, this is the most common chronic renal disorder in pregnancy with diabetic nephropathy pregnant women, and moderate to severe renal failure have a 50% chance of worsening in pregnancy. • Preeclampsia is present in more than 50% cases.	• Adequate glycaemic control. • BP to be controlled to $\leq$ 150/90 mmHg. • In cases of severe renal failure, consider early delivery.
Lupus Nephritis[83]	• Lupus nephritis occurs in 50% cases of SLE and in pregnancy is one of the most serious complications of SLE • Clinical manifestations are proteinuria, hematuria, elevated serum creatinine, hypertension, thrombocytopenia and hyperuricemia. • In women with active lupus nephritis at conception have 50% risk of fetal loss.	• In severe lupus nephritis (serum creatinine> 1.4 mg/dL, proteinuria >500 mg/24 Hr. hypertension) with manifestations early in pregnancy of pregnancy may be recommended. • Adverse pregnancy outcomes should be anticipated if active lupus at conception, serum creatinine > 1.36 mg/dL, BP > 140/90 mm Hg and antiphospholipid antibodies. • Corticosteroids, hydroxyl chloroquine, azathioprine, cyclophosphamide (avoid in first trimester), cyclosporine to be used to treat lupus flare as required. • Antihypertensive medications to be given. • Heparin and low dose aspirin if antiphospholipid antibodies positive. • Increased risk of postpartum flare, but no need to increase immunosuppressive dosage.

placed higher in the abdomen. In pregnant patients with ESRD undergoing dialysis there is significant increase in preterm births, IUGR and fetal loss.[84]

Dialysis regimens should mimic physiologic changes seen in the renal system during pregnancy (i.e. lower sodium and bicarbonate concentration in the dialysate). Dose of potassium, calcium and phosphates should be adjusted as per serum levels.

After completion of first trimester, dialysis should be performed daily (20–24 hrs/week) to ensure that the pre dialysis BUN < 50 mg/dl or Serum Creatinine < 4.5 mg/dl and fluid removal should be limited to 400 ml/session.[85]

In ESRD, anaemia is noted in all patients who become pregnancy. Hence haemoglobin, serum iron and ferritin should be assessed monthly.

When the Hb becomes less than 8 gm/dL (Hct < 25%) then IV iron or IV/SC Erythropoietin (EPO) should be given to raise the Hb to greater than 10 gm/dL. EPO does not cross the placenta and does not cause fetal polycythemia or anomalies. Rare adverse effects of EPO include increased maternal thrombogenic activity, hypercalcaemia, hyperphosphatemia, seizures and severe hypertension. Hence, EPO is contraindicated in women with uncontrolled hypertension. If there is a rise of Hb > 1 gm/dL in 2 weeks, the EPO dose must be reduced as hypertension is likely to develop.[86]

Fetal monitoring is mandatory after each dialysis session due to acute fluid shifts. Fetal growth scans and umbilical artery Doppler should be performed regularly to look for fetal compromise. Polyhydramnios should also be looked for in cases of haemodialysis. Dialysis may be accompanied by preterm labour; however, it is generally transient and resolves without treatment.[87]

Delivery should be planned at 34–36 weeks of gestation. Preferably pregnancy should not be continued beyond 38 weeks. Cesarean section rates are 50%. After CS, peritoneal dialysis can be resumed with smaller 1L exchange volumes 24 hours after surgery. Haemodialysis to be used if there is leakage.

Infants will experience osmotic diuresis at birth. Hence, careful monitoring and appropriate correction of electrolyte abnormalities should be done. Hypocalcaemia and tetany in the newborn should be looked for and treated.

Renal Transplant and Pregnancy

Pregnancy can be safely undertaken one year after transplant, provided there are no rejections, allograft function is adequate (serum creatinine < 1.5 mg/dL and urinary protein excretion < 500 mg/24 hrs), immunosuppressive medications are responsive and well tolerated and there are no infections.[88]

Fetal survival is generally good (i.e. 95%) once the pregnancy crosses beyond the first trimester. However, if serum creatinine is greater than 1.5 mg/dL then fetal survival drops to 75%.

The rates of maternal complications are high (up to 70%) and include worsening of renal function, worsening hypertension and infectious morbidity. The rate of preterm delivery in these patients is more than 50%. Majority of clinical evidence suggests that if the serum creatinine is more than 2.3 mg/mL, then all such patients will experience progression of renal failure and will require renal replacement therapy within the next two years of delivery. Hence, pregnancy should be contraindicated in such patients.[89]

During pregnancy the immunosuppression should be maintained similar to prepregnancy levels. Antepartum exposure to immunosuppressive drugs usually results in low birth weight babies. Cyclosporine is well tolerated in pregnancy and no teratopathies have been seen with its use. Prolonged use of steroids has resulted in an increase in preterm birth rates and increased risk of midline facial defects.[90]

The use of sirolumus, mycophenolatemofetil, OKT3, ATG, cyclophosphamide, methotrexate, chlorambucil and leflunomide are to be avoided in pregnancy due to limited data regarding their safety.[91]

BUN, S. Creatinine and electrolytes should be monitored every 10 days. Allograft function should be assessed with monthly USG and technetium scan should be performed at least in each trimester.

Monthly urine cultures are necessary as UTI is the most common infection in these patients. Asymptomatic bacteriuria should be treated for two weeks followed by suppressive therapy.

Preeclampsia should be screened for. It is vital to exclude allograft rejection and postrenal obstruction. Renal biopsy may be required to distinguish between the two.

The fetus should be scanned at 18 to 20 weeks and subsequently USG should be done to evaluate interval growth. Umbilical artery Doppler is beneficial to assess fetal well-being.

During labour and delivery prophylactic antibiotics and 'stress' doses of corticosteroids should be administered. In the absence of any complications, delivery should be attempted at term. Cesarean delivery should be reserved only for obstetric indications. However, cesarean delivery is to be preferred in combined pancreas–kidney recipients.[89]

Breastfeeding is not absolutely contraindicated in patients on immunosuppressive medications as no adverse effects have been in the breastfed infants.[92]

OTHER MEDICAL DISORDERS: AN INDIAN PERPECTIVE

J Prakash et al observed that in cases of acute kidney injury (AKI) in pregnancy HELLP syndrome was noted in about 40% of patients. Preeclampsia/eclampsia was the etiological factor leading to acute renal failure (ARF) in 38.3% of

the cases. There is significant decrease in the incidence of AKI in pregnancy over the last three decades. Attempts to prevent unwanted pregnancies and thereby septic abortion will reduce abortion-associated ARF in early pregnancy. Puerperal sepsis and preeclampsia/HELLP syndrome were commonly responsible for ARF in third trimester and postpartum periods. They observed that urinary tract infection (UTI) occurred in 9% of pregnancies.[93]

Dadhwal et al conducted a retrospective study evaluating the pregnancy outcome of patients with APAS. Forty-two patients received medical therapy in the form of heparin and aspirin for 3 years. The pregnancy outcome (in terms of abortions, intrauterine deaths and live birth rate) was compared before and after treatment with heparin and low-dose aspirin. Among the treated patients, preeclampsia was recorded in 13 (30.9%) and 9 patients (21.4%) had intrauterine growth restriction (IUGR). There were 2 (4.7%) intrauterine deaths, 4 patients (9.5%) had missed abortions and 3 (7.1%) had abruptio placentae. After treatment, live birth rate was 85.7% in the index pregnancy as compared to 4.6% of before treatment. Hence, they concluded that the treatment of pregnant women with APAS results in marked improvement in the live birthrate. However, complications like preeclampsia and IUGR occur even after treatment, requiring strict monitoring and timely delivery.[94]

Thomas et al estimated that there are over 2.5 million women with epilepsy (WWE) in India, with up to 52% of them being in the reproductive age group. This study was carried out in the Kerala registry of epilepsy and pregnancy. All complications during pregnancy, delivery and postpartum period were recorded according to the registry protocol. They concluded that there was no significant increase in the risk of complications of pregnancy or delivery except for spontaneous abortions, anaemia, and seizures in the peripartum period, which were more frequent in WWE. Frequency of cesarean section was not increased in WWE. In most women with epilepsy, there is no undue risk to pregnancy and childbirth.[95]

Tripathy et al conducted a prospective study at Cuttack, India, from 1986 to 2001 to determine the pregnancy outcome in women having proper treatment for TB. The study included a total of 111 pregnant women diagnosed as having pulmonary and glandular TB. They concluded that there were no statistical differences in duration of gestation, preterm labour, and other complications of pregnancy, labour, and puerperium between the pregnancy groups. No congenital anomalies were noted in the babies born to the groups. There was no effect of pregnancy on the course of TB in terms of sputum conversion, disease stabilization and nonrelapse even after 2–5 years of followup and a further delivery in a few cases. Adequately treated pregnant women with TB are not at higher risk than nonpregnant TB patients. Neither the disease nor chemotherapy is threatening to the mother or newborn. However, nowadays the combination of HIV, TB, and pregnancy poses a new challenge.[96]

Meena et al screened 2400 pregnant women attending the antenatal clinic, using asthma questionnaire. The prevalence of asthma during pregnancy was 2.1%, among them, intermittent asthma was noted in 25 (48.1%) women, mild persistent asthma in 6 (11.5%), moderate persistent asthma in 10 (19.2%) and severe persistent asthma in 11 (21.2%). During the course of pregnancy, 36% women had no change in the symptomatology, while improvement of asthma was noted in 32.5% women and worsening in 32.5%. During the study, 22 (42.31%) women were diagnosed newly as having asthma. In the asthmatic women, there was no significant adverse maternal and fetal outcome as compared to control. They concluded that asthma is under diagnosed and under treated during pregnancy, and overall morbidity of asthma among women and neonates does not change during pregnancy.[97]

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Chapter 18

Tropical Diseases in Pregnancy

Shirish N. Daftary

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[1] 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.[2] Parasitemia peaks during the second trimester of pregnancy followed by peak occurrence of anemia.[3]

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.[4,5] 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.[6] Ibeziako et al. (1990)[7] 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.[3] 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.[8]
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, hepatospleno-megaly, 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.[9]

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.[10] 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[9]
- 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 nonpregnant 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.[11,12] 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.[13]

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)[14] 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)[15] 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* (Fig. 18.1) 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

Fetal Effects

- Low birth weight
- IUGR

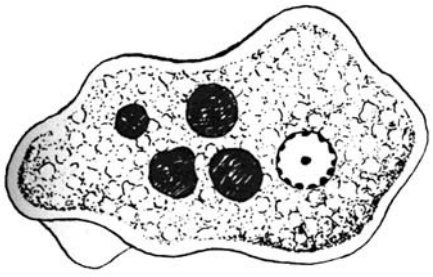

FIGURE 18.1 Trophozoites of *E. histolytica*.

Treatment

WHO (1986)[16] 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.[17] Bacterial overgrowth is responsible for fat malabsorption. Nodular lymphoid hyperplasia of the small intestine with IgA immunoglobulin deficiency is a common association.[18]

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.

Diagnosis

Routine stool examination commonly reveals cysts and occasionally trophozoites of *G. lamblia* (Fig. 18.2). 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

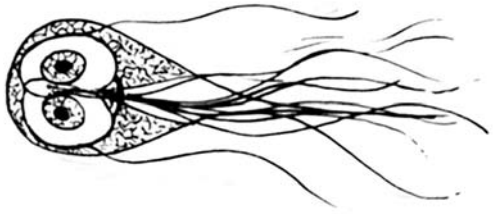

FIGURE 18.2 Trophozoites of *G. lamblia.*

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, *intestinal nematodes*, *cestodes*, *trematodes*, and *tissue nematodes* will be discussed. 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[19]
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)[20] 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 (Fig. 18.3).
- 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

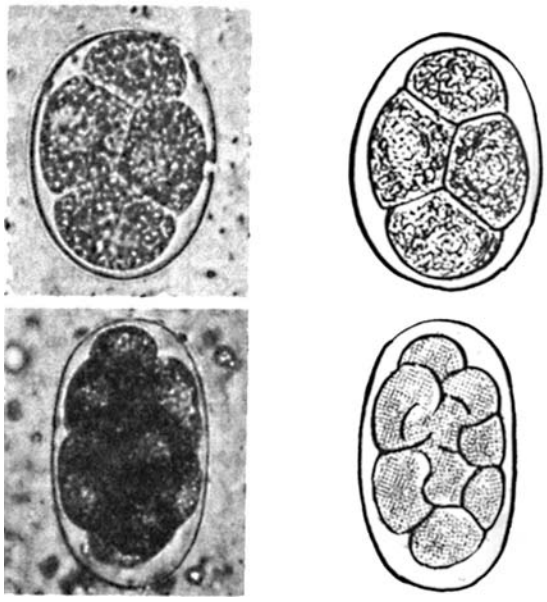

FIGURE 18.3 Four- to eight-celled hookworm (*A. duodenale*) morula.

- Risk of preterm delivery
- IUGR
- Chronic ill-health

Effects on the Fetus

- Prematurity
- Low birth weight
- Transplacental and transmammary transfer cause infantile disease
- Increased mortality in affected infants[19]

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.[21]
- 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.[21]

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 (Fig. 18.4).
- 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.

Effects on the Mother

- Chronic malnutrition and suboptimal health
- Chronic indigestion
- Abdominal cramps
- Rarely acute abdomen

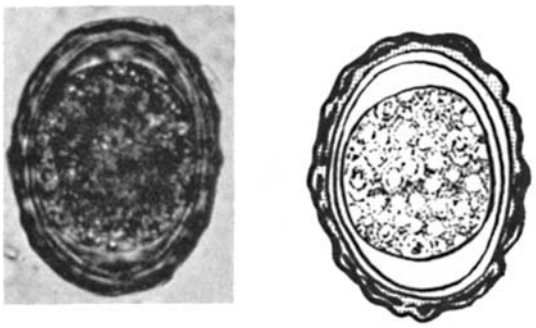

FIGURE 18.4 Fertile and nonfertile eggs of *A. lumbricoides*.

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* (Fig. 18.5).

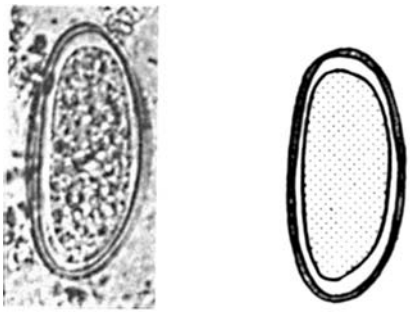

FIGURE 18.5 Eggs of *E. vermicularis.*

- 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.

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 (Fig. 18.6).
- Proctoscopy may reveal presence of adult worms.
- Blood count often shows eosinophilia.

Maternal Effects

- Nil in mild cases
- 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.

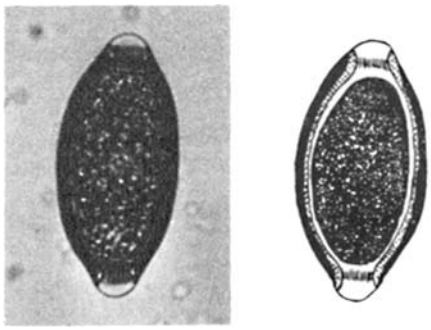

FIGURE 18.6 Barrel-shaped eggs of *T. trichiura.*

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.
   - Humans are 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 (Fig. 18.7)
- Enzyme electrophoresis of glucose phosphate isomerase helps in species differentiation

Maternal Effects

- None to those arising out of concomitant nutritional deficiencies and anemia

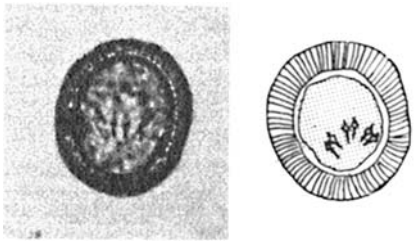

FIGURE 18.7 Eggs of *T. saginata.*

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.
- 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)[22] 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[23])
- 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.[24]

Diagnosis

- Microscopic examination of urine, stools, and vaginal discharge for eggs (Fig. 18.8)
- 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

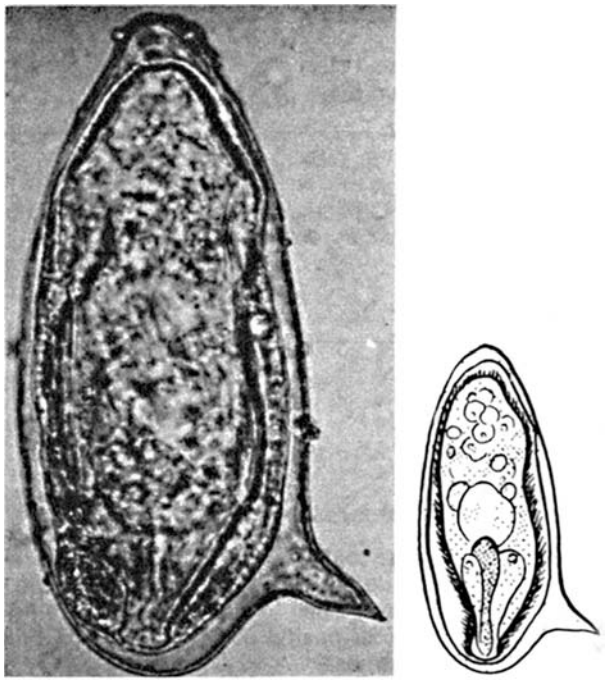

FIGURE 18.8 Eggs of *S. mansoni*.

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
- 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)[25] 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.[26] 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%.[27-30] Of these 90% were attributed to viral hepatitis.[31]

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.[32]

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 infect ion, 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, breast-feeding 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.[33]
   - 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[34]
- 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.[35]

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).[36,37]

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%.[37]

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.[35]

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[38]
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%.[39]
- It does not result in a chronic carrier state.[39]
- Vertical transmission has been reported.[38]

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.[40] 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.

- 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.[41]
- Sunita Mittal et al. (1996)[42] 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.
- Mittal et al. (1996)[42] 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.
- Gill et al. (1996)[43] 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.
- In a general study by Ahmad et al. (2001),[44] 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%.
- Sharma et al. (1996)[45] 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.
- Gupta et al. (1992),[46] 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%).

- Nayak et al. (1989)[47] 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.
- Khuroo et al. (2003)[48] 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.
- Patra et al. (2007)[49] 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[50] 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 18.1.

TABLE 18.1 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 18.2).
4. Dosage of antituberculosis drugs are given in Table 18.3.
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.

TABLE 18.2 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 18.3 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

- 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.
   - Monitor signs of drug side effects. It is advisable to monitor liver involvement and platelet count in each trimester.
   - Monitor fetal growth from mid-pregnancy onwards.
   - Monitor fetal health.
   - All obstetric interventions should be based on obstetric indications.
   - During vaginal delivery, cutting short the second stage with outlet forceps assistance is the practice in India.
   - Neonate to be under care of neonatologist.
   - 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

- 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.
- 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.
- 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.
- 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*.
- Helminthiasis is common in tropical developing countries. Poverty, overcrowding, illiteracy, poor sanitation, and defective hygiene predispose to parasitic infection.
- 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.
- 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.
- 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.

- *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.
- *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.
- 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.
- Hydatid cysts are uncommon, found in animal-rearing communities.
- Filariasis is yet another parasite spread by mosquito bite. Elephantiasis of the vulva can cause dystocia. DEC is the drug of choice.
- 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.
- 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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Chapter 19

Abnormal Labour

Kim Hinshaw and Sara Kenyon

Chapter Outline

INTRODUCTION

Operative delivery rates (both vaginal and caesarean) continue to rise throughout the world and are associated with significantly higher risks of maternal and neonatal complications including birth trauma, postpartum haemorrhage and abnormal placentation in future pregnancies. Almost 50% labours are felt to be affected by dystocia in the first or second stages of labour and this particularly affects first labours. In this chapter, we will review both normal and abnormal progress in labour, outline how labour length is changing since Friedman described the labour curve almost 60 years ago. In the last decade, review of the historical evidence and comparison with newly emerging data suggests that labour progress in the early active phase (up to 6 cm) is slower than originally described. The research evidence for interventions which can be offered in labour will be reviewed with the aim of helping the reader to offer optimum intrapartum management in abnormal labour and minimize intervention.

BACKGROUND

Most labours will progress normally with minimal intervention, allowing couples to participate actively in one of life's most positive emotional experiences, with the ultimate reward of a new and healthy baby. All professionals involved in supporting women and their partners through the birth experience, should acknowledge that this is indeed a privileged position to hold. We should remember that our role is to focus on communication, supporting women's wishes, avoiding unnecessary intervention where possible, but remaining alert to any abnormalities in progress that might compromise the safety of mother or baby.

Globally, a significant number of labours require obstetric intervention and the commonest reason is 'dysfunctional labour' (occurring in either the first or second stage). However, there is significant inequality in the degree of intervention. One example is the huge variance in caesarean section rates (CSRs).[1-3] The World Health Organization recommends an optimal CSR of 10–15% but this varies from an inappropriately low rate of 0.4% in Chad (Africa) up to 45.9% in Brazil (South America).[1] Whilst very low rates are associated with increased maternal and neonatal morbidity and mortality, there is no evidence to show benefit from rates at the higher end of the range. In the 54 countries with a CSR $<10\%$, it was estimated that 3.18 million additional CS were 'needed' at a cost of USD 432 million, whilst the 69 countries with CSR $>15\%$ performed 6.20 million 'unnecessary' sections. This equates to an annual global 'excess cost' of USD 2.32 billion, unavailable for other health initiatives.

In this chapter, we will review both historical and contemporary evidence with the aim of defining what constitutes normal progress in labour. This may be at variance with the norms that many of us have been taught, but recent evidence confirms a change in length of active labour over the last 50 years. We will review the diagnosis of dysfunctional labour and critically appraise the various interventions that are used to manage abnormal labour. Our aim in writing this chapter has been to help colleagues to adopt an

approach of non-intervention and careful observation where appropriate, and to highlight effective interventions which should be considered when labour progress is poor.

NORMAL LABOUR – CLINICAL ASSESSMENT

Labour is divided into three stages of unequal length. In terms of labour progress, we recognize that the first stage of labour has a latent and active phase, and the second stage has a passive and active phase (see Table 19.1).

It is vitally important that we recognize the differences between these four different phases, as this is pivotal in helping to decide when and how to intervene as labour progresses. The differences between primigravid and multigravid labour are important clinically and relate to differences in the four 'P's' – Patient (mother), Powers, Passenger (fetus) and Passage.[4] Women undergo a unique psychological experience in their first labour and this is affected by their perception of pain, level of hydration, mobility, etc. In terms of the 'powers', uterine activity in the primigravida is relatively inefficient and labour is longer. In the multigravida, contractility is efficient and the 'passages' are more pliant and dilate easily (both cervix and vagina). The capacity of the pelvis is 'untried' in first labour and relative disproportion (often in association with an occipito-posterior or 'OP' position) is common.[5] The relationship and position of the presenting part to the bony pelvis must be carefully assessed and recorded as descent and rotation occur during labour (see Figures 19.1a, 19.1b). Even in late labour, it is common for position to be reported as 'not defined'. Clinical assessment may be difficult, but supplementing clinical skills with simple ultrasound assessment is a relatively easy skill to learn. Digital examination is incorrect in diagnosing position in up to two-thirds of cases in the first stage and up to one-third, in the second stage.[6] Delay in labour progress is unusual in multigravid labour but should be treated with great caution as it may be associated with true disproportion. A brow presentation should always be excluded, after which oxytocin may be considered but must be used with care. The primigravid uterus will exhibit 'inertia' as labour becomes prolonged, but the multigravida uterus will continue to contract strongly with a small risk of uterine rupture.

TABLE 19.1 Contemporary Definitions for the Three Stages of Labour*

First stage of labour – Latent phase
A period of time (not necessarily continuous) associated with: the start of painful uterine contractions (may be irregular) some degree of cervical change (includes effacement and dilatation up to 4 cm)
First stage of labour – Active phase
Development of regular painful contractions Progressive cervical dilatation from 4 cm Descent and rotation of the presenting part Ends at full dilatation of the cervix
Second stage of labour – Passive phase
The finding of full dilatation of the cervix prior to involuntary expulsive contractions
Second stage of labour – Active phase
Expulsive contractions with the finding of full dilatation of the cervix Other signs of full dilatation (e.g. anal dilatation) The presenting part is visible Active maternal efforts to push in the absence of expulsive contractions Ends with delivery of the baby
Third stage of labour
The time from birth of the baby to complete expulsion of the placenta and membranes

*Reproduced from: National Collaborating Centre for Women and Child Health. Care of Healthy Women and their Babies during Childbirth. NICE Clinical Guideline No.55. London: RCOG; 2008, with the permission of the Royal College of Obstetricians and Gynaecologists.

THE FRIEDMAN CURVE AND THE PARTOGRAM

It is almost 60 years since Friedman undertook a graphico-statistical analysis of nulliparous labour and produced his classic labour curve.[7] This was based on a selected group of 500 primiparous patients and has been used to define normal progress since. Labour progress accelerates at the point of transition from the latent phase into the early active phase (at 3 cm dilatation), followed by linear progress at 1cm/hour. Friedman described a short decelerative phase near the end of the first stage. He also analysed a subgroup of 200 'uncomplicated' labours and produced an 'ideal' labour curve which showed faster progress, shifted to the left of the 'mean curve' which is shown in Figure 19.2. This was a group which he felt reflected normal, uncomplicated progress through labour.

The partogram or 'cervicograph' was described by Philpott and Castle in 1972 and became embedded in clinical practice worldwide in various forms.[8] The 'action line' recommended by the WHO is set 4 hours to the right of an 'alert line', allowing an unambiguous diagnosis of prolonged labour and timely intervention (see Figure 19.3). The Philpott partogram was based on the slowest 10% of primigravid labours in Rhodesia and its' aim was to allow timely transfer to tertiary units in order to prevent obstructed labour. This reduced the risk of a ruptured uterus, the cause of 70% of maternal deaths in some rural areas.

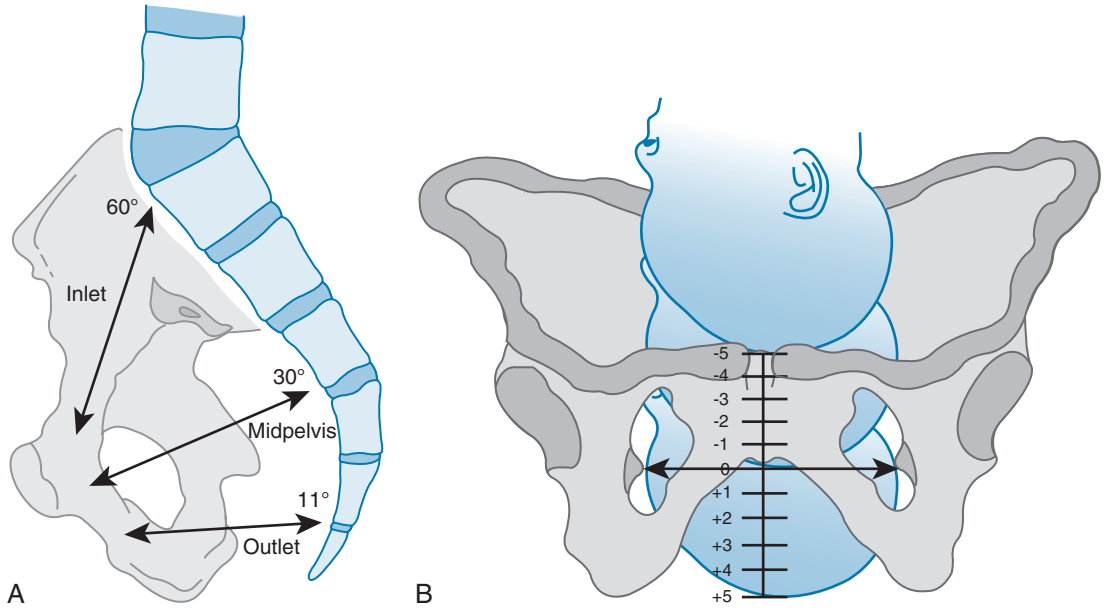

FIGURE 19.1 **(A)** Lateral view of the pelvis – inclination to the horizontal. **(B)** Descent - relative to the level of the ischial spines.

In a randomized controlled trial (RCT) of 3000 women in the UK, 2- and 4-hour action lines were compared.[9] In the 2-hour group, significantly more women had labours that crossed the action line (854/1490 vs 673/1485; RR 1.27, 95% CI 1.18–1.37) and received more obstetric intervention (772/1490 vs 624/1485; RR 1.23, 95% CI 1.14–1.33). Earlier intervention did not reduce the likelihood of CS, nor did it improve women's satisfaction with birth. A subsequent Cochrane systematic review (n = 7704) confirmed no overall differences with use of the partogram vs. no partogram in terms of CSR (RR 0.64, 95% CI 0.24–1.70) or instrumental delivery (RR 1.00, 95% CI 0.85–1.17). However, the review concluded that use of the partogram may still be useful for transfers in areas with poor access to health care resource. Studies in Mexico and Africa also showed some reduction in CSR, when the partogram was used with early intervention for delayed progress in labour.[10] This example highlights a very important point: evidence-based interventions may or may not be applicable to every population, depending on their geographical, social or health environment. This principle is applicable to other evidence-based recommendations presented later in this chapter. However, the partogram still provides an important, concise overview of all constituents of labour.

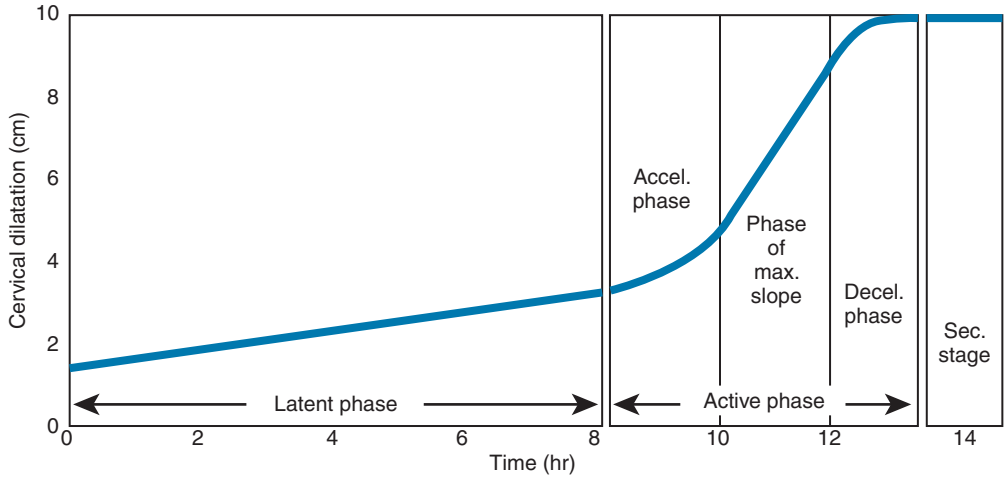

FIGURE 19.2 Labour curve in nulliparous labour [after Friedman EA. Primigravid labor; a graphico-statistical analysis. *Obstet Gynecol.* 1955;6(6): 567–589.]

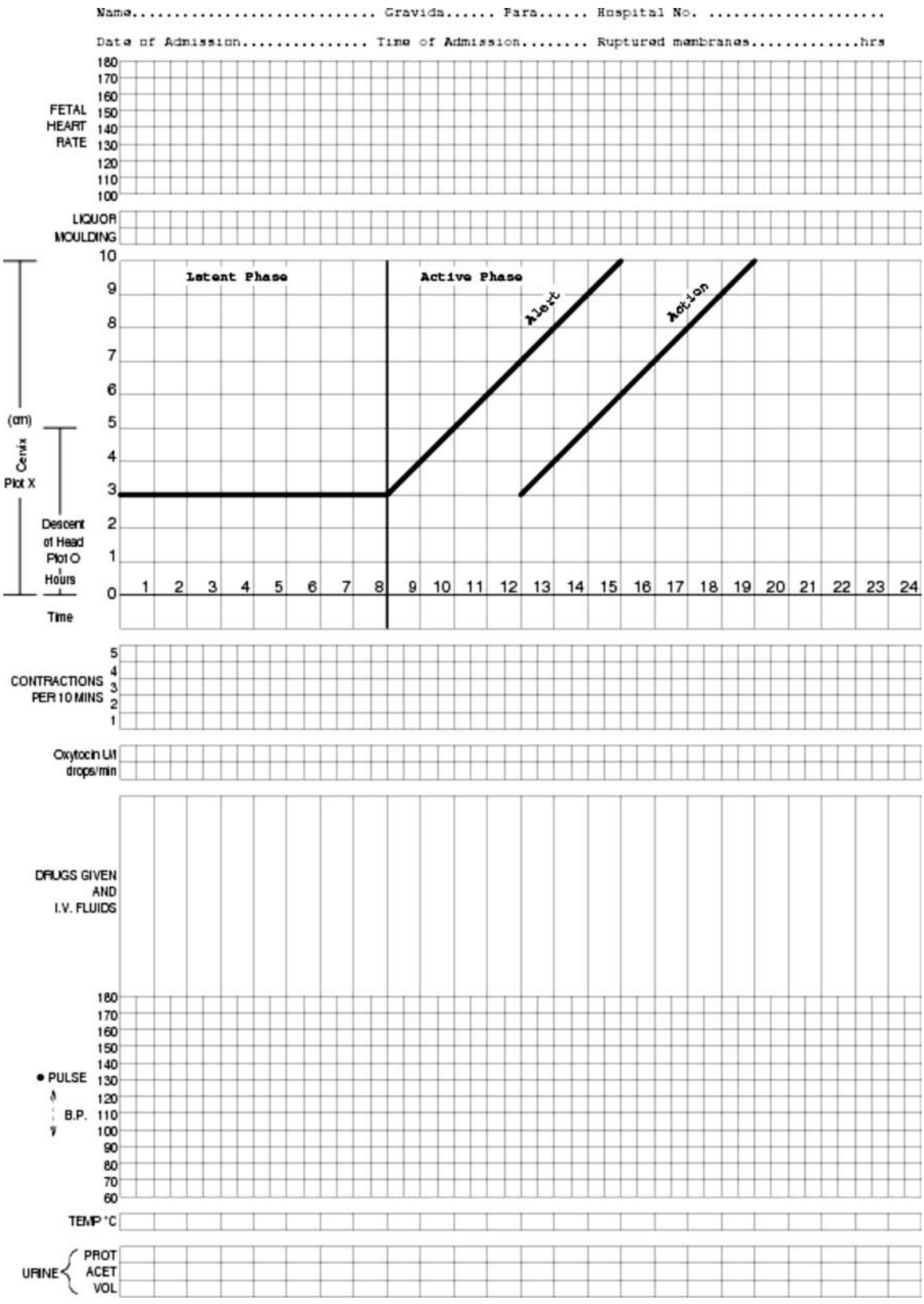

FIGURE 19.3 Example of a partogram to record progress in labour, including 'Alert' and 'Action' lines.

PROGRESS IN LABOUR – REVISING NORMAL DEFINITIONS

Evidence emerging over the last 10 years suggests that our previous view of normal progress in active labour as defined by Friedman (1cm/hour) has been incorrect.[11] O'Driscoll used the same criterion in the 'active management of labour' package, with an intervention applied as soon as cervical dilatation was <1cm/hour (amniotomy and oxytocin).[12] Zhang and colleagues have subsequently validated the correct curve for physiologically normal first stage labour in a large cohort of 62,415 women.[13] They also reviewed historical data relating to Friedman's curves and highlighted flaws in the analysis caused by two incorrect statistical assumptions:

(a) Firstly, cervical dilatation data are 'interval-censored': It is assumed that progress between two fixed points in time is at a linear rate (i.e. that from time '0' when 3 cm dilated, to time '+4 hours' when 7 cm dilated, progress occurs steadily at a fixed 1cm/hour). It is perfectly feasible that progress between time '0' and time '+2 hours is only 1cm, followed by 3 cm dilatation between time '+2 hours' and '+4 hours'. The same endpoint is reached.

(b) Secondly, because cervical examinations in any labour are repeated, they are necessarily related, and therefore, from a statistical point of view, are not truly independent events.

When analysis of the historic and contemporary data was undertaken, using statistically correct methodology, Zhang was able to confirm that the active first stage of labour progresses at a slower rate up to 6 cm, then accelerates up to full dilatation. The accelerative phase at 3cm and the decelerative phase at 8–9 cm in the Friedman curve were analytical 'errors'. We, therefore, have new labour curves available which should be used to define normal progress in labour in the 21st century. **Labour may take 6 hours or more to progress from 4 to 5 cm and a further 3 hours to progress to 6 cm. Using the new curves, it is apparent that primigravid and multigravid women progress at the same rate up to 6 cm. Thereafter, multigravid women progress much faster.** This is critically important data, which confirms that we should consider changing our practice. The new curves imply that we should be prepared to observe rather than intervene in labour that appears to be progressing slowly before 6 cm. In the USA, 38% of nulliparous women in spontaneous labour and 63% of those induced are delivered by emergency CS for 'failure to progress' when they have not yet reached 6 cm.[11] Laughon et al compared two US cohorts from the 'Collaborative Perinatal Project' and 'Consortium on Safe Labor' - ('CPP'; n = 39,491; born 1959–66 vs 'CSL'; n = 98,359; born 2002–08) and demonstrated a significant increase in the length of labour over the 50-year period.[14] The first stage of labour in the CSL group was a median of 2.6 hours longer for nulliparous and 2.0 hours for multiparous labour (adjusted for BMI, etc) – see Figures 19.4 and 19.5. The authors suggest that the prolongation is mostly due to changes in practice patterns, rather than to changes in the two study populations. Labour is significantly longer, despite a 19% increase in use of oxytocin. It would appear that many of the interventions we use are not only ineffective, but may actively contribute to increased operative delivery rates. It is interesting to note that the shape of the labour curves in Figures 19.4 and 19.5, is exactly as described by Zhang et al,[13] with slower progress in normal labour before 6 cm dilatation.

A comprehensive, evidence-based review of all aspects of intrapartum care was published in the UK in 2008 and

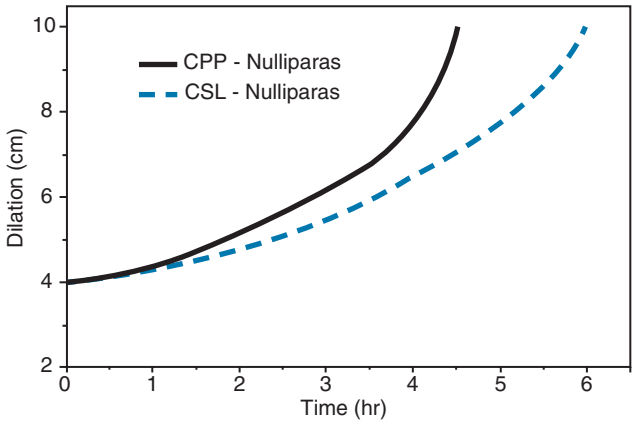

FIGURE 19.4 Average labour curves comparing progress for nulliparous women with singleton term pregnancies in CPP and CSL studies. From: Laughon SK, Branch DW, Beaver J, Zhang J. Changes in labour patterns over 50 years. *Am J Obstet Gynecol.* 2012;206(5):419 e1–9. (Used with permission).

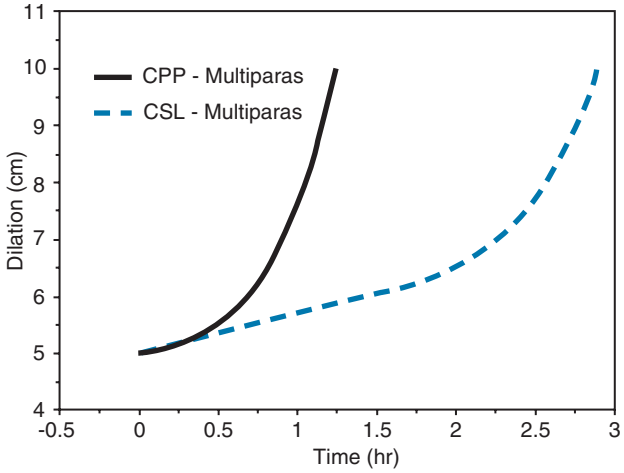

FIGURE 19.5 Average labour curves comparing progress for multiparous women with singleton term pregnancies in CPP and CSL studies (note: time differences for labour duration compared to Figure 19.4). From: Laughon SK, Branch DW, Beaver J, et al. Changes in labor patterns over 50 years. *Am J Obstet Gynecol.* 2012;206(5):419 e1–9. (Used with permission).

included guidance on the normal length of the various stages and phases of labour.[15] These are detailed in Table 19.2. Consensus agreement defined the start of the active first stage as 4 cm dilatation with an average length (range) of 8.0 (1.0 to 19.4) hours for nulliparous women. Taken in context with the contemporary labour curves described by Zhang et al, the upper limit of 19.4 hours may not be as 'abnormal' as we may previously have thought. This data may encourage obstetricians to consider *delaying intervention* for some cases of perceived 'dysfunctional labour', particularly at dilatations <6 cm. As a profession, obstetricians have generally offered intervention relatively early in the management of slow labour, even in low-risk women. This is usually in the form of forewater amniotomy +/ oxtocin infusion. Williams et al reviewed the labours of 3160 'low risk' primiparous women in the UK (1998) and found high rates of intervention: 72% had more vaginal examinations than expected, 53% underwent amniotomy, 38% were augmented with oxytocin and > 25% underwent instrumental delivery.[16] National Institute for Health and Care Excellence (NICE) guidance recommends that in established labour, delay is suspected with dilatation <2cm in 4 hours when amniotomy can be considered.[15] Delay is confirmed with subsequent dilatation <1cm in 2 hours, when an obstetrician should be informed.

Other intrinsic factors have measurable effects on the labour curve and should be considered when assessing labour progress. Increasing BMI is associated with delay in the labour curve[17-19] and an increased risk of caesarean section.[20] Median duration of labour was significantly longer in obese women, (Class I [BMI 30–34.9] = 9.1 hours, class II [BMI 35–39.9] = 9.2 hours and class III [BMI > 40] = 9.8 hours) compared to normal-weight women (BMI 18.5–24.9) = 8.8 hours ($p < 0.001$). Labour >12 hours increased with rising BMI: OR (95%CI) = 1.04 (1.01–1.06) (OR per 5-units BMI-increase).[17] In a large study of singleton pregnancies (n = 436,414), when compared to women with no net change in BMI, women with excessive BMI changes had an 80% increased incidence of caesarean delivery (OR =1.78).[20] Increasing gestational age is also associated with a significant incremental increase in labour length: (423.6 +/- 180.9 mins) at 36 weeks rising to (568.2 +/- 273.8 mins) at 40 weeks ($p < 0.013$)].[21] Even fetal sex influences labour length with male gender associated with a statistically longer active first stage (4.6 vs. 4.0 hours; $p = 0.002$).[22] Finally, in managing twin labour, it is useful to remember that progress is significantly slower than in singleton labour. In a retrospective review of 891 twin sets, labouring >34 weeks, the active first stage was longer in both nulliparous (median difference 3.1 hours) and multiparous patients (median difference 2.4 hours), even when controlled forconfounding factors.[23]

DYSFUNCTIONAL LABOUR

The clinical classification that is commonly used to describe abnormal progress in labour is outlined in Table 19.3. 'Dystocia' is a generic term applied to poor or inadequate progress at any

TABLE 19.2 Recommended Duration of the Stages of Labour[a]

	Lower value	Upper value	Clinical interpretation
Nulliparous*			
Latent phase	1.7 hours	15.0 hours	No comment made
Active first stage	1.0 hours	19.4 hours	Average 8.0 hours (usually no longer than 18.0 hours)
Multiparous*			
Latent phase	Not studied	Not studied	No comment made
Active first stage	0.5 hours	14.9 hours	Average 5.0 hours (usually no longer than 12.0 hours)

*n = 6 descriptive studies - includes women with epidural analgesia

	Mean (SD)	Upper limit (mean + 2SDs)	Clinical interpretation
Nulliparous (n=3664)**			
Second stage	54 (44) mins	142 mins	0.5–2.5 hours (without epidural) 1.0–3.0 hours (with epidural)
Multiparous (n = 6389)**			
Second stage	1 8 (21) mins	60 mins	Up to 1 hour (without epidural) Up to 2 hours (with epidural)

**n = 3 descriptive studies - excludes women with epidural analgesia and/or oxytocin.

[a]Reproduced from: National Collaborating Centre for Women and Child Health. Care of Healthy Women and their Babies during Childbirth. NICE Clinical Guideline No.55. London: RCOG; 2008, with the permission of the Royal College of Obstetricians and Gynaecologists.

TABLE 19.3 Abnormalities of Labour (with the Associated Commonly Used Clinical Classification)

Abnormalities of labour
Lack of progress in the latent phase ('prolonged latent phase')
Lack of progress in the active phase ('primary dysfunctional labour' and 'secondary arrest')
Lack of progress in the second stage ('delay in the second stage')

point in the first or second stage of labour. The true incidence is hard to ascertain but delay in labour, definedas the need to use oxytocin augmentation, affects between38 and 47% of spontaneous nulliparous labours at term.[9,16,24] Another term often used is 'failure to progress'. However, the word 'failure' may have negative connotations for the woman herself, especially if labour has been prolonged and she is exhausted. Overall, it is better to avoid using the term in discussions with the woman herself. The outcome of labour is related to the type of labour dysfunction. Instrumental and CS rates increase, the later the labour dysfunction occurs (20% with a normal pattern labour, 25% following a prolonged latent phase, 45% in primary dysfunctional labour and up to 55% in secondary arrest).[25] In considering use of effective interventions that will minimize obstetric intervention in dysfunctional labour, it is useful to remember that the pattern of maternity care offered in the antenatal period, influences labour progress and outcome. In the UK, midwifery-led care for appropriate low risk women is associated with lower epidural and operative vaginal delivery rates, with no increase in poor maternal or perinatal outcome.[26]

Causes of Labour Dysfunction

Table 19.4 outlines the main causes of dysfunctional labour and clinical management should concentrate on addressing these issues. Labour dysfunction is often described as 'hypotonic' (in the presence of inadequate uterine contractions) or 'hypertonic' (in the presence of incoordinate or excessively frequent uterine contractions). Hypotonic uterine activity is most commonly associated with nulliparous labour and early active phase dysfunction (i.e. 'primary dysfunctional labour' with poor progress between 4 and 7 cm dilatation).

Hypertonic uterine activity is a rare spontaneous event (1 in 3000 labours) and is more commonly seen in association with late active phase dysfunction (i.e. 'secondary arrest'). This may follow primary dysfunctional labour but also occurs after normal progress through the early active phase. The labour curve shows a decelerative/arrest pattern from 7 cm up to almost 10 cm dilatation. The commonest association is with occipito-posterior (OP) position in nulliparous women. This is an increasingly common and difficult dysfunction to deal with, as the woman is often exhausted after several hours in active labour. The risk of associated fetal compromise rises in the late first and

TABLE 19.4 Clinical Classification of Causes of Slow or Arrested Labour

Labour phase dysfunction	Causes
1st stage – latent phase dysfunction	
Prolonged latent phase	Idiopathic or iatrogenic Dehydration Maternal exhaustion
1st stage – active phase dysfunction	
Primary dysfunctional labour	Usually nulliparous with inadequate ('hypotonic') uterine activity
Secondary arrest	In-coordinate uterine activity ('hypertonic') Relative disproportion (associated with occipito-posterior position) Inadequate uterine activity ('hypotonic') Cervical 'dystocia' True disproportion (passenger too large or passage too small) Tumours – e.g. fibroids, ovarian cyst
2nd stage dysfunction	
Delay in the second stage	As for 1st stage – active phase dysfunction

second stages, particularly if there is delay in progress.[27-29] Hypertonic activity is often 'incoordinate'; contractions are not only increased in frequency (4–5 per 10 minutes), but the pattern becomes irregular with coupling of two or more contractions, without a rest period between. The baseline uterine tone also rises. Abnormal uterine activity may be monitored using external or internal pressure transducers (toco-dynamometry). The former is less invasive but the latter offers objective data about the strength, frequency and duration of contractions. However, a systematic review of three studies (n = 1945) showed no differences in multiple labour and neonatal outcomes, implying that simple external monitoring is appropriate.[30]

Cephalopelvic disproportion (CPD) is another cause of failure to progress in labour. 'True disproportion' is relatively rare and occurs when the presenting part of the fetus is too large and/or the maternal pelvis is too small. 'Pelvic dystocia' is uncommon in developed countries but may occur after pelvic trauma with significant distortion. In developing countries, the problem usually relates to dietary deficiencies resulting in a distorted and misshapen pelvis (e.g. Vitamin D deficiency and rickets). 'Relative' CPD is more common and is associated with fetal malpositions (e.g. OP) or malpresentations (e.g. brow). The management of 'OP labour is detailed in the sectionon the second stage. Cervical dystocia may be

found after cervical surgery and particularly 'cold cone' procedures. Fortunately with use of techniques such as large loop excision (LLETZ), significant scarring is uncommon.

THE FIRST STAGE - LATENT PHASE

Diagnosing active labour relies on objective assessment of uterine activity, cervical dilatation and/or descent and rotation of the presenting part of the fetus. In most cases, it is relatively easy to decide whether a woman is or is not in active labour. However, the same is not true for the latent phase, particularly when trying to decide if the latent phase is prolonged or dysfunctional. We see many women who feel they are in established labour, but show no signs of cervical change over many hours, despite overtly painful contractions. They become disheartened and require a lot of support on a one-to-one basis.[31-34] NICE guidance makes no comment on the average length of the latent phase, although the length can range up to 19.4 hours.[15] The cause in most cases is 'idiopathic' (i.e. unknown). It is unclear whether dehydration and maternal exhaustion are the 'cause' or 'consequence' of a prolonged latent phase. Even if labour progress subsequently progresses normally in the active phase, the presence of a prolonged latent phase increases the overall risk of operative intervention.

Managing the Prolonged Latent Phase

There is very little evidence to guide professionals in the management of dysfunctional labour in the latent phase. This is a time when hospital staff generally feel that a woman should be 'coping' at home, but this is not what the women themselves feel when they are having prolonged periods of painful uterine contractions with no apparent progress. In a randomized trial of 237 women, significantly fewer allocated to 'home care' (early visit and assessment at home) arrived at hospital in the latent stage of labour, compared to women offered telephone triage [OR(95%CI) 0.37(0.19–0.72)]. Significantly fewer women in the home care group received narcotics [OR(95%CI) 0.55(0.32–0.96)].[32] What is clear is that early intervention by amniotomy must be considered very carefully before 4 cm dilatation. The risk of 'failure to progress' is high, particularly in nulliparous patients with an uneffaced cervix. They may not enter the active phase of labour and require caesarean delivery if augmentation with oxytocin fails. This phase of labour is the one with least evidence available to guide practice and should be a focus for future research.

THE FIRST STAGE – ACTIVE PHASE

Diagnosing Delay in the First Stage of Labour

NICE guidance[15] outlines criteria for the diagnosis of delay in the established first stage of labour (>4 cm dilatation). Assessment needs to take into consideration all aspects of progress in labour including:

- cervical dilatation <2 cm in 4 hours for first labours
- cervical dilatation <2 cm in 4 hours or a slowing in the progress of labour for second or subsequent labours
- descent and rotation of the fetal head
- changes in the strength, duration and frequency of uterine contractions.

As outlined earlier in this chapter, there is a need to revise our management of early active phase dysfunction.[11,13,14] Given that cervical dilatation accelerates as labour advances, Zhang et al have recommended the adoption of a graduated and flexible approach to diagnosing dysfunctional labour, with vaginal assessments perhaps only 4 hourly under <6cm dilatation but more frequently in the accelerative phase >6cm.[35] This would facilitate early diagnosis of protracted progress in the latter part of the active first stage and allow prompt intervention in cases of developing 'secondary arrest'.

Management of Primary Dysfunctional Labour

This has mostly relied on elements of the active management of labour (AML) 'package' described by O'Driscoll.[12] The package was introduced to avoid prolonged nulliparous labour. It has been supported and criticized in equal measure. It is often viewed as 'interventionalist' as it recommends the two interventions of forewater amniotomy and oxytocin infusion as soon as labour progress is <1 cm/hour. Routine use of AML is no longer supported by NICE (UK). However, AML is a complete package with many other important elements beyond amniotomy and oxytocin: antenatal education, correct diagnosis of labour, one to one midwifery care in labour and critical audit of all caesarean sections. AML has incorrectly been promoted as 'lowering the CS rate' which was not its intended purpose. The following summary looks at outcomes related to amniotomy and use of oxytocin in the management of confirmed dysfunctional labour:

- Amniotomy
  - no significant difference in abnormal fetal heart rate (FHR) tracing following amniotomy[15]
  - high-level evidence that the duration is shortened by amniotomy (~ 1 hour)
- Oxytocin versus placebo (n = 3 trials)[36]
  - no significant differences in instrumental or CS rates
- Early use of oxytocin versus delayed use (n = 5 trials)[36]
  - no significant differences in instrumental or CS rates
  - significant reduction in length of labour (~ 2 hours)
  - increase in uterine hyperstimulation associated with FHR changes
  - no significant differences in neonatal or maternal outcomes

- Effect of augmentation on electronic FHR abnormalities[15]
  - no direct evidence of abnormal FHR tracing with oxytocin augmentation
  - no increase in rate of CS for fetal distress

Based on the summary above, obstetricians should consider whether early resort to amniotomy and oxytocin is required in 'primary dysfunctional labour'. If we are to embrace the revised labour curves described by Zhang et al, then deferring these interventions and applying them to confirmed delay after 6 cm dilatation may be the way forward. Further research is required to confirm if outcomes are improved. Oxytocin can be administered as low or high dose infusions. "High dose" regimens start as an initial dose of ≥4 mU/min and dose increments of at least 4 mU/min; "low-dose" start with an initial dose of 1–4 mU/min with increments of 1–2 mU/min. Incremental increases should occur no more than every 30 minutes with maximum rates up to 40mU/min. Two systematic reviews suggest that high-dose regimens are associated with a reduction in the CS rate: Wei et al reviewed 10 trials (n = 5423) with a 15% fall in CSR [RR (95%CI) 0.85(0.75–0.97)].[37] Kenyon et al reviewed four trials (n = 644) with a fall in CSR of 38% [RR(95%CI) 0.62(0.44–0.86)][38] Further research is recommended.

Primary dysfunctional labour will mostly affect nulliparous women. Multiparous women with confirmed delay in the first stage should be seen and fully assessed by an obstetrician and this should include an abdominal palpation and vaginal examination, before making a decision about use of oxytocin.[15] After implementing oxytocin augmentation, continuous electronic fetal heart rate monitoring should be used. The decision to proceed to emergency caesarean section is made clinically and must include assessment of the whole situation, including the length of protracted progress/arrest, the dose of oxytocin used, fetal and maternal condition as well as maternal wishes.

Management of Secondary Arrest

Diagnosis and management of arrest in the late first stage of labour can be managed in a similar way to early first stage dysfunction. However, in nulliparous labour 'hypertonic' uterine activity is common and an OP position can be confirmed in 30% of cases. Only 5–7% remain in that position by the time of delivery.[39] Maternal condition may be less favourable because of the time already spent in active labour. Attention should be paid to the degree of hydration that may require fluid replacement via intravenous infusion. Oxytocin infusion can be considered, but the obstetrician needs to be aware of the increased risk of hyper-stimulation/tachy-systole in the presence of preexisting hypertonic uterine activity. Even low doses of oxytocin can result in increased incoordinate uterine contractions and long runs of coupled contractions. These are often low amplitude, with a high baseline uterine tone. In this situation, contractility is inefficient and further progress tends to be at a very slow rate. Diagnosis of persistent OP position can be difficult clinically with increasing degrees of moulding and caput on vaginal assessment. Ultrasound has a clear role in complementing clinical assessment and is easy to teach and perform.[6,39] The decision to proceed to caesarean section usually results from complete arrest of cervical dilatation. With persistent OP position, the anterior cervical lip may become trapped between the impacted fetal head and the symphysis pubis. The lip can become increasingly oedematous if the fetal head remains deflexed. The decision to undertake CS should include a comprehensive review of the whole clinical situation as described in the previous section.

THE SECOND STAGE

The second stage of labour is a critical time for both mother and fetus and must be monitored closely. Overall, the risks of both maternal and perinatal adverse outcomes increase with second stage duration >3 hours for nulliparous and >2 hours for multiparous women.[29] Women require ongoing support through this important phase of labour and the birth attendant must be aware of the mother's wishes and plans for managing her delivery. The aim is to continuously provide information, support, and encouragement to the woman and her companion.[40] NICE makes the following recommendations about managing delay in the second stage[15]:

- Birth would be expected to take place within 3 hours (nulliparous) or 2 hours (multiparous) of the start of the active second stage in most women.
- A diagnosis of delay in the active second stage should be made when it has lasted 2 hours (nullip) or 1 hour (multip) and women should be referred to a health care professional trained to undertake an operative vaginal birth if birth is not imminent.

It is important to differentiate between the 'passive' and 'active' phases of the second stage. If a nulliparous patient is encouraged to push too soon, the risk of operative delivery is significantly increased. Full dilatation is frequently confirmed, in the absence of an urge to push and without clinical signs that the head is low in the pelvis (e.g. no anal dilatation and the presenting part not yet visible). Assuming that fetal condition is good, evidence suggests that a period of 'passive descent' should be encouraged to allow the presenting part to descent to the pelvic floor.[41-44] This will encourage rotation and is particularly useful in the presence of an epidural. The length of the passive phase should be at least one hour,[15] although Fraser et al showed maximum benefit (in terms of minimizing operative delivery) with passive descent for up to two hours in nulliparous women.[41] The time may be reduced for multiparous women. If delay

is diagnosed in the passive phase, there is no evidence to support starting an oxytocin infusion in the second stage.[15] However, in the presence of poor descent in a nulliparous patient, particularly with a persistent OP position, an effective epidural and a normal FHR pattern, the judicious use of oxytocin may encourage descent and rotation. Further research is required to confirm whether the rate of operative delivery is reduced. Without an epidural, careful re-assessment is required if a woman does not develop an urge to push after one hour of passive descent.

Most attendants encourage the use of active ('Valsalva') pushing in order to achieve delivery. A systematic review comparing Valsalva with spontaneous pushing (3 trials; n = 425; nulliparous; no epidural) confirmed no difference in instrumental/operative deliveries [RR(95%CI) 0.70(0.34–1.43)]. Although length of labour was significantly shorter in women who used Valsalva [mean difference (95%CI) 18.6(0.5–36.7)mins], urodynamic assessment three months postpartum was negatively affected by Valsalva pushing.[45] The authors concluded that evidence does not support routine use of Valsalva pushing in the second stage of labour.

EFFECTIVENESS OF OTHER INTERVENTIONS IN DYSFUNCTIONAL LABOUR

The following section summarizes the effects of other interventions in dysfunctional labour. All reported positive benefits were statistically significant:

1. **Continuous support in labour**[47]: Cochrane (22 trials; n = 15,288). Normal delivery (8% more likely); Labour shorter (mean -0.58 hours); Caesarean and instrumental rates (22% & 10% less likely)
2. **Intravenous fluids for reducing the length of labour**[48]: Cochrane (9 trials; n = 1781; nulliparous). The evidence does not provide robust evidence to recommend routine administration of intravenous fluids.
3. **Restricting oral fluid and food intake during labour**[49]: Cochrane (5 trials; n = 3103). Caesarean and instrumental rates (no effect). No justification for restriction of fluids and food in labour at low risk of complications.
4. **Maternal positions and mobility during first stage labour**[50]: Cochrane (25 trials; n = 5218). Walking/upright vs. recumbent (1st stage 1 hour 22 mins shorter); Caesarean (29% less likely)
5. **Position in second stage of labour for women with epidural anaesthesia**[51]: Cochrane (22 trials; n = 7280). Instrumental rate (22% less likely in upright position); blood loss >500ml (1.65 times more likely). Further definitive trials are ongoing.
6. **Position in second stage of labour for women without epidural anaesthesia**[52]: Cochrane (5 trials; n = 798). Insufficient data to say anything conclusive about the effect of position in the second stage of labour for women with epidural analgesia.
7. **Effect of epidural on operative delivery rates**[53]: Retrospective (n = 1000 nulliparous). Increased use of epidural analgesia had no effect on CS rates (epidural rate rose from 10 to 57% over 3 years). RCTs suggest increased risk of operative vaginal delivery.
8. **Effect of epidural vs. parenteral opioid analgesia on labour progress**[54]: Meta-analysis (10 trials; n = 2369; mixed nullip and multip). Epidural is not associated with increased risk of instrumented delivery for dystocia or CS. Labour with epidural is longer.
9. **Symphysiotomy for feto-pelvic disproportion**[55]: Cochrane – no randomized trials. 'Global bodies should produce guidelines for the use (or non-use) of symphysiotomy based on the best available evidence'. (Current evidence is from observational studies).

Table 19.5 summarizes the key recommendations relating to progress in labour, adapted from NICE UK national guidance.

MANAGING DYSFUNCTIONAL LABOUR – THE FUTURE

Dysfunctional labour affects up to 50% of women in their first labour and continues to concern all members of the obstetric team. Our management has relied on historical interpretations of the normal labour curve and in this chapter, we have detailed how emerging evidence reveals an altered shape to that curve, so that slower progress in the early active phase of labour (up to 6 cm) should be regarded as normal. We must be cautious and critical in applying the interventions that we have become familiar with and apply in our daily practice, as we may be inadvertently contributing to the increasing intervention rates, particularly seen in developed countries.

Basic scientific research continues to offer increasing knowledge of the physiology and pathophysiology that may underlie dysfunctional labour. Myometrial lactic acidosis associated with a small decrease in oxygen saturation may be contributing factors to dysfunctional labour. This may account for the relative ineffectiveness in management of dysfunctional labour with oxytocin.[56] Terkawi et al investigated the role of genetics in influencing labour progress and have shown that women who are homozygous for "G" at oxytocin receptor gene rs53576 transitioned from the latent to active phase of labour later, resulting in slower progress. They also demonstrated that the catechol-O-methyltransferase rs4633 genotype TT is associated with a more prolonged latent phase labour.[57]

In predicting and treating dysfunctional labour, several interesting areas are emerging. Pelvimetry was previously used after caesarean section to try and predict true

TABLE 19.5 Key Recommendations Relevant to Labour Progress – NICE Guidance*

Support in labour
A woman in established labour should receive supportive one-to-one care.
Normal labour
Clinical intervention should not be offered or advised where labour is progressing normally and the woman and baby are well.
Coping with pain
The opportunity to labour in water is recommended for pain relief. Before choosing epidural analgesia, women should be informed about the risks and benefits, and the implications for their labour.
Delay in the first stage of labour
When delay in the established first stage of labour is confirmed in nulliparous women, advice should be sought from an obstetrician and the use of oxytocin should be considered. The woman should be informed that the use of oxytocin following spontaneous or artificial rupture of the membranes will bring forward her time of birth but will not influence the mode of birth or other outcomes.

*Reproduced from: National Collaborating Centre for Women and Child Health. Care of Healthy Women and their Babies during Childbirth. NICE Clinical Guideline No.55. London: RCOG; 2008, with the permission of the Royal College of Obstetricians and Gynaecologists.

disproportion, but was abandoned because of its poor predictive value.[58] However, a recent study of 426 women showed that AP diameter at the midpelvis <10th centile is associated with an increased risk of caesarean section [RR (95%CI) 4.8 (3.9–5.8) p<0.01]. The area under the receiver operator characteristics curves for AP diameter was 0.88.[59] Uterine electromyography (EMG) can identify inefficient contractions leading to first-stage labour arrest in term nulliparous women who end up with caesarean delivery. Electrical activity in the myometrium during contractions is characterized by its power density spectrum (PDS) and early work confirms that PDS for women delivered by CS for first-stage arrest is significantly higher (0.55 Hz), than those delivering vaginally without (0.49 Hz) or with (0.51 Hz) augmentation ($p = 0.001$ and $p = 0.01$).[60] In the clinical field, there is an increasing literature assessing the use of ultrasound in labour, particularly looking at the likelihood of predicting both operative vaginal and caesarean delivery. The difficulties and challenges in managing dysfunctional labour in the 21st century are clear and a list of good practice points (Important Points) is provided at the end of the chapter.

SUMMARY

This chapter has emphasized the importance of recognising what constitutes normal progress in labour as a prerequisite to managing labour dystocia. Recent evidence suggests that labour length is increasing with slower progress expected in the early active phase (<6 cm). However, careful observation and timely intervention will still be required dependent on the individual situation and location where a woman's labour occurs. The woman should be intimately involved in decisions relating to management of her labour, even when progress is not normal. We have reviewed the management of abnormal labour during all three phases – latent first stage, active first stage and second stage, and have summarized both the historic and contemporary views. Recent research, including evidence from systematic reviews, has been presented to help the practitioner offer the most effective interventions when managing dysfunctional labour. An awareness of what interventions are effective will lead to improved outcomes and maximize patient safety, while minimizing operative delivery rates. Several familiar interventions will only reduce labour length, without affecting the caesarean section rate. Obstetric management in labour dystocia in primigravid women requires a combination of experience, science, and art, with the primary aim of avoiding operative delivery whenever possible, without detriment to the mother or fetus. This will ensure that risk in future labours is minimized, without the need for intensive intrapartum monitoring or intervention. Experiential learning and close collaboration between all members of the labour ward team is required in order to optimize outcome in dysfunctional labour. Particular care must be taken when signs of labour dystocia occur in multigravid women, both in the first and second stage. The risk of uterine rupture is real and must always be considered.

Important Points

- Progress in labour must be carefully assessed against expected norms for the population and the situation in which an individual woman labours
- 'Secondary arrest' in the late first stage of labour is associated with the highest risk of operative intervention
- Recent evidence suggests that normal progress in the early active first stage (<6 cm) is slower than previously expected and careful observation is appropriate

- The following interventions are known to shorten the length of labour and/or reduce operative intervention rates: amniotomy (shortens only) +/- (high dose) oxytocin augmentation, continuous support, mobilization and upright position
- The following interventions are of unproven benefit or may increase the likelihood of dysfunctional labour: withholding nutrition/fluids in labour, routine use of 'active management'
- Dysfunctional labour in a multigravid patient may indicate true disproportion with an increased risk of uterine rupture – assess comprehensively and use oxytocin augmentation with caution

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Chapter 20

Fetal Surveillance in Labour

Rohana Haththotuwa, Muhunthan K, and Sabaratnam Arulkumaran

Chapter Outline

INTRODUCTION

The purpose of intrapartum fetal surveillance is to avoid fetal deaths due to birth asphyxia or babies born in poor condition that would lead to neurological injury such as cerebral palsy. However confidential inquiries over the last two decades suggest that substandard care in labour leads to poor outcome despite using modern technology of cardiotocography (CTG).[1,2] Inability to interpret the CTG trace, i.e., poor pattern recognition; failure to correlate to the pathophysiology that causes the CTG changes, not taking into consideration the clinical situation that may suggest the feto-placental reserve and delay in taking appropriate action due to poor communication and team work are the identified reasons for the poor outcome.

The surrogate markers of birth asphyxia are Apgar scores at birth, cord arterial acid–base balance, the need for assisted ventilation and the neurological status of the newborn after birth. Of these parameters, neonatal encephalopathy grades II (neonatal convulsions) and III (coma) have a strong correlation to cerebral palsy.[3] It is known that pure intrapartum hypoxia contributes to less than 10%, whilst the combination of an antenatal and intrapartum insult may contribute to about 25% of those who suffer from neonatal encephalopathy.[4]

The brain tends to get injured due to infection, trauma, metabolic disorders and asphyxia. The time of gestation at which the asphyxia occurs will determine which part of the brain would get affected (Table 20.1). Asphyxia in animal models have provided us with information when we evaluate injury in human fetuses.[5]

'Acute profound hypoxia' results in athetoid type cerebral palsy (CP). Partial prolonged hypoxia results in spastic quadri-paretic CP. Magnetic resonance imaging (MRI) would show the scarring that reflects the injury at any date after the injury and will be a permanent marker. MRI studies of babies with cerebral palsy in Gothenborg, Sweden with a stable population have revealed that nearly 28% of the babies had some asphyxia contribution for their injury in the peripartum period.[6]

INDICATIONS FOR CONTINUOUS ELECTRONIC FETAL MONITORING

There are number of antenatal and intrapartum high-risk factors that are known to be associated with poor outcome and most guidelines recommend continuous electronic monitoring in these cases and are given in Table 20.2.[7] Intermittent auscultation is recommended for those identified as low risk.

INTERMITTENT AUSCULTATION

In low-risk labour, the fetal heart should be auscultated every 15 minutes for aduration of one minute soon after a contraction during the first stage of labour and after every 5 minutes or after every other contraction during the second stage of labour. It is a good practice to palpate the maternal pulse to make sure one is listening to the fetal heart and not to a maternal pulse. The contractions are assessed by palpation that provides a good estimate of the frequency an approximation of the duration and does not provide good information of the amplitude. In practice it is plotted in a partogram as the frequency over 10 minutes (dots for duration of <20 seconds; lines if 20–40 seconds and fully

TABLE 20.1 Patterns of Asphyxial Injury Seen in Term Animals

Brainstem, thalamus and hypothalamic area get affected with acute profound hypoxia and are reflected as prolonged bradycardia.
Prolonged partial hypoxia that is reflected by intermittent decelerations over a long period of time which is associated with acidosis causes brain swelling and cortical necrosis.
Prolonged partial hypoxia without acidosis causes white matter injury.
Total asphyxia preceded by prolonged partial hypoxia with mixed acidosis causes injury to the cortex, thalamus and basal ganglia.

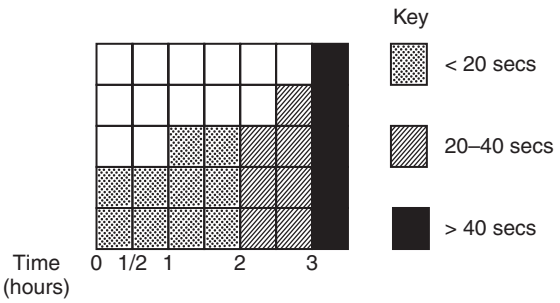

FIGURE 20.1 Monitoring and recording of uterine contractions based on clinical palpation.

shaded if >40 s) (Fig. 20.1). Intermittent auscultation (IA) could be done by a fetal stethoscope or by using a fetal Doptone. One should encounter meconium in the amniotic fluid, or have difficulty with auscultation, or an abnormal heart rate then electronic fetal heart rate monitoring (EFM) is advisable. It is known EFM in low-risk mothers increases surgical interventions without reduction in cerebral palsy.

CONTINUOUS CARDIOTOCOGRAPHY (CTG) / ELECTRONIC FETAL HEART RATE MONITORING (EFM)

Continuous tracing of the fetal heart rate (FHR) can be obtained with the use of an ultrasound transducer or by applications of a scalp electrode. Modern fetal monitors use auto-correlation technology that provides a good trace with the ultrasound transducer and hence the use for a scalp electrode is reduced. The scalp electrode is also contraindicated in cases of hepatitis B, AIDS and if Herpes infection is suspected.

An external transducer placed between the uterine fundus and the umbilicus to record the uterine contractions. The forward movements of the uterus with the contractions compress the toco-transducer's diaphragm to reflect the uterine contraction. From a recording of these events, the frequency, duration and approximate amplitude are calculated. Internal tocography is invasive and is not used in clinical practice as its benefit in labour is not proven.[8]

Technical error of inadvertently recording the mother's heart rate should be avoided by listening to the fetus prior to application of the ultrasound transducer. The use of CTG machines is standardized in terms of paper speed (1 cm/min in the UK and 3 cm/min in the USA) and the scale in which the FHR is displayed on the recording paper.[9]

In labour, there are number of interventions like sitting up, use of bed pan, performing a vaginal examination, etc. that would change the FHR and hence these activities should be recorded in the notes.

Central monitoring system allows the senior midwife or consultant to have an overview of the CTGs in all the rooms. It is a great tool for teaching and research by making use of the archived information. A 'second or fresh eye' approach provides better scrutiny of the traces.

TABLE 20.2 Recommended High-Risk Situations for the Use of Continuous EFM

Maternal	Fetal	Intrapartum Risk Factors
Induction of labour Trial of vaginal delivery after previous caesarean section Hypertensive disorders of pregnancy Prolonged pregnancy (>42 weeks) Prolonged rupture of membranes (>24 hours) Diabetes Antepartum haemorrhage Medical disorders, e.g. systemic lupus erythematosus	Intrauterine growth restriction (IUGR) Fetus at pre-term gestation Oligohydramnios Abnormal antenatal fetal tests (e.g., Doppler velocimetry of fetal vessels) Twin pregnancy (Triplets are usually delivered by CS due to difficulties in monitoring) Meconium stained liquor Pyrexia in labour or suspected intrauterine infection	Oxytocin augmentation Epidural analgesia – especially at the time of administration and soon afterwards; more risks when the head is low in the pelvis Vaginal bleeding in labour especially if associated with pain or uterine irritability Maternal pyrexia Fresh meconium-stained liquor

ADMISSION CTG

A 20 minutes CTG tracing with a few contractions on arrival to the labour ward, called the *admission CTG,* to screen for those fetuses that may not have the physiological reserve to tolerate labour is practiced in some countries like Sweden.[12] In the United Kingdom, it is not recommended by the National Institute of Clinical Excellence (NICE) because of inadequate evidence. Despite the recommendation the admission test is used by some when there is insufficient midwifery staff to provide one-to-one care and perform auscultation of the FHR for one minute every 15 minutes in the first stage and every 5 minutes in the second stage of labour.

Features of the CTG

On the CTG trace, the upper channel has the fetal heart rate (FHR) recording. Four features related to the FHR need to be identified and described; the baseline rate, baseline variability, accelerations and decelerations (Table 20.3). Individual features have the norms and the deviation from the norms and are described as reassuring or normal, non-reassuring and abnormal (Table 20.4). Based on the description of these four features, the CTG trace is classified as normal, suspicious or pathological (Table 20.5). The lower channel of the CTG has the contraction recording and has four features; baseline tone, frequency, duration and

TABLE 20.3 Definitions of Individual Features of Fetal Heart Trace as Described by NICE[7]

Term	Definition
Baseline fetal heart rate	The mean fetal heart rate when this is stable excluding accelerations and decelerations. It is determined over a period of 5–10 mins and expressed in bpm.
Normal baseline FHR	110–160 bpm
Moderate bradycardia	100–109 bpm
Moderate tachycardia	161–180 bpm
Abnormal bradycardia	<100 bpm
Abnormal tachycardia	>180 bpm
Baseline variability	Minor fluctuations in baseline FHR occurring at 3–5 cycles/minute. It is measured by estimating the difference in beats per minute between highest peak and lowest trough of fluctuation in a one minute segment of the trace.
Normal base line variability	Greater or equal to 5 bpm – 25 bpm between contractions
Non-reassuring baseline variability	Less than 5 bpm for 40 mins or more but less than 90 minutes
Abnormal baseline variability	Less than 5 bpm for 90 minutes or more
Accelerations	Transient increase in FHR of 15 bpm or more and lasting 15 seconds or more (Fig. 20.2)
Decelerations	Transient episodes of slowing of FHR below the baseline level of more than 15 bpm and lasting 15 seconds or more.
Early decelerations	Uniform, repetitive, periodic slowing of fetal heart rate with onset early in the contraction and return to baseline at end of contraction (Fig. 20.3.)
Late decelerations	Uniform, repetitive, periodic slowing of FHR with onset of deceleration 20 s later than onset of contraction or nadir of deceleration more than 20 s after the peak of the contraction or end of deceleration 20 s after the end of contraction. In the presence of a non-accelerative trace with baseline variability <5 bpm the definition would include decelerations of <15 bpm (Fig. 20.4).
Variable decelerations	Variable, intermittent, periodic slowing of FHR with rapid onset and recovery. Time relationships with contraction cycles are variable and they may occur in isolation (Fig. 20.5)
Prolonged decelerations	An abrupt decrease in FHR <80 bpm. It is suspicious if it is <3 mins and is pathological if it is >3 mins.
Sinusoidal pattern	A regular oscillation of the baseline resembling a sine wave with little baseline variability. This smooth, undulating pattern, lasting at least 10 mins, has a relatively fixed period of 3–5 cycles per minute and an amplitude of 5–15 bpm above and below the baseline (Fig. 20.6)

Reproduced from guidelines collated by RCOG in association with NICE (2001).[9]

TABLE 20.4 Classification of the Individual FHR Features (Intrapartum Care Guidelines of the National Institute of Health and Clinical Excellence - NICE 2007)[7]

Feature	Baseline Rate (bpm)	Variability	Decelerations	Accelerations
Reassuring (Fig. 20.2)	110–160	≥5	None	Present
Non-reassuring	100–109	<5 for >40 minutes but <90 minutes	Typical Variable decelerations with over 50% of contractions occurring for >90 mins	The absence of accelerations with an otherwise normal CTG is of uncertain significance
	161–180			
			Single prolonged deceleration<80 bpm up to 3 min	
Abnormal	<100	<5 for ≥90 minutes	Atypical variable or late or both decelerations occurring over 50% of contractions in a 30 min period	
	>180			
	Sinusoidal pattern for more than 10 minutes		Single prolonged deceleration <80 bpm for >3 minutes	

TABLE 20.5 Classification of CTG (Taking into Consideration all the Four Features of the CTG According to Intrapartum Care NICE Guidelines - 2007)[7]

Category	Definition
Normal	A CTG where all four features are classified as 'reassuring'
Suspicious	A CTG where one feature is classified as 'non-reassuring' and the other features are reassuring
Pathological	A CTG where two or more features are classified as non-reassuring or one or more classified as abnormal

amplitude of the contractions. These features can be assessed accurately by internal tocography. External tocography does not measure the baseline tone or pressure, provides a relative measure of the amplitude, a near approximation of the duration and an accurate measure of the frequency. Decelerations seen in the FHR trace is interpreted in relation to the contractions.

The CTG is considered as normal if all the four features are within the defined parameters for normal, i.e., baseline rate 110–160 bpm; baseline variability of 5–25 bpm; accelerations of 15 bpm for 15 s X 2 in a 15 min window. Acidosis is unlikely with a normal trace with accelerations.[10] As the fetus grows in maturity, it adapts regular behavioural patterns and at term the fetus develops periods of active and quiescent episodes. The quiescent episode is reflected by no or sporadic accelerations and reduced variability. This alternates with periods of active episodes reflected by cluster of accelerations and normal baseline variability (Fig. 20.2). The repeated alternate episodes of active and quiet periods are called '*cycling*'. The absence of cycling reflects the possibility of a previous neurological injury (e.g., intracranial bleeding). One has to be aware that there may be other reasons for the absence of cyclicity – e.g., infection, medication, prolonged quiet epoch, hypoxic fetus, post recovery period after maternal anaesthesia or metabolic problems. The outcome of these babies would depend on the causative factor for such a CTG trace and the severity of the insult.

The CTG trace with absence or minimal baseline variability, no accelerations, and repeated shallow late decelerations (pre-terminal CTG trace) may suggest a fetus that may be already hypoxic (Fig. 20.7). Often there may be clinical features of infection, bleeding, thick meconium with scanty fluid, severe pre-eclampsia, intrauterine growth restriction (IUGR), post-term or absent fetal movements suggesting that the cause is directly or indirectly related to hypoxia. This should not be confused with a trace that is reactive but within the period of the quiet epoch; it shows reduced baseline variability and shallow decelerations that coincides with the contractions. This pattern has been observed with fetal breathing episodes in an otherwise healthy fetus.[11]

One has to identify the pathophysiology that underlies the suspicious or pathological CTG in order to take appropriate action. Based on the situation this may be change of maternal position, hydration or reduction or stopping of oxytocin infusion. Continued observation is an acceptable form of management if there were no clinical high-risk

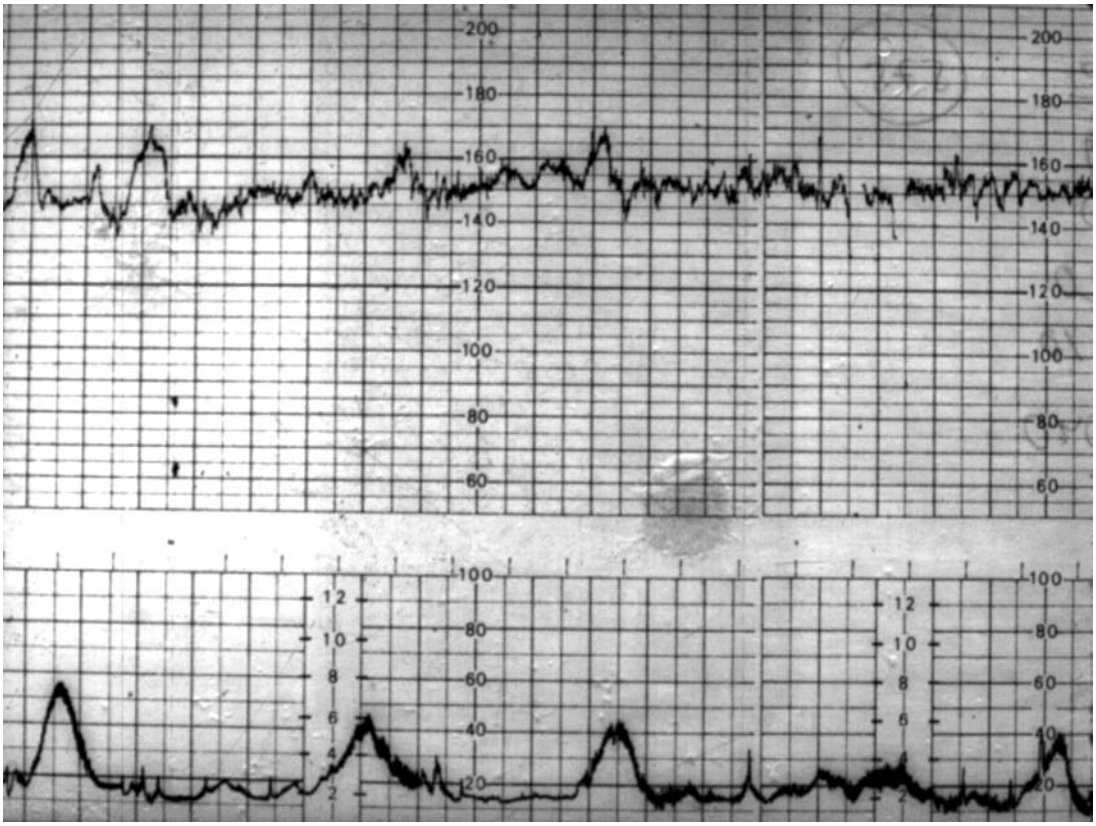

FIGURE 20.2 Reactive CTG with accelerations and also exhibiting an active and quiet epoch.

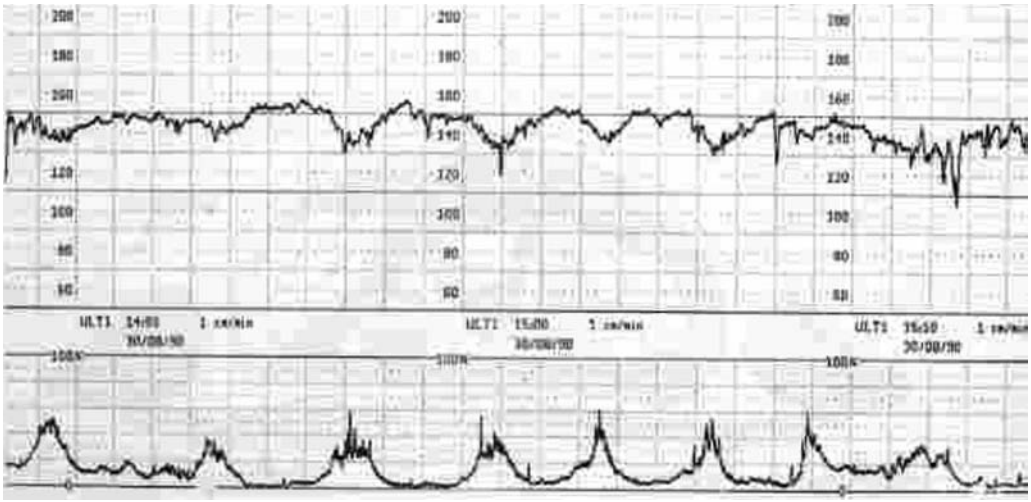

FIGURE 20.3 CTG trace with early decelerations.

factors that were of concern and only one feature in the CTG is abnormal, e.g., atypical variable decelerations but the baseline rate and the baseline variability is normal. The CTG is an investigation report like estimating a Hb% and the action will depend on the severity of anaemia detected and the clinical situation. Similarly in labour the action proposed would depend on parity, cervical dilatation and rate of progress, high-risk factors and the severity of the pathological trace (whether one, two or three features of the CTG is abnormal). The lack of understanding or non-consideration of these and acting solely based on the CTG increases operative delivery rates. Fetal scalp blood sampling to measure the acid–base balance can help to identify the fetuses that need to be delivered.

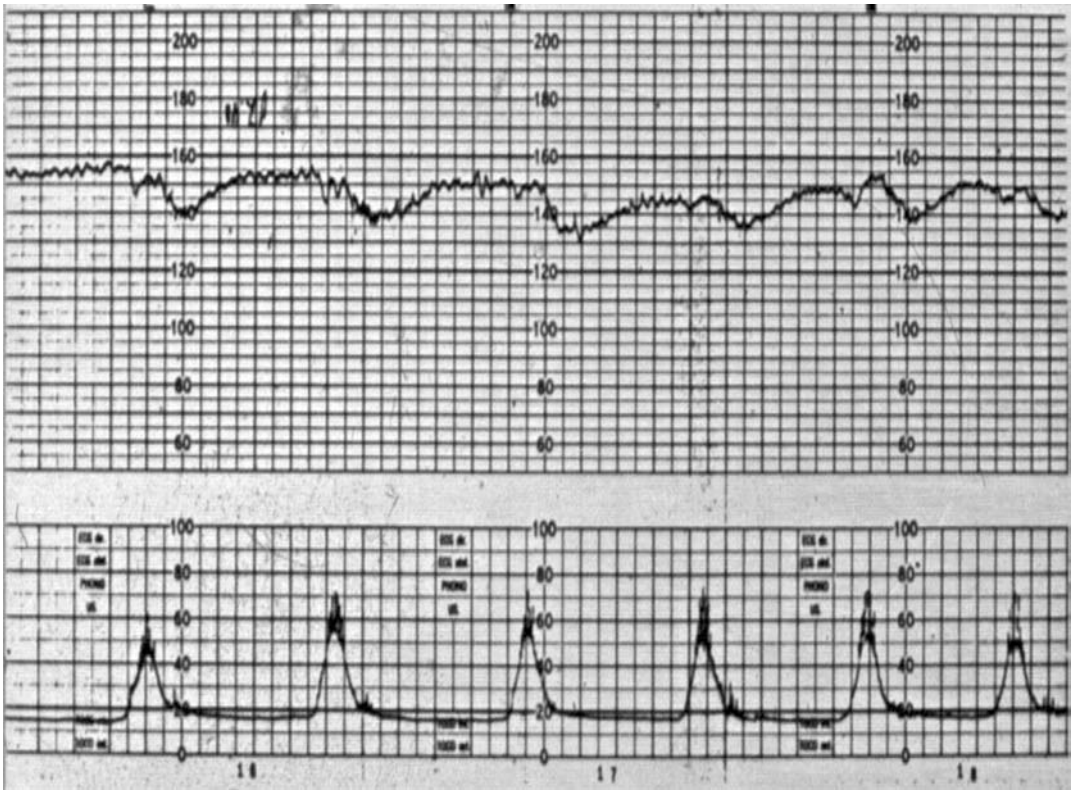

FIGURE 20.4 CTG trace with late decelerations.

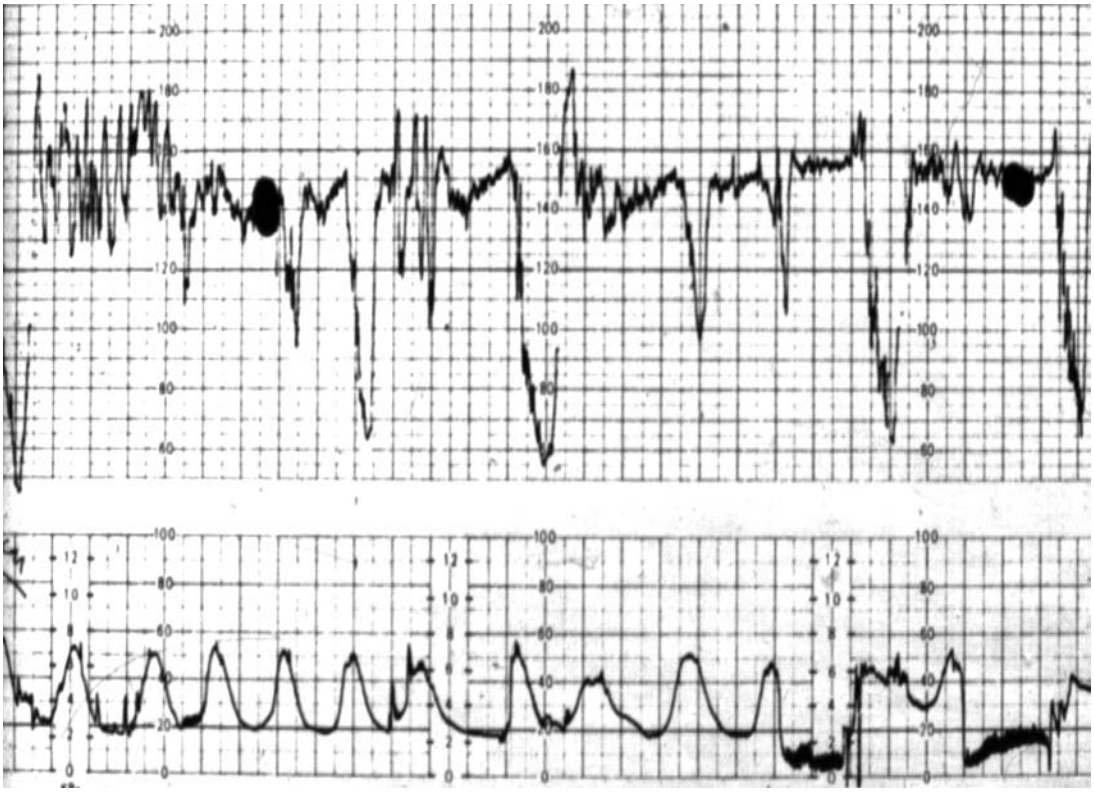

FIGURE 20.5 CTG trace with variable decelerations.

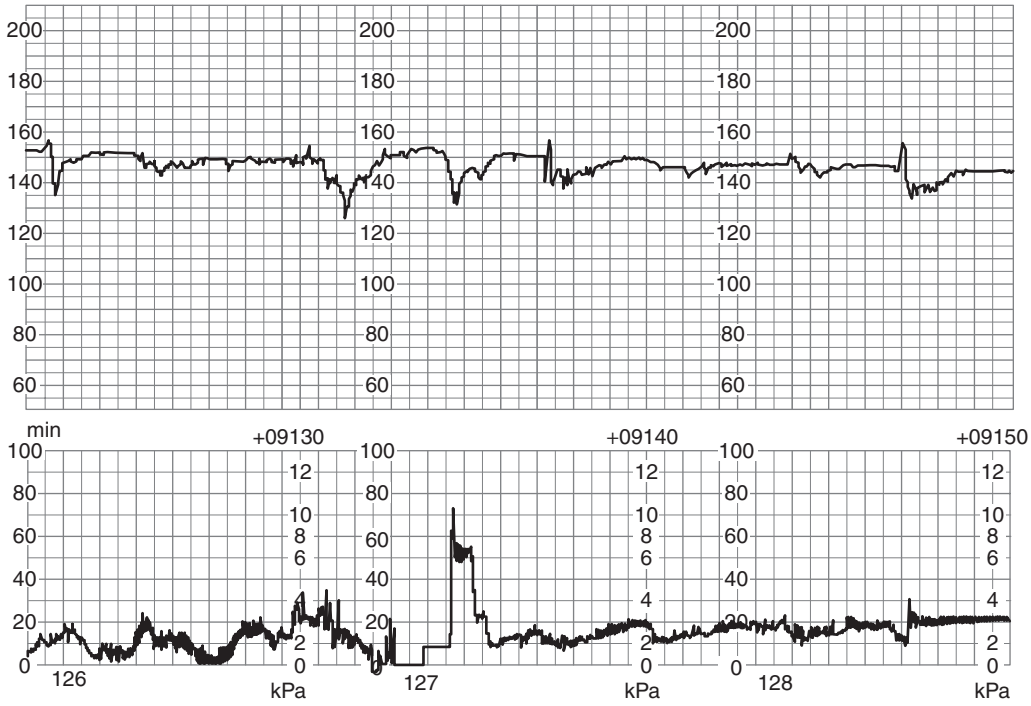

FIGURE 20.6 CTG suggestive of pre-existing hypoxia - terminal trace.

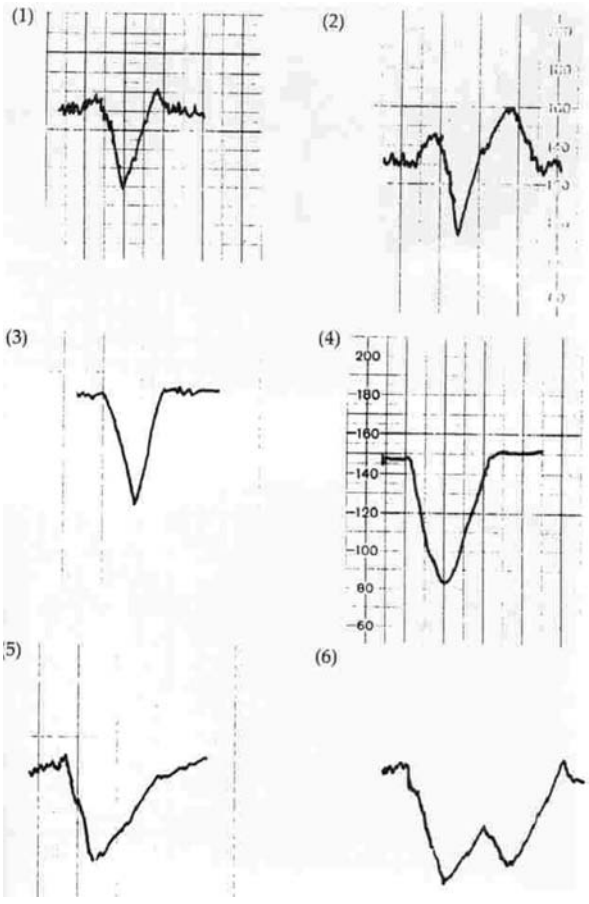

FIGURE 20.7 Variable decelerations - typical (1) and atypical (2-6).

Although the normal baseline rate is defined as 110–160 bpm and the rate 100–110 bpm and 160–180 bpm are considered as non-reassuring features, there is no concern to the fetus with these baseline rates, provided the baseline variability is normal (reassures the integrity of the autonomic nervous system), there are accelerations (reassures integrity of the somatic nervous system) and there are no decelerations (i.e., no stress). Early and variable decelerations in the late first or second stage of labour are not uncommon due to compression of the head. If there is no rise or fall in the baseline rate and the duration of the deceleration is shorter than the time spent at the baseline rate and there is normal baseline variability, there is no concern of fetal compromise. When there are any additional features to a simple typical variable deceleration, they are called *atypical variable decelerations*, e.g., biphasic decelerations are variable followed by late deceleration in continuity with the contraction. Others included in this category are deceleration that is >60 beats in depth for >60 s in duration or the deceleration that takes longer to return to baseline rate (Fig. 20.6).

Abnormal features of the CTG in labour may be due to one of many factors. Maternal posture, epidural, reduced amniotic fluid due to rupture of membranes, uterine hyperstimulation by prostaglandins or oxytocin infusion are iatrogenic factors that could be reversed with appropriate action. Inherent problems such as cord compression with oligohydramnios due to placental insufficiency in IUGR cannot be easily reversed. Interpretation of CTG is 'pattern recognition'. The

next step should be to identify the pathology that would have caused the CTG changes and to see whether they could be alleviated, e.g., by change of maternal position, hydration, stopping or reducing the oxytocins. Abruption, cord prolapse or scar rupture are acute events and need to be identified clinically although they would present with prolonged deceleration. Immediate delivery within 15 minutes is ideal in such situations, if one were to make sure of good clinical outcome.

If all the four features of the CTG are abnormal there is a high chance of acidosis with progress of time. Of all the features, continued absent baseline variability is more significant and is greater with a baseline rate that has risen with repeated atypical variable or late decelerations. One needs to be concerned when there is fetal tachycardia in relation to the admission heart rate, reduced baseline variability <5 bpm for >90 minutes with repeated complicated variable or late decelerations. Prolonged decelerations >3 minutes are likely to cause acidosis and is depended on the cause of the prolonged deceleration, the actual rate, the duration of the deceleration and the baseline variability. The fetal condition will depend on the duration of the pathological pattern but will vary from fetus to fetus based on the perceived physiological reserve.

Fetal heart rate accelerations indicate that the fetus is not hypoxic and has the capacity to increase the baseline fetal heart rate as a response to catecholamine surge due to hypoxic stress. The fetus increases its cardiac output by increase of the rate than of the stroke volume. Cord compression may show variable decelerations but yet the baseline rate would be normal with accelerations suggesting that the fetus is not hypoxic and the variable decelerations are due to baroreceptor response and not suggestive of hypoxia. Repetitive cord compression may cause hypoxia when the FHR accelerations cease followed by a gradual increase in the rate as a response to catecholamine surge. With increasing hypoxia, the depth and duration of the decelerations increase. Even with such increase in the baseline rate, if the autonomic system does not get sufficient oxygen, there is a decrease in the baseline variability and when it becomes absent along with the earlier features of increase in baseline rate and repetitive decelerations there is a high chance of fetal acidosis within one to two hours. One should consider altering the posture, stopping oxytocin, hydration and the use of tocolysis even in the absence of hyperstimulation to allow the fetus to resuscitate itself in utero. If no action is taken, the FHR rapidly decrease resulting in terminal prolonged deceleration that is difficult to recover and fetal death is inevitable.

Maternal intrauterine infection is associated with increased incidence of fetal hypoxic ischaemic encephalopathy and cerebral palsy. Hypoxia and infection has an adverse synergistic action on the brain. The first sign of intrauterine infection may be fetal tachycardia. When it spreads to the maternal side, it becomes evident with maternal pyrexia. In the absence of infection fetal tachycardia without decelerations may be due to dehydration or maternal pain necessitating pain relief and hydration when the FHR would settle to its normal rate.

All staff in the labour ward should recognize preterminal CTGs that has the characteristics of absent baseline variability and shallow late decelerations in a CTG trace that had no reactive segment (Fig. 20.5). Such a trace suggests a blunted response of the nervous system due to contraction-induced hypoxia. In some the trace may show hardly any features and may be like a straight line and in such cases neurological damage may have already occurred. However one could not be 100% certain of the condition of the fetus and it is prudent to conduct an immediate delivery with the neonatologist to assess and resuscitate the fetus. Prolongation of labour in such cases may expose the fetus to further uterine contractions that could worsen the fetal condition resulting in severe metabolic acidosis and death.

When the FHR is 140 bpm, there are 1400 circulations through the placenta and fetal organs. When the FHR drops to 80 bpm, there are only 800 circulations in 10 minutes, i.e., 600 circulations are missed thus having less oxygen/carbon dioxide transfer via the placenta which can lead to rapid buildup of respiratory and metabolic acidosis. Prolonged deceleration <80 bpm > 3 minutes could be due to reversible factors like maternal position, uterine hyperstimulation or maternal hypotension. Actions can be taken to resolve these issues with the return of the FHR back to its normal rate. The major concern is whether the cause of the prolonged deceleration is severe abruption, cord prolapse or caesarean scar rupture when immediate delivery is the only option unless the fetus can be delivered vaginally.

In those with reversible causes, the FHR should recover to its original baseline FHR by 6 minutes in the vast majority of cases. If not recovered by 6 minutes, all preparations should be taken and the mother should be taken to OT if the FHR had not recovered by 9 minutes.

Some urgency is needed and action to intervene is taken by 6 minutes if the prolonged deceleration was preceded by a pathological FHR pattern and in those with reduced feto-placental reserve such as in those with thick meconium and scanty fluid, IUGR, possible intrauterine infection, preterm, post-term and those with intrapartum bleeding. Those with no such concern up to 9 minutes could be given prior to transfer to operating theatre. All resuscitative measures such as nursing the mother on the left lateral position, stopping oxytocin infusion, hydration of the mother should be undertaken and consideration should be given for acute short-acting tocolysis especially if there is evidence of uterine hyperstimulation. Operative delivery, abdominal or vaginal should be commenced by 12 minutes with the aim of delivering the newborn by 15 minutes. Difficult

instrumental vaginal deliveries may take more time to perform and may be traumatic and should be avoided in such situations – this to some degree would be based on the clinical experience.

Skills and drills training improve the performance in reducing the decision to delivery interval in such emergencies. There should be regular cyclical audit to evaluate performance and to explore avenues to constantly improve on performance.

FETAL SCALP BLOOD SAMPLING

Taking a capillary sample of blood in the peripheral tissue of the fetal scalp to assess the performance and reserve of the fetal central organs of fetal brain and heart is not ideal but is helpful. Capillary pH is likely to be worse compared with the arterial and hence one consolation may be that actions taken based on capillary pH will prevent jeopardy of the fetus. FHR pattern interpretation is fraught with inter- and intraobserver variation. The presence of two or more suspicious, or one or more pathological features is classified as pathological. However the 'degree' of pathological nature is likely to have a range; atypical variable decelerations, with normal baseline rate and normal variability is pathological but is likely to be better than a fetus that has atypical variable decelerations, tachycardia and loss of baseline variability.

FBS may not be needed in all cases. The need for FBS would be dictated by the clinical situation and the CTG. Resuscitative measures of positioning, stopping oxytocin infusion and hydration should be tried to restore the CTG to normal.

The clinician should make an assessment of the degree of pathological features observed, the clinical 'fetal reserve', parity, cervical dilatation and rate of progress of labour and possibility of immediate instrumental vaginal delivery. Based on that assessment a fetal scalp blood sample (FBS) could be performed if it was judged to be necessary. The NICE guidelines recognize EFM as a screening tool and recommend the use of FBS. Cochrane review based on meta-analysis suggests a reduction in CS deliveries for fetal distress if FBS is used.

Those maternal infections that if transmitted to the fetus could give rise to life-threatening illness on the short or long-term are contraindications to FBS, e.g., HIV, hepatitis B or C, herpes. It is best avoided in fetal bleeding disorders such as haemophilia. In the preterm gestation (<34 weeks), fetal acidosis gives rise to respiratory distress syndrome and sequel. Hence FBS is avoided and CS is undertaken. FBS is not advised during or soon after the recovery of a prolonged deceleration. Performing FBS will delay a much needed intervention especially if the FHR does not return to normal. The pH could be deceptively low due to respiratory acidosis and it gets corrected when the FHR recovers to normal FHR.

TABLE 20.6 Normal and Abnormal Values of pH and Base Excess

pH	Base Excess
Normal: >7.25	< −8 mmol/l
Suspicious: 7.20–7.24	
Abnormal: <7.20	– 12 m mol/l

FBS is an uncomfortable procedure for the mother and due care and explanation is a must before, during and after the procedure. Based on the cervical dilatation, a suitable size amnioscope should be used. The amnioscope is advanced through the vagina and the cervix and kept firm against the scalp with a suitable light source providing the visibility of the scalp. The scalp skin is cleaned/ dried with tiny gauze swabs followed by spray of ethyl chloride to make the area hyperaemic. This is followed by application of thin film of paraffin to make the blood emerging become a blob rather than spreading over the skin. A small stab with a 2 mm blade is made and sample of blood (about 35 microlitres) is collected for blood gas analysis in a preheparinized capillary tube. FBS is less likely to be successful when the cervical dilatation is <3 cms or when the head is not fixed in the pelvis and is likely to move away with the pressure of the application of the amnioscope or at the time of making an incision. Reliable FBS results provide guides for further management (Table 20.6). Reliability is dependent upon obtaining a good quality sample of blood without contamination with amniotic fluid or air bubbles. Current training of junior doctors include obtaining FBS on a mannequin – this helps to reduce the procedure time and prevents the blood from clotting due to the slow flow.

The threshold for intervention is a pH of 7.20 or less when immediate delivery is indicated. A pH between 7.21 and 7.25 requires closer observation of the CTG trace and repeat FBS within 30 minutes and a drop in pH indicates delivery. If the pH is >7.25 based on CTG abnormalities persist for over one hour or worsen (decelerations getting deeper and wider and an increase in baseline rate or reduction of baseline variability), a repeat FBS should be performed after a suitable interval. If a FBS was done in labour, it would be prudent to perform cord blood gases to assess the condition of the newborn.

FETAL SCALP LACTATE

An alternative to blood gas analysis at FBS is to measure the lactate which is a direct indication of metabolic acidosis. The range for normality varies based on equipment used.[13] Most hand held machines require 5 μl of blood for lactate measurement compared with 35 μl that is required

for blood gas analysis. With 'Lactate-pro' machine, the normal range has been established as 2.9–3.08 mmol/l. With a pathological CTG and a lactate level >3.08 mmol immediate delivery is indicated.[14] Because of the smaller sample size needed for lactate measurement, the failure rate is about 5% compared with 18% for blood gas analysis are proving to be popular.[15] The lactate levels obtained at FBS correlates with cord blood gas analysis and 2 year follow up of neonates. Lactate measurement is recommended for clinical use based on available evidence and is used as a routine in many units in Scandinavian countries.[16]

FETAL PULSE OXIMETRY

Fetal oxygen saturation in labour by pulse oximetry is performed using different wavelengths of the infrared and the knowledge of differential absorption of the light by deoxygenated and oxygenated haemoglobin. One of the main obstacles for conducting large RCTs was the production of a good oximetry sensor that could be applied to the fetus. The earlier sensors were flexible sigma shaped and were passed beyond the head and pulled down to get it wedged between the uterine wall and the cheek of the fetus. With progress of labour and descent and rotation of the head, the contact became less than optimal with no or poor oximetry readings. A sensor that could be secured to the scalp with a spiral electrode has become popular. The readings from the sensor are passed via the standard fetal monitor and the oxygen saturation plotted continuously on the toco channel that displays 0–100. The oxygen dissociation curve of the fetus is different to that of the adult and the fetal oxygen saturation could vary between 30% and 80%. In the same fetus wide fluctuation of oxygen saturation is seen but the level does not drop <30% (3rd centile). If the oxygen saturation remains <30% for greater than 10 minutes, there would be a tendency for fetal acidosis.[17] From the time fetal pulse oximetry was introduced into the clinical arena, there were great expectations but the repeated Cochrane reviews has shown this method to be of little clinical use in reducing neonatal morbidity or caesarean section rate.[18]

FETAL ECG WAVEFORM – ST SEGMENT ANALYSIS (STAN)

The analysis of the ST segment of the ECG has been used in adult clinical medicine to identify ischaemia. Fetal ECG waveform analysis in animal pups of different species has shown rise in ST segment and increasing heights of T waves with hypoxia/ischaemia. Prospective descriptive studies in human labour enabled the identification of ECG changes with hypoxia and for introduction of this parameter as an adjunct to CTG for intrapartum fetal surveillance.[19]

The pathophysiology underlying these changes can be explained by the increased catecholamine levels that cause

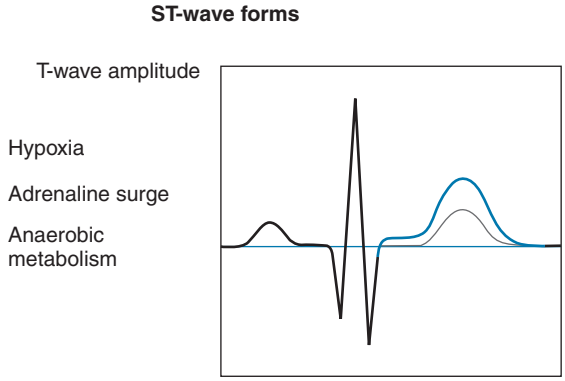

FIGURE 20.8 ECG waveform changes with hypoxia and adrenaline surge. *(With permission from Neoventa)*

the myocardial glycogen to be broken down to glucose and its passage with the K^+ into the cells. The liberated glucose enters the myocardial cells with the potassium ions causing the ST changes (Fig. 20.8). The ST segment changes can be periodic rise coinciding with the contractions or a steady rise in the baseline T/QRS. Intermittent stress linked with hypoxia and adrenaline surge but less hypoxia when uterine contraction subsides is reflected by the episodic rise and continuation of the hypoxia and increase of catecholamine level is reflected by a steady rise in the baseline T/QRS ratio. At times the ST segment is distorted as a biphasic pattern. If the distortion is above the isoelectric line drawn based on the p wave, it is called biphasic type 1; if it cuts the isoelectric line, it is called type 2 and if the biphasic ST segment is below the isoelectric line, it is called type 3. The biphasic pattern is linked to reduced refractory period for the myocardium to repolarize and could be seen with hypoxia, in preterm fetuses, with infection and in some cardiac conditions (Fig. 20.9).

Automated analysis of the fetal ECG needs a spiral scalp electrode on the fetal scalp and a maternal skin reference electrode on the maternal thigh and equipment to perform automated ST analysis. Thirty raw ECG signals are averaged into a single ECG for analysis and the T/QRS is plotted as a cross on the CTG paper in a scale of 0.0–0.50 just below the toco channel and is also displayed on the screen. The machine calculates the baseline T/QRS ratio in the first 20 mins and using that as the baseline measure any rise in the T wave or ST segment is reflected as a significant ST event (Fig. 20.10). The type of the ECG change, i.e., episodic rise, continuous baseline rise or biphasic change and the magnitude of these changes need to be considered (Fig. 20.11), followed by manual interpretation of the CTG. The changes in the CTG and the ECG would dictate the need for intervention and this would depend on the clinical situation and may be temporizing the situation such as position change, hydration, stopping oxytocin infusion or a decision to deliver the fetus. Clinical trials suggest that ECG waveform analysis is an adjunct to CTG monitoring and it

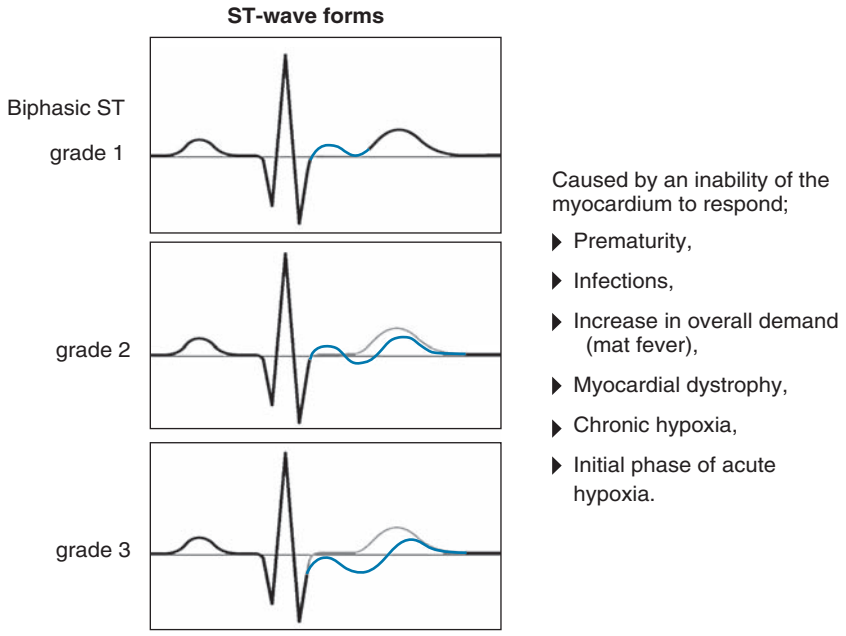

FIGURE 20.9 Biphasic ST waveforms. *(With permission from Neoventa)*

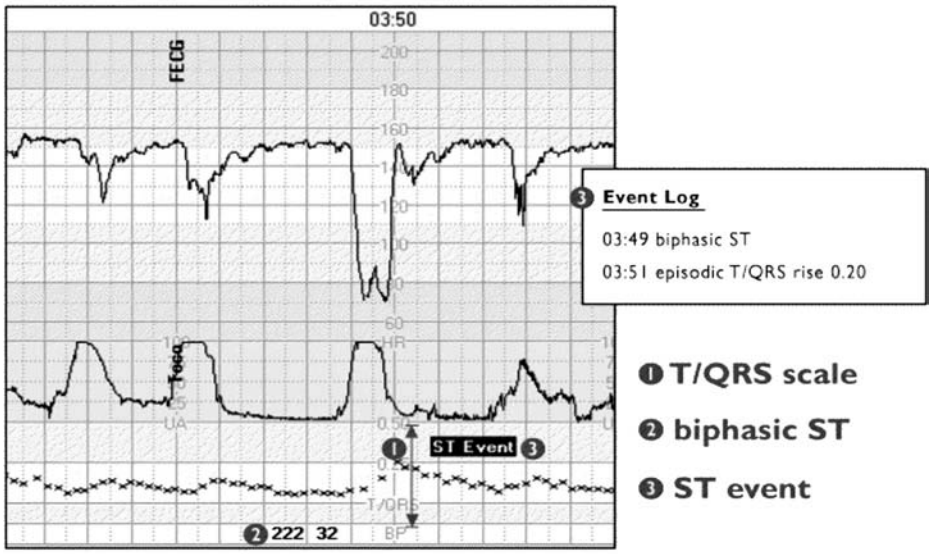

FIGURE 20.10 CTG and ST waveform analysis with ST event logs shown on screen. *(With permission from Neoventa)*

helps to reduce the incidence of fetal scalp blood sampling, metabolic acidosis, hypoxic ischaemic encephalopathy and total operative delivery rates.[20] Although rare, it is also possible in rare circumstances for the CTG to become pre-terminal without ECG changes.[21] The revised guidelines emphasizes the need for review of a pathological CTG by a senior person despite no ECG waveform changes and to intervene in 60 minutes in the presence of a pathological CTG in the second stage despite no ECG changes.[22] The FIGO classification of CTG is recommended for ST waveform analysis, the major difference being that the normal baseline rate is considered as 110–150 bpm and simple variable decelerations <60 s for <60 beats is considered normal.[23] Except of these differences, the NICE classification of CTG and interpretation of the features are similar.[7]

Most clinical studies on ST waveform analysis were done on fetuses greater than 36 weeks and it is known that preterm fetuses may exhibit several biphasic events and hence is not used in preterm labour. A reactive CTG does not warrant ST analysis as reactivity suggests a non-acidotic

ST analysis

These guidelines may indicate situations in which obstetric intervention[1] is required.

ST Events	Normal CTG	Intermediary CTG	Abnormal CTG	Preterminal CTG
Episodic T/QRS rise	• Expectant management • Continued observation	• >0.15	• >0.10	• Immediate delivery
Baseline T/QRS rise		• >0.10	• >0.05	
Biphasic ST		• 3 Biphasic log messages[2]	• 2 Biphasic log messages[2]	

[1]Intervention may include delivery or maternal-fetal resuscitation by alleviation of contributing problems such as over-stimulation or maternal hypotension and hypoxia.

[2]The time span between the Biphasic messages should be related to the CTG pattern and the clinical situation.

FIGURE 20.11 Guidelines for the use of CTG and STAN based on the type of ECG change and its magnitude. *(With permission from Neoventa)*

fetus. ST changes seen with a normal reactive CTG does not warrant action and may be due to transient catecholamine surge. A preterminal with no baseline variability and repeated shallow late decelerations (Fig. 20.6), or prolonged deceleration <80 bpm for >3 mins) warrants immediate delivery as no ST changes may appear in the former trace and it may be late to appear with prolonged deceleration and delay the much urgently needed intervention.

FETAL STIMULATION TESTS

Spontaneous accelerations in the CTG have been shown to be a reflection of a non-acidotic fetus. The observation of acceleration with scalp blood sampling and its association with non-acidotic fetuses has encouraged clinicians to adapt fetal stimulation tests.[24] The absence of accelerations to the stimulus suggests that the fetus may be acidotic and the need for FBS or delivery depending on the clinical situation.[25] Despite the absence of randomized controlled studies, the American College of Obstetricians and Gynecologists has recommended fetal acoustic stimulations as a possible adjunct to CTG in intrapartum fetal surveillance.[26]

Important Points

Based on available literature a Clinician's Guide to Interpretation of CTG was formulated two decades ago and the principles described still holds good to improve clinical practice and is given below.[27]

- Accelerations and normal baseline variability are hallmarks of fetal health.
- Accelerations with reduced baseline variability should be considered suspicious but may not be of concern.
- Periods of decreased baseline variability may represent fetal sleep but is of little concern if a reactive segment was seen prior to this episode and there was no rise in baseline rate and there were no decelerations.
- Hypoxic fetuses may have a normal baseline rate between 110 and 160 bpm with no accelerations and baseline variability <5 bpm for >40 mins.
- With baseline variability <5 bpm even repetitive shallow late decelerations <15 bpm are ominous in a non-reactive CTG.
- Placental abruption, cord prolapse and scar rupture can give rise to acute hypoxia and should be identified and dealt with clinically.
- Hypoxia and acidosis may develop faster with an abnormal trace in patients with scanty thick meconium, intrauterine growth restriction, intrauterine infection with pyrexia, and those who are pre- or post-term.
- In preterm (especially less than 34 weeks of gestation), hypoxia and acidosis can predispose to hyaline membrane disease, respiratory distress syndrome and may contribute to intra-ventricular haemorrhage and its sequelae warranting early action in the presence of pathological trace.
- Injudicious use of oxytocin, epidural anaesthesia and difficult deliveries can worsen hypoxia.
- During labour, if decelerations are absent, asphyxia is unlikely but cannot be excluded.
- Pathological patterns may represent effects of drugs, fetal anomaly, infection, cerebral haemorrhage and not only hypoxia.

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Chapter 21

Birth Asphyxia

Vikram Sinai Talaulikar and Sabaratnam Arulkumaran

Chapter Outline

INTRODUCTION

The universal aim of maternity care provision is birth of a healthy baby to a healthy mother. All birth attendants strive to achieve a good standard of care during labour to prevent an outcome such as 'birth asphyxia' and avoid its short or long-term consequences for the child. However, despite their best efforts, occurrences of birth asphyxia continue to happen in obstetric practice. Such cases can have profound implications not only for the child and the parents, but also the practising obstetrician or midwife.

Besides the injury, pain, suffering, loss experienced and costs of future care; the parents often feel let down and want to know the reasons for the adverse outcome. They expect accountability for actions from the health-care staff and wish to prevent recurrence of the event. Obstetric malpractice claims and their escalating costs have already become a major concern for maternity service providers across most of the developed world.[1] Malpractice claims can have significant long-term consequences for the working lives of midwives or obstetricians. Malpractice fears are also believed to have contributed in small part to the rising primary caesarean section rate (defensive practice) and played a considerable role in the downtrend in vaginal birth after caesarean statistics in some countries.[2]

MAGNITUDE OF THE PROBLEM

Intrapartum deaths occur in 0.75 out of 1000 births and hypoxic ischaemic encephalopathy (HIE) affects 2–3 out of thousand neonates born in the United Kingdom (UK). Worldwide, the WHO estimates that between 4 and 9 million newborns suffer birth asphyxia each year. Of these about 1 million infants die and a similar number survive with long-term disabilities related to birth injury.[3] Prompt detection and management of obstetric complications have the potential to prevent many of these deaths and disabilities.

DEFINITION OF BIRTH ASPHYXIA

The term '*birth asphyxia*' is best avoided as it is often difficult to conclusively prove that asphyxia occurred and time it in relation to the birth. Hypoxic ischaemic encephalopathy (HIE) appears to be a more specific term which describes the clinical and laboratory evidence of acute or subacute brain injury due to asphyxia (fetal hypoxia and acidosis). Birth asphyxia is one of the causes of neonatal encephalopathy which may also be caused by metabolic disorders and infections.[4] These alternative conditions should therefore be excluded before a confident diagnosis of HIE can be accepted.

Various criteria have been developed by different national bodies to define the term 'birth asphyxia'.

The American College of Obstetricians and Gynecologists (ACOG) issued the following in 1992.[5] For perinatal asphyxia to be linked to a neurological deficit in the child, all of the following criteria must be present: (a) profound umbilical artery metabolic or mixed acidaemia (pH <7.00), (b) persistence of an Apgar score of 0–3 for longer than 5 min, (c) neonatal neurological sequelae (e.g., seizures, coma, hypotonia) and (d) multiorgan system dysfunction (e.g., cardiovascular, gastrointestinal, haematologic, pulmonary, renal). In 1995, the Task Force on Cerebral Palsy and Neonatal Asphyxia of the Society of Obstetricians and Gynaecologists of Canada issued a policy statement in which they stated the same criteria with addition of umbilical artery base deficit of >16 mmol/L.[6]

An international consensus statement subsequently developed in 1999 redefined the following essential and/or additional criteria for birth asphyxia (intrapartum event leading to cerebral palsy).[7]

Essential criteria are:

- Profound umbilical artery metabolic acidaemia (pH <7.0 and base deficit (BD) >12 mmol/L).
- Early onset of severe or moderate encephalopathy in infants >34 weeks.
- Cerebral palsy of a spastic quadriplegic or dyskinetic type.
- Exclusion of other identifiable aetiologies, such as trauma, coagulation disorders, infectious conditions or genetic disorders. (The 4th criterion was added by ACOG in 2003).[8]

Additional criteria from the International Consensus Statement[7]:

- A sentinel hypoxic event occurring immediately before or during labour.
- A sudden rapid sustained deterioration in FHR pattern.
- Apgar scores of <7 after 5 minutes.
- Early evidence of multi-organ ischaemic injury.
- Early imaging evidence of acute cerebral involvement.

HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) – GRADING, IMAGING AND CLINICAL COURSE

Neonatal encephalopathy is clinically defined as a syndrome of disturbed neurological function occurring during the first week after birth characterized by difficulty in initiating and maintaining respiration, depression of tone and reflexes, altered level of consciousness and convulsions. Inadequate oxygen carrying in the blood (hypoxemia) and reduced blood circulation can lead to hypoxia. Hypoxic brain insult can lead to neonatal encephalopathy (NNE) in 12–36 hours. NNE due to hypoxia is termed as *hypoxic ischemic encephalopathy* (HIE). There are three grades—grade 1 is associated with involuntary movements, grade 2 is associated with convulsions and grade 3 presents with coma. The symptomatology may remain for up to 7–14 days despite treatment.[9] If asphyxia is suspected, further investigations and involvement of a multidisciplinary team are required. The team should include the obstetrician, neonatal nurse, paediatrician, neonatal neurologist and radiologists. Investigations such as electrophysiology, computerized tomographic (CT) scan, neonatal magnetic resonance imaging (MRI) and ultrasonography are used in assessing clinical course and long-term neurological function.

TABLE 21.1 Clinical Grading of Hypoxic Ischaemic Encephalopathy

Grade 1	Grade 2	Grade 3
• Hyper-alert, jittery and dilated pupils. • Strong Moro reflex. • Resolves within 24 hours without long term sequelae.	• Lethargic with seizures. • Weak suck and Moro reflex. Mild hypotonia. • 15-30% chance of severe sequelae. Duration 2–14 days	• Flaccid, stuporous, comatose • No suck, no Moro and prolonged seizures. • Raised intracranial pressure. Lasts for weeks. • 100% chance of severe sequelae.

HIE can vary in severity from grade 1 (mild) to grade 3 (severe). HIE is graded using clinical signs as summarized in Table 21.1. Full-term infants who suffer from Grade 2 or 3 encephalopathy are known to have a higher risk of long-term neurological damage. The prognosis is likely to be good if the CT/MRI looks normal. In cases with evidence of radiological damage – it is usually most obvious in the periventricular area which is most susceptible and appears as periventricular leucomalacia. Cerebral oedema indicates a recent event as it sets in usually within 6–12 hours of an insult and clears by 4 days afterwards.[10]

The major imaging signs of HIE on MRI vary depending on the type of hypoxia. Prolonged partial hypoxia as seen with several repetitive decelerations and absent baseline variability in a CTG trace presents with bilateral cortical atrophy and acute profound hypoxia represented as prolonged deceleration in a CTG trace presents with atrophy of the thalamus and basal ganglia region.[11,12]

PATHOPHYSIOLOGY OF BRAIN DAMAGE IN HIE

Neuronal cell death in HIE is both necrotic and apoptotic. Necrosis is often the result of a severe injury with cellular energy depletion and loss of membrane integrity resulting in

leakage of cytoplasmic contents and a secondary inflammatory reaction. Apoptosis is mainly seen with less severe or later phases of injury and is a highly controlled process of cell death. It is suggested that once cerebral injury occurs, substances such as glutamate tend to accumulate in the extracellular space causing over activation of neuronal receptors (NMDA) which results in excessive cellular influx of calcium. This increased intracellular calcium leads to activation of cell degrading enzymes such as lipases, proteases and endonucleases. Calcium also increases the free radical formation and these enhance the process of lipid peroxidation as well as mitochondrial and DNA damage.

MANAGEMENT

Following successful resuscitation of the newborn, the management consists of supportive care to maintain temperature, perfusion, ventilation and a normal metabolic state including glucose, calcium and acid–base balance. Early detection by clinical and biochemical monitoring and prompt management of complications must be done to prevent extension of cerebral injury.

Current management of neonates with birth asphyxia therefore focuses on (a) correction of haemodynamic and pulmonary disturbances, such as hypotension, hypoventilation, and acidosis, (b) correction of metabolic problems (glucose, calcium, magnesium and electrolytes), (c) treatment of seizures if present and (d) other advanced/specific therapies. Moderate hypothermia (33–34°C) initiated within 6 hours of birth and maintained up to 24–72 hours in infants with moderate encephalopathy reduces the mortality and long-term disabilities. A Cochrane review was conducted to determine the effect of therapeutic hypothermia in encephalopathic asphyxiated newborn infants on mortality, long-term neurodevelopmental disability and clinically important side effects.[13] Eleven randomized controlled trials comprizing 1505 term and late preterm infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia were included. Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age [typical relative risk [RR] 0.75 (95% CI 0.68 to 0.83); typical RD -0.15, 95% CI -0.20 to -0.10]. Cooling also resulted in statistically significant reductions in mortality [typical RR 0.75 (95% CI 0.64 to 0.88), typical RD -0.09 (95% CI -0.13 to -0.04)]; and in neurodevelopmental disability in survivors. Some adverse effects of hypothermia included an increase sinus bradycardia and a significant increase in thrombocytopenia.

Other specific therapies include use of high-frequency ventilation, inhaled nitric oxide for pulmonary hypertension and extra-corporeal membrane oxygenation (ECMO) as indicated. The efficacy of xenon gas, erythropoeitin and allopurinol in combination with the established treatment of hypothermia is being researched closely. Antioxidants, stem cell treatment and DNA repair mechanisms are paving the way for new treatment opportunities in the future.

LONG-TERM SEQUELAE AND PROGNOSIS

Although the timing and severity of the fetal injury is often difficult to determine if the injury occurs sometime before delivery, the infant will not develop spontaneous breathing at birth. If despite advanced life support, there is no sign of spontaneous breathing up to 20 min after birth, the outcome is likely to be extremely poor.[4]

In many cases, hypoxic injury followed by resuscitation may lead to apparent recovery followed by deterioration beginning 6–8 hours later. Several variables at delivery have been evaluated to establish their correlation with long-term neurological outcomes. Cardiotocography (CTG) and Apgar scores have not been found useful due to their non-specific nature. Umbilical cord arterial blood gas analysis at birth has emerged as an important method, used to support or refute a diagnosis of intrapartum asphyxia. Most maternity units now routinely determine umbilical cord arterial and venous blood acid–base status on deliveries where there has been any concern during labour, e.g., operative deliveries, cases where a fetal scalp blood sample was done, pathological CTG trace, those with meconium-stained amniotic fluid, bleeding in labour, preterm infants, multiple gestations, vaginal breech deliveries and the depressed infant at birth. However it is important to note that although metabolic acadaemia at birth is seen in about 2% of all births, vast majority of these infants do not develop cerebral palsy.

HIE grading (Grades 1–3 as described above) appears to be more useful in assessing long-term outcomes. Infants with grade 1 have a very good prognosis (most develop normally) whereas infants with grade 3 may die (50–70%) or have severe impairment.

Half the infants with grade 2 have severe neurodevelopmental impairment while those with grade 2 for less than 5 days generally do well.

Sequelae of HIE include mental retardation, epilepsy and cerebral palsy. Cerebral palsy is a non-progressive brain syndrome which may not be apparent until after the first year of life and which cannot be confidently diagnosed at birth. It is characterized by non-progressive abnormal control of movement or posture. In many circumstances it is impossible to say whether the cerebral insult was antenatal in origin or whether it occurred in labour. It has been suggested based on epidemiological data that in 90% of the cases, the cerebral injury is antenatal, while in remaining 10% attributable to either antenatal or intrapartum events. Although there is a strong association of cerebral palsy with prematurity, antepartum haemorrhage, fetal growth restriction, infections and chromosomal or congenital anomalies - many cases remain unexplained.[10]

MEDICO-LEGAL ISSUES SURROUNDING BIRTH ASPHYXIA

The intrapartum cardiotocography (CTG) trace forms a central piece of documentary evidence in litigations related to adverse perinatal outcomes which are alleged to have arisen due to events that took place during the labour and/or delivery of the baby. The legal process of the claim involves establishment of causation, liability and quantum. Once a claim is intimated, it is for the claimant to establish that there has been breach of duty, that is standard of care fell below what would be expected and the clinician did not act in accordance with what would be considered appropriate by a responsible body of medical opinion. The claimant must also establish 'causation' by showing that this failure has caused or materially contributed to the claimant suffering injury, loss or damage. Some of the questions which may arise during establishment of causation will relate to timing, type or severity of the injury and it is not always possible based on the CTG to accurately determine this. Determining 'liability' involves a scrutiny of the medical records to establish whether the standard of clinical care fell short of acceptable practice and whether appropriate action was taken in the presence of a pathological CTG. The timing of intervention and the definition of acceptable practice are major areas of dispute.

Liability is usually judged on what a reasonably competent practitioner would have done (the 'Bolam test'). The 'Bolitho principle' is based on the premise that the actions taken could be explained rationally to be logical and acceptable. Whether the decision and action taken were logical is decided by the judge.

The main reasons for litigation are not just for recovery of costs determined by injury, pain, loss and future care of a brain damaged child; but the parents also want to know what happened and why, and expect the healthcare staff to be held accountable for their actions. Majority of medico-legal cases have similar problems which can be laid down to a few factors such as (a) inability to interpret CTG trace or incorporate the entire clinical picture, (b) delayed or inappropriate action, (c) technical aspects and (d) record keeping. The best defence against litigation is good clinical practice with adherence to evidence-based guidelines. It is important that all staff on labour ward receive regular mandatory training in the interpretation of CTG as well as support and/or supervision when necessary. There should be a mechanism for the rapid review of adverse obstetric events and dissemination of key learning points to all staff.

BIRTH ASPHYXIA AND THE CHALLENGE OF INTRAPARTUM FETAL MONITORING

Intrapartum intermittent auscultation of fetal heart rate (FHR) and the CTG are the most widely used methods of fetal surveillance in labour throughout the world.

Intermittent Auscultation (IA)

Although intermittent auscultation has the advantages such as ease of monitoring, low cost and minimal training requirements; its use is associated with significant challenges while monitoring fetuses during labour. The most important of these are the facts that it is not possible to appreciate the pattern of fetal variability by auscultation alone and that it also does not provide objective evidence like a paper trace for medicolegal purposes. Also, in most situations of a busy maternity service when it is not possible to ensure that each healthcare personnel attend a single woman in labour, the success of auscultation will go down.

National Institute for Health and Clinical Excellence (NICE) guidelines presently recommend intermittent auscultation as a modality of choice for intrapartum fetal monitoring in low-risk pregnancies. Intrapartum intermittent auscultation of the FHR is a reasonable monitoring method for low-risk pregnancy as long as staffing patterns can guarantee a one-to-one care for each woman.[14]

Cardiotocography (CTG)

Electronic fetal monitoring (EFM) was introduced with the aim of reducing perinatal mortality and morbidity like cerebral palsy. Since its introduction in 1960s, the intrapartum and the admission use of the electronic fetal monitoring increased rapidly in well-resourced countries. Despite its shortcomings continuous intrapartum CTG remains the predominant method of intrapartum fetal surveillance wherever facilities allow, mainly because of medico-legal reasons (it provides a graphical trace record), also because it is helpful in identifying asphyxiating conditions during labour and because there is no other better independent monitoring modality yet established for widespread clinical use.

When intrapartum CTG was introduced in clinical practice, it was hoped that this method would reduce the incidence of cerebral palsy and mental retardation by 50%. However this dream was not realized. As reviewed by Freeman (2002) in his paper,[15] the disappointing outcomes associated with EFM may be due to the following:

- In a large number of cases the asphyxial damage may begin before labour and they would not benefit from intrapartum interventions.
- Acute asphyxia associated with events such as prolapsed cord, ruptured uterus, ruptured vasa praevia, abruption, maternal cardiorespiratory collapse and shoulder dystocia may not sometimes allow sufficient time for intervention before damage is done.
- A large proportion of surviving very low birth weight infants contribute to the existing cases of cerebral palsy.
- Fetal inflammatory response to infection/pyrexia may be responsible for a proportion of cases of cerebral palsy.

- The amount of asphyxia required to cause permanent neurological damage is very near the amount that causes fetal death, the number of patients who develop cerebral palsy caused by intrapartum asphyxia is probably quite small.

It is also possible that in some of the studies, the study sample size was not large enough to adequately determine the relationship between monitoring modality and neonatal mortality and/or morbidity rates. Furthermore, wide variations in the terminology used to define FHR pattern characteristics and differences in the criteria used to manage FHR patterns associated with presumed fetal acidaemia make it difficult to draw conclusions from meta analysis.[16]

Although abnormalities of the FHR are very common (in up to 75% of CTGs), true hypoxic events will occur in only 3/1000 labours so most observed CTG abnormalities are false positive. Despite the questions about its efficacy and controversy regarding increased rates of operative delivery associated with its use, continuous CTG remains the predominant method of intrapartum fetal monitoring. Although CTG is sensitive in detecting abnormalities of fetal heart rate (FHR), its specificity for detection of fetal hypoxia is low and therefore confirmatory tests such as fetal scalp blood sampling or analysis of fetal electrocardiography (ECG) become necessary.

Clinical Interpretation of CTGs – Adhering to Standards

There appears to be a consensus regarding the reassuring value of a normal reactive CTG pattern (Fig. 21.1) with accelerations, normal baseline, good variability without any decelerations. The clinical importance of a normal cardiotocograph (CTG) is that it establishes that the fetal neurological and cardiovascular systems are sufficiently intact and able to react to defend the fetus against intrapartum insults. A recent useful concept is that the normal trace should also have periods of reduced FHR variability, which alternate with periods of increased FHR variability with or without accelerations – known as the fetal 'cycling activity'. On the other hand, patterns containing absent variability associated with persistent late decelerations, severe atypical variable decelerations or prolonged decelerations are considered pathological and ominous (Fig. 21.2); and indicate the need for immediate delivery to avoid further hypoxic damage.

However difficulty arises when the CTG trace falls between the above two extremes and the obstetrician needs to decide the further action depending on the interpretation of the trace as well as overall clinical assessment of the case. Also, hypoxia is not the only damaging factor during labour. Recent studies suggest fetal inflammatory response due to infection/pyrexia as a cause of central nervous system damage.[17,18] Mismanagement of labour therefore may not always be the only factor relevant to the neonatal outcome. Several intrinsic fetal disorders cause neurological disability with abnormal CTG and the poor outcome may be coincidental.

Patterns of Hypoxia and Nature of Birth Injury

'*Hypoxaemia*' describes the condition where there is a reduction in the placental or cord blood flow causing a reduction in the level of oxygen in the peripheral arterial circulation of the fetus. This can happen in a normal labour with uterine

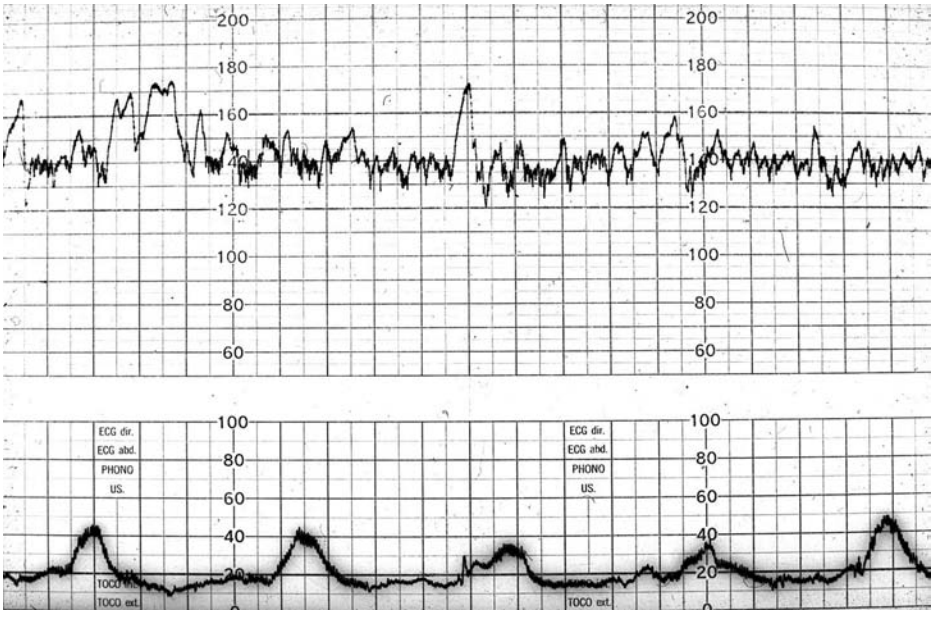


FIGURE 21.1 Normal reactive CTG with accelerations, normal baseline, good variability without any decelerations.

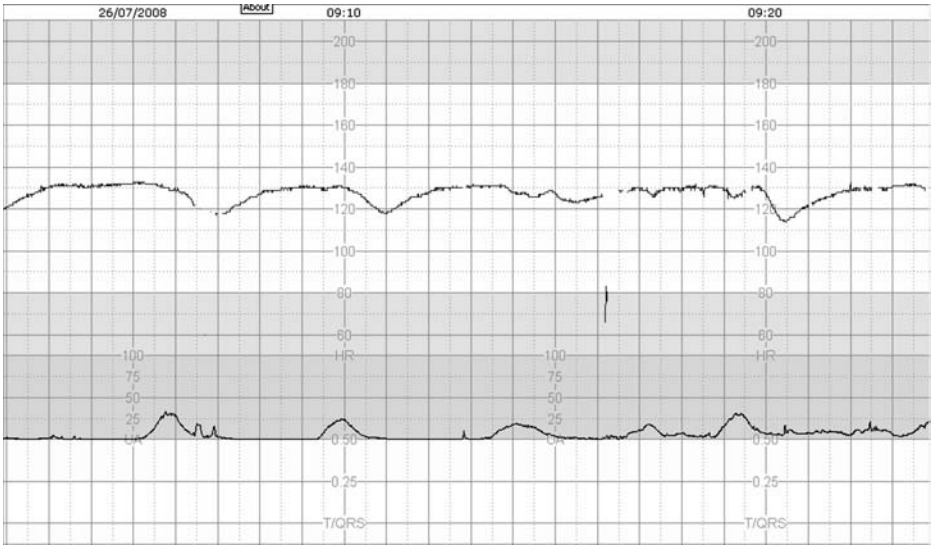


FIGURE 21.2 Pathological (pre-terminal) CTG with absent variability associated with shallow late decelerations.

contractions and majority of fetuses can cope well with such episodes for long periods of time without injury. '*Hypoxia*' describes the condition where the blood flow is interrupted for more prolonged periods of time and results in a reduction in the delivery of oxygen to the peripheral tissues of the fetus. If hypoxia continues for prolonged periods, the fetus switches to anaerobic metabolism to create energy and metabolic acidosis starts developing. In early stages, buffering will allow a normal pH to be maintained for sometime. In fetuses with compromised reserves such as preterm or growth-restricted fetuses, metabolic acidosis occurs earlier. Fetal infection also reduces the reserve to cope with hypoxia. '*Asphyxia*' describes the extreme condition where the oxygen delivery to tissues fails to leading to metabolic acidosis in addition to hypoxia. This leads to critical organ damage which may cause brain injury or fetal death in utero.

The nature of asphyxia can determine the type of brain injury and the neurological outcome as described by Myers in 1975:[19]

- Total asphyxia causes damage to the brainstem and thalamus (athetoid or dyskinetic cerebral palsy).
- Prolonged hypoxia with acidosis causes brain swelling and cortical necrosis (spastic quadriplegic cerebral palsy).
- Prolonged hypoxia without acidosis causes white matter damage.
- Total asphyxia preceded by prolonged hypoxia with mixed acidosis causes damage to the cortex, thalamus and basal ganglia.

Long Standing or Chronic Hypoxia

It happens due to reduction in placental blood flow over a long period of time and is associated with underlying conditions such as pre-eclampsia or fetal growth restriction. In the antenatal period the fetus will cope for a significant period of time by redistribution of the blood flow to vital organs, reduction in growth or activity and buffering against lactic acid. Surveillance with Doppler ultrasound can detect the point where decompensation is likely so that delivery can be recommended.[3] In labour, it may present with a CTG trace with no baseline variability and shallow late decelerations (Fig. 21.2).

Gradually Developing Hypoxia

In gradually developing hypoxia accelerations do not appear, the baseline rate increases and the variability reduces with progress of time. The decelerations get deeper and wider with increasing hypoxia. One needs to consider the clinical picture of parity, cervical dilatation, rate of progress and high-risk factors, and either perform fetal scalp blood sampling (FBS) or consider delivery.

The natural response for the fetus with hypoxic stress that previously had a reactive CTG would be the appearance of decelerations (variable due to cord compression or late due to placental insufficiency), the disappearance of accelerations (fetal response to conserve energy), gradual rise in the baseline rate (due to hypoxia and catecholamine surge), deepening and widening of the decelerations (with increasing hypoxia to the myocardium) and finally progressive reduction of the baseline variability (after a maximum baseline rate has been achieved and with further lack of oxygen there is depression of the autonomic nervous system). Within reasonable time (60–90 min) of no baseline variability in the CTG, i.e., flat baseline variability with tachycardia and repeated late or atypical variable decelerations, delivery should be carried out if one were to avoid a baby with low Apgar scores and cord blood metabolic acidosis. An alternative would be to perform a fetal scalp blood sample (FBS) for

determination of the acid–base balance and then to decide the management based on the FBS results.

The following series of CTGs provide information as to how the CTG changes take place when there is progressive gradual increase in hypoxia. (Fig. 21.3 a–f).

Now the actions should be delivery or fetal scalp blood sampling to decide on further management or if she is on oxytocin infusion to stop the infusion till the FHR returns to normal and the decelerations become less pronounced in depth and duration.

A

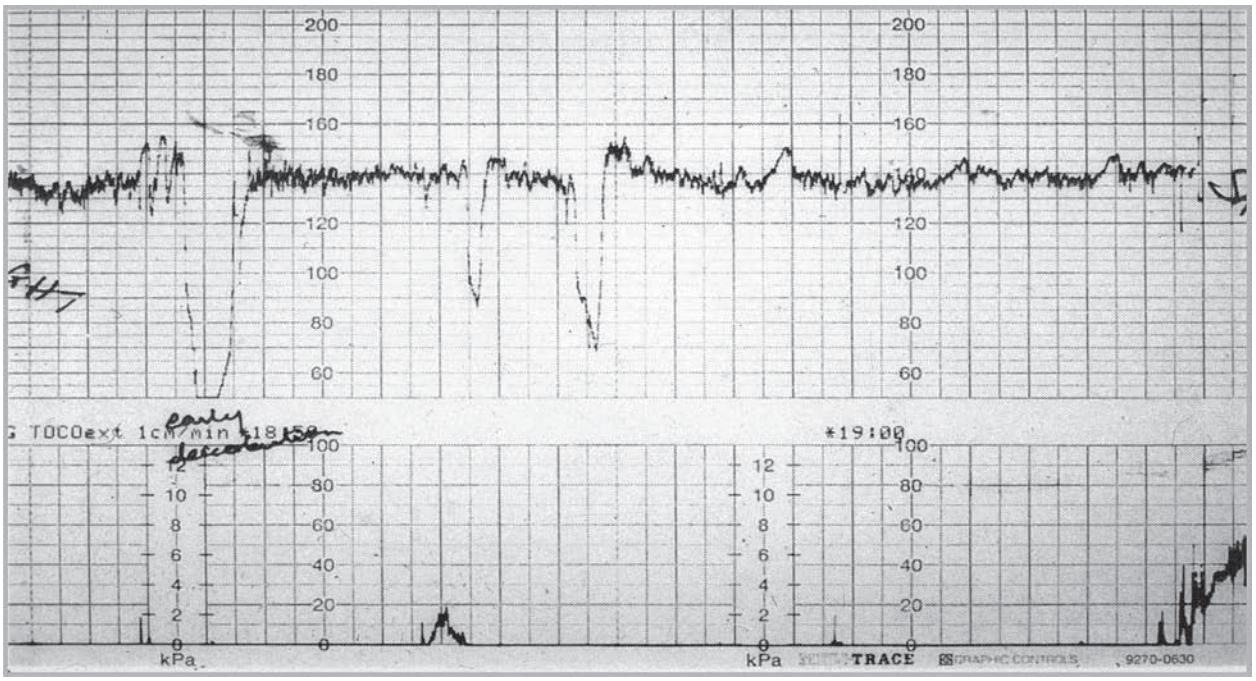


FIGURE 21.3(a) The CTG shows a baseline rate of 140 bpm, normal baseline variability >5 bpm and accelerations. Variable decelerations are mistakenly marked in this trace as early decelerations.

B

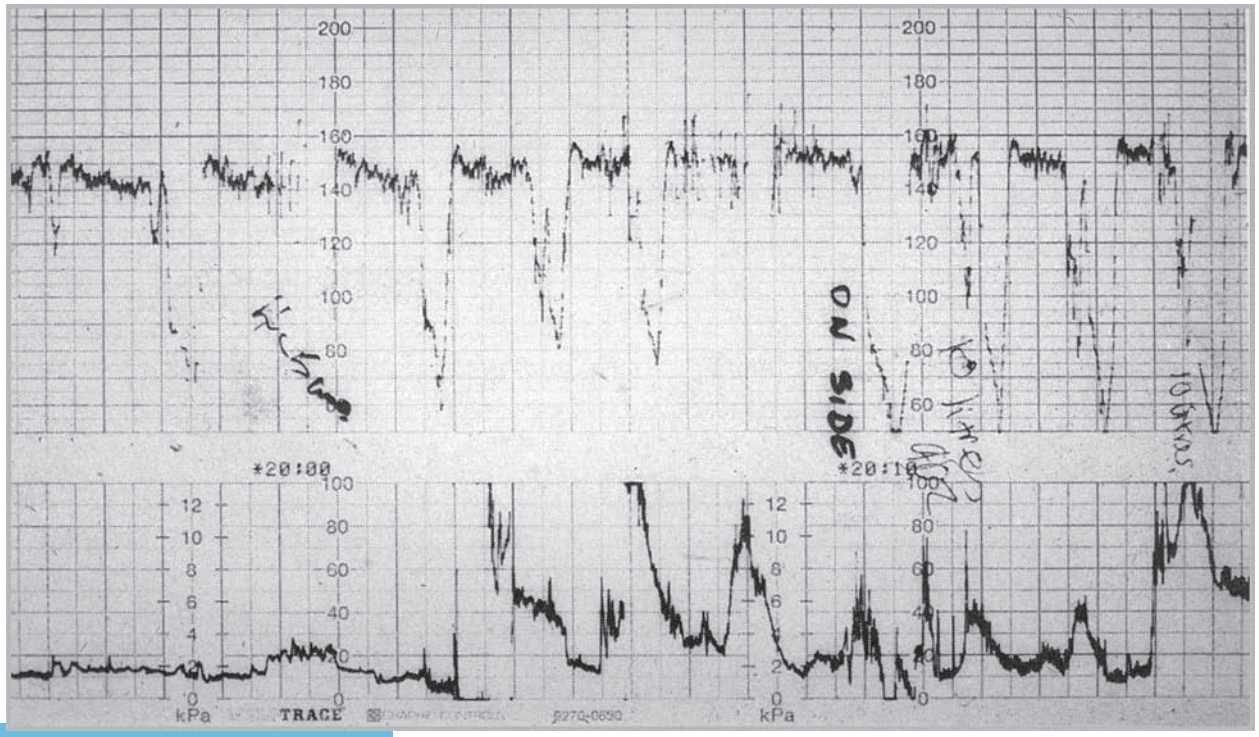


FIGURE 21.3(b) The baseline rate has risen to 150–155 bpm with deepening and widening of the decelerations.

C

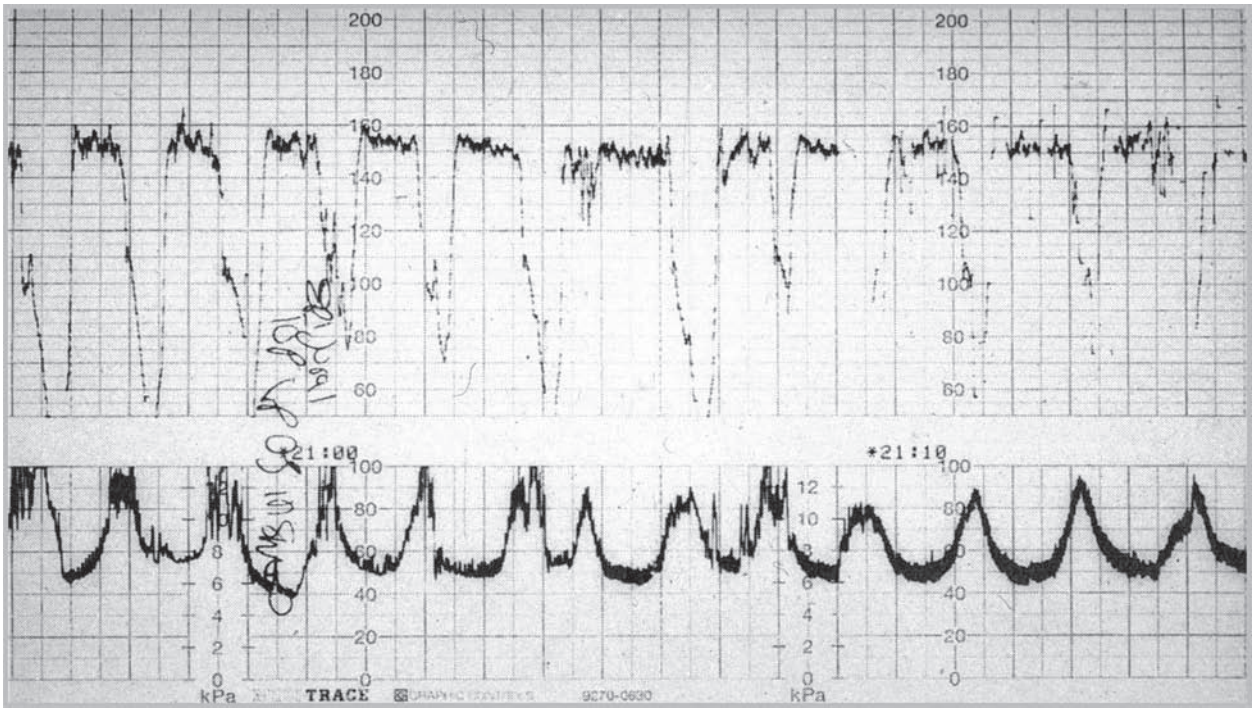


FIGURE 21.3(c) The woman had an epidural. The CTG is of concern now as the decelerations are becoming atypical variable decelerations (depth =/>60 bpm and duration >60 s).

D

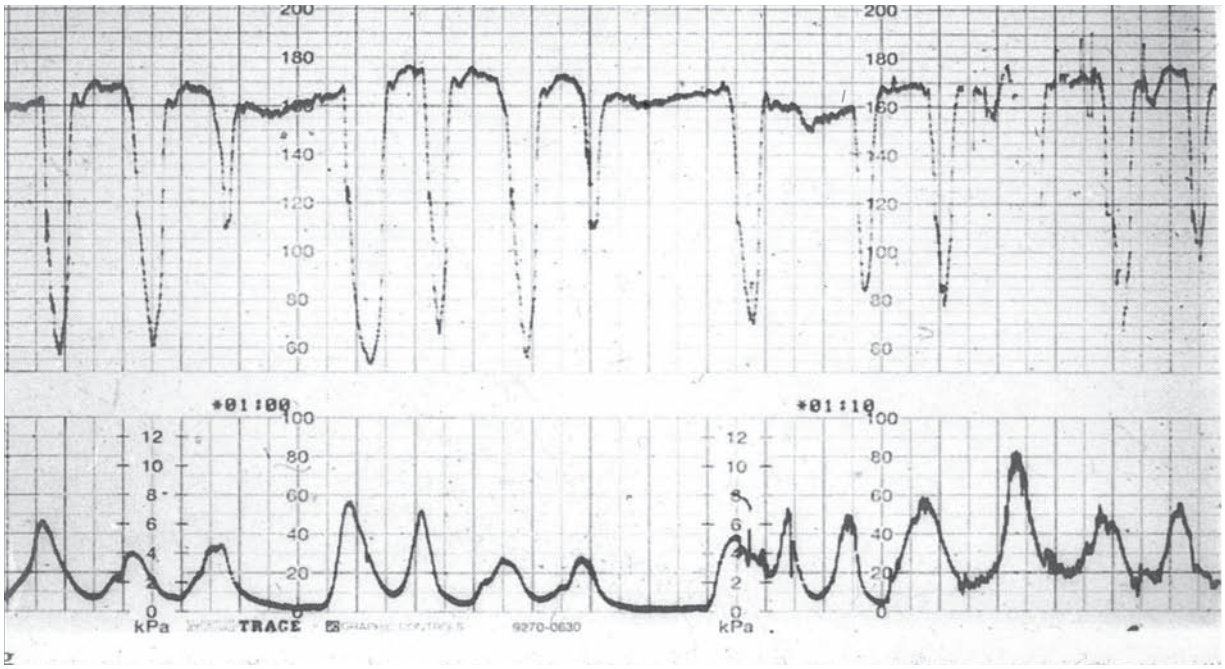
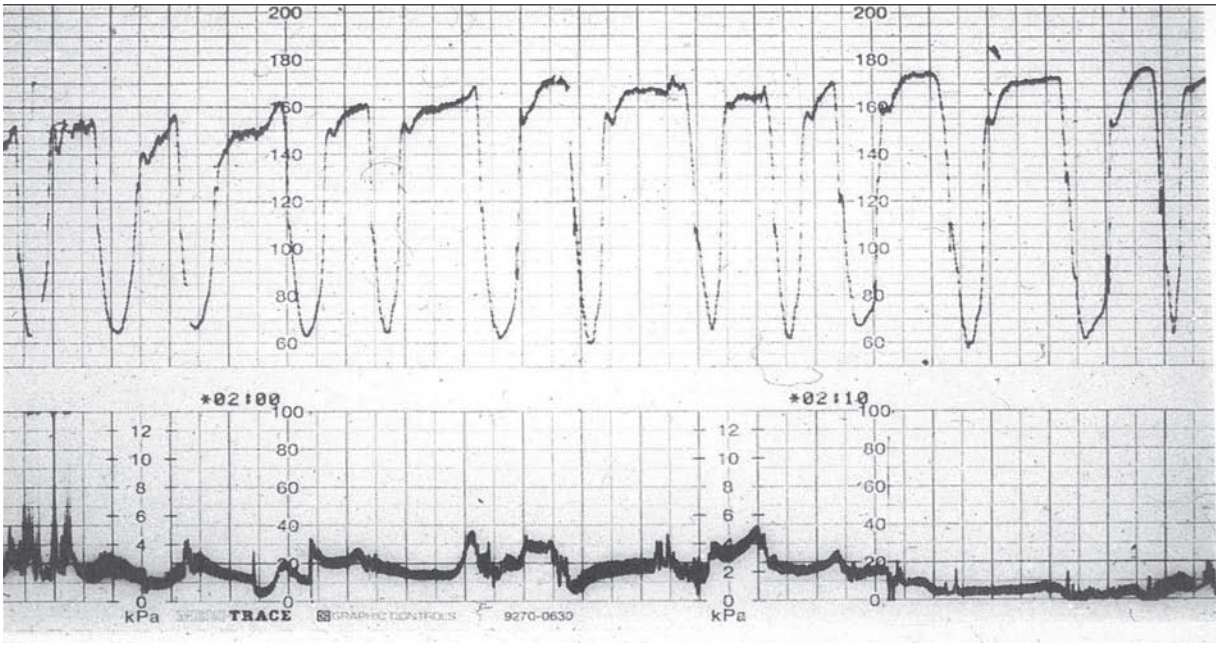
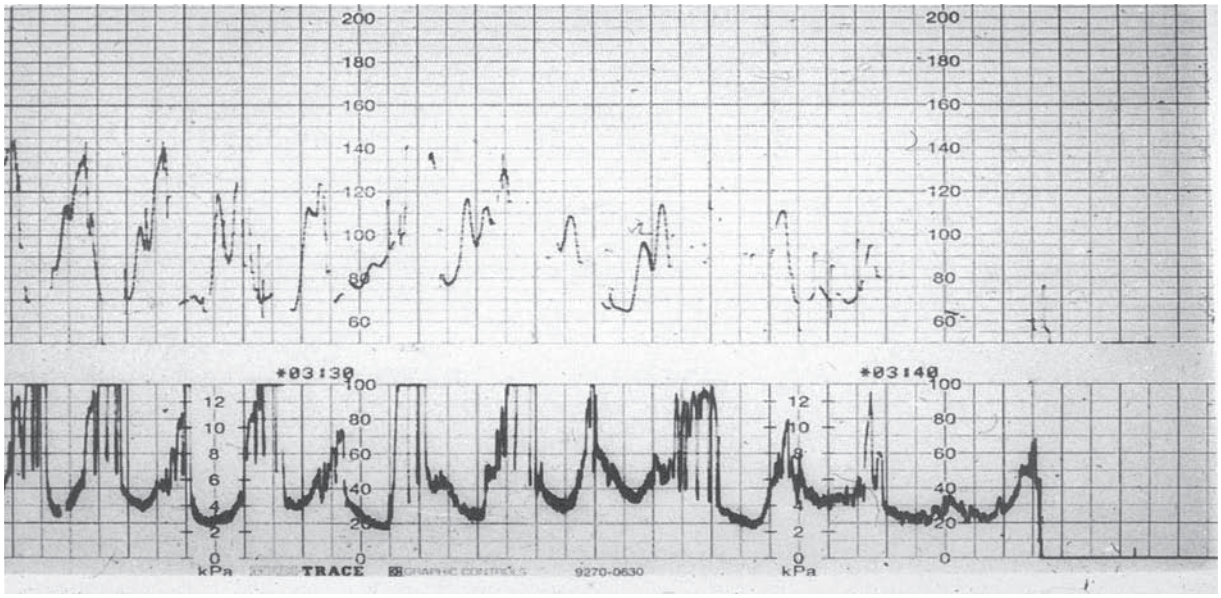


FIGURE 21.3(d) Now the baseline rate has risen to 165–170 bpm with hardly any baseline variability, i.e., lack of oxygen affecting the autonomic nervous system.



E

FIGURE 21.3(e) No action was taken and the decelerations become deeper and wider with a baseline rate that is maximally elevated (from 140 bpm on admission to 170 bpm) and with no baseline variability.



F

FIGURE 21.3(f) Since no action was taken, with increasing metabolic acidosis, the heart fails by showing a terminal bradycardia.

A forceps delivery was carried out in this case but sadly the result was a stillbirth. This labour was of spontaneous onset and no oxytocin was used.

The fetuses that have reactivity (accelerations) and cyclicity (quiet and active epochs) are unlikely to get hypoxia without significant CTG changes such as decelerations and a rise in baseline rate as shown above. If the fetus in above case scenario was born one or two hours earlier and suffered neurological injury, then that would have been due to prolonged partial hypoxia generally resulting in bilateral cortical atrophy that leads to quadriparesis.

Acute Hypoxia

It is characterized by a sudden reduction in placental/cord blood flow and develops over minutes. Causes include acute accidents such as cord accident, abruption, hypertonic

contractions or uterine dehiscence and CTG often shows prolonged deceleration or bradycardia (Fig. 21.4). Management demands rapid delivery or treatment of hyperstimulation to prevent death or long-term damage.

Subacute Hypoxia

This may occur due to recurrent cord compression in labour. It may be particularly worsened in situations like oligohydramnios or prolonged pregnancies. Figure 21.5 shows the CTG associated with subacute hypoxia with prolonged decelerations where the FHR spends more time below the baseline rate (>90 s) and shorter duration at the baseline rate (<30 s). Hypoxaemia reflecting lack of oxygen in the blood and hypoxia which is lack of oxygen in the tissue can be over a long time due to the mobilization of stress response by the fetus mediated by catecholamine surge. With hypoxia and metabolic acidosis in the tissue, i.e., asphyxia the enzymatic reactions in the cells and tissues fail. The brain, heart and the adrenals retain more circulation compared with other tissues and these organs also suffer when the pH is less than 7.0 and the base excess is greater than 12. Some of the babies so exposed can end up with asphyxia mediated brain injury which may or may not recover based on the degree of asphyxia and subsequent management.[20]

BEST PRACTICE CLINICAL RECOMMENDATIONS FOR INTRAPARTUM FETAL SURVEILLANCE

Evidence-based safe clinical practice (as per the national guidelines) and good communication are the best defence against adverse obstetric outcomes and litigations.

Intermittent Auscultation

When performing auscultation, a Doppler device is preferable to Pinard's or stethoscope. The mother should be asked about fetal movements and a basline FHR recorded. An attempt should then be made to feel the fetal movements per abdomen and look for any fetal heart rate accelerations associated with these movements. When the uterus contracts, presence or absence of any obvious decelerations immediately after the contractions should be noted and an attempt made to estimate the depth and duration of deceleration, and whether it recurs with the next few contractions with the mother on her left

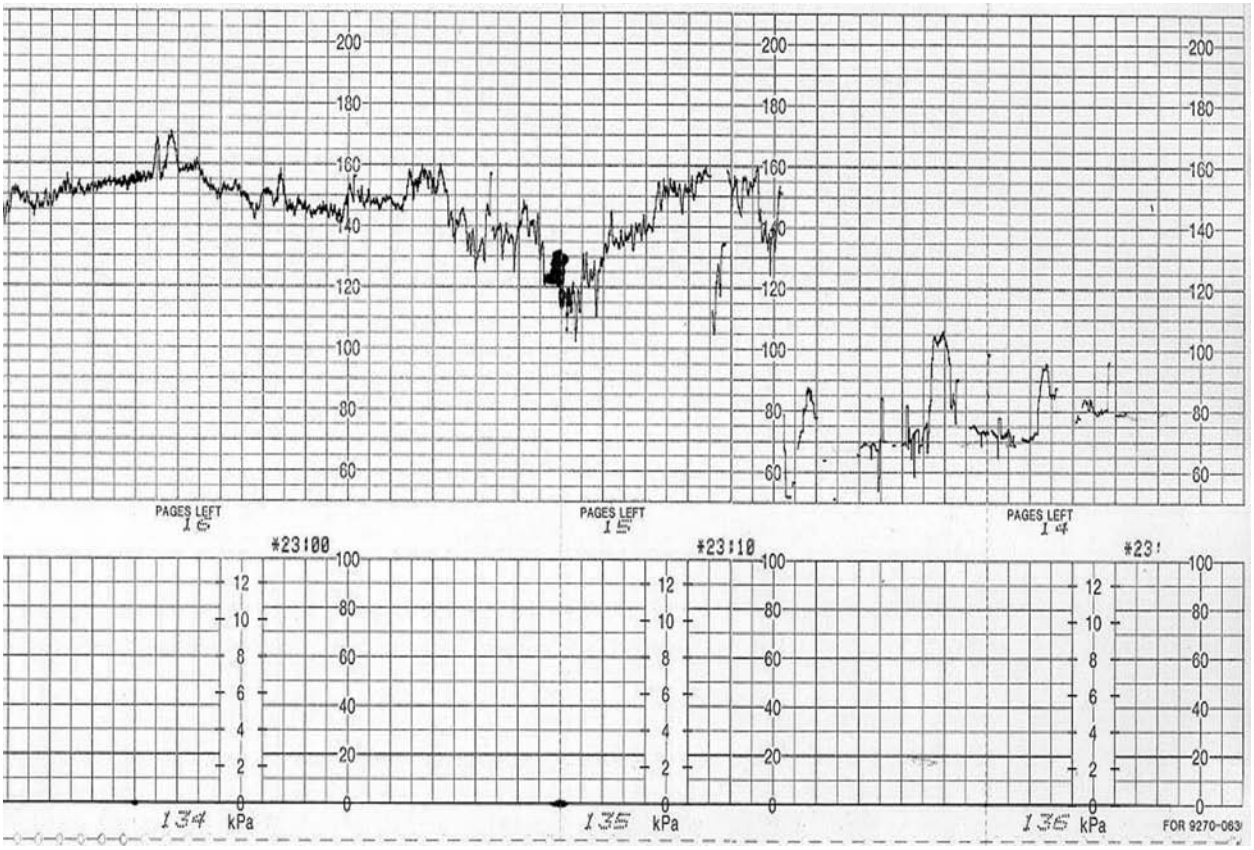


FIGURE 21.4 Sudden bradycardia/prolonged deceleration. This can lead to acute hypoxia and total asphyxia causing damage to the brainstem and thalamus if delivery is delayed and results in athetoid or dyskinetic type of cerebral palsy.

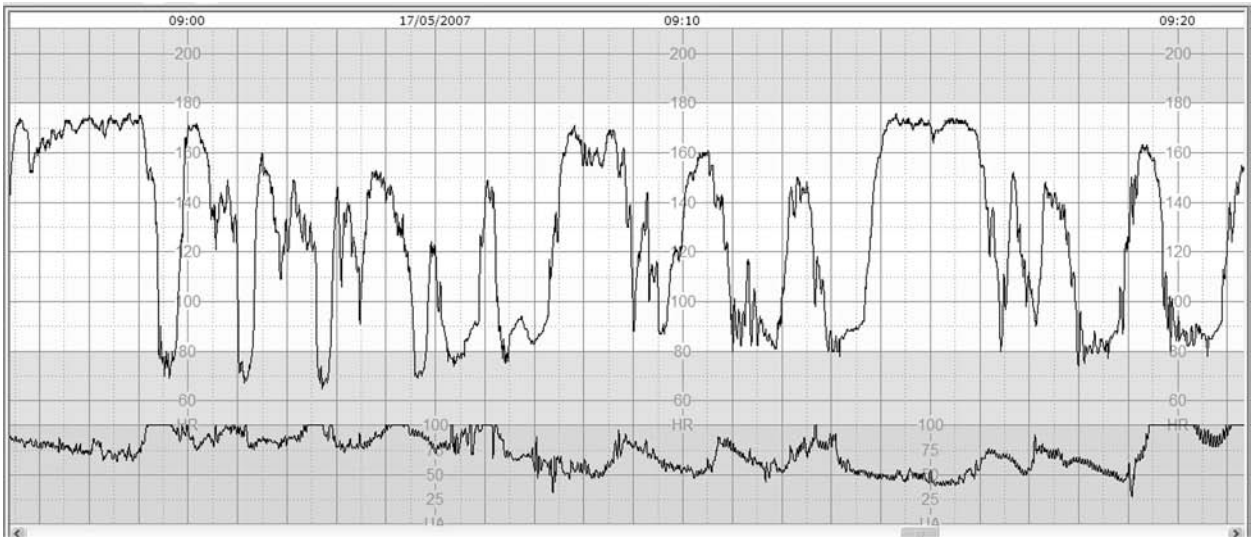


FIGURE 21.5 Prolonged decelerations where the FHR spends more time below the baseline rate and shorter duration at the baseline rate. Such pattern is associated with subacute hypoxia and cortical injury leading to spastic quadriparesis.

lateral side. Feeling of fetal movements associated with FHR accelerations and no decelerations should reassure the mother and the healthcare professional of good fetal health. Subsequent observations should be auscultation of FHR soon after contraction every 15 min for 1 min in the first stage of labour and every 5 min or after every alternate contraction in the second stage. A change to electronic monitoring should be considered (where available) when recurrent or prolonged decelerations or abnormalities of baseline especially a rising baseline rate are detected on auscultation.

Cardiotocography

Important points to consider while recording or evaluating a CTG trace are:

- **Patient identity:** The name of the woman, the date and time of commencement of recording should be entered on every trace.
- **Maternal pulsations:** FHR should be auscultated prior to application of the electronic probe to avoid picking up maternal pulsations. In addition, the maternal pulse should be identified and recorded separately. If there is doubt, ultrasound should be used to locate the fetal heart and a fetal scalp electrode may be a better alternative in such a situation.
- **Poor quality of the trace:** The FHR tracing is difficult to interpret when there is persistent signal loss. The situation should be corrected by adjusting the transducer, or obtaining the signal via a scalp electrode, or changing the connections and/or machine.
- **Misinterpretation of CTGs:** CTG interpretation is subject to variation outside the extremes of normal and grossly pathological traces and has become a common source of alleged negligence in obstetric litigations. In the UK, National Institute for Health and Clinical Excellence (NICE) has attempted to standardize the interpretation of CTGs, while in the US the National Institute of Child Health and Human Development (NICHD) workshop has proposed the three tier system of interpretation of FHR patterns[2,14,22] While interpreting a CTG trace, emphasis should be paid to observe for reactivity (accelerations) and cycling (quiet and active sleep cycles) that indicates a non-hypoxic fetus with a normal behavioural pattern. Absence of cycling may be due to drugs, infection, cerebral haemorrhage, chromosomal or congenital malformation, previous brain damage. A non-reactive trace with baseline variability <5 bpm and shallow decelerations (<15 beats) that lasts for >90 min suggests an existing hypoxia. In the presence of a clinical situation like prolonged pregancy, growth restriction, absent fetal movements, antepartum haemorrhage or infection – such a trace should prompt earlier delivery.
- **Inappropriate action with suspicious or pathological CTG:** Once a diagnosis of suspicious or pathological FHR trace is made – action must be taken depending on the severity of CTG abnormality. This may mean continued observation, change in maternal position, administration of tocolytic, hydration, omission of oxytocin infusion in cases with suspicious traces and in addition fetal blood sampling/immediate operative delivery in cases with pathological traces. Accurate documentation of the time of observation and any other actions taken is very important from a medico-legal view point. The importance of considering the clinical picture in planning management is essential. In the presence of an

abruption, cord prolapse or scar rupture intervention should take place when the diagnosis is made as they warrant immediate delivery (within 15–30 min). In these situations a CTG may suddenly present with acute bradycardia. In cases of bradycardia <80 bpm the pH can decline by 0.01 every min and with prolonged decelerations that have transient recovery to the baseline rate the pH can decline by 0.01 every 2–3min. Fetal scalp blood sampling (FBS) is an inappropriate action in such situations and is likely to compromise the baby. Special arrangements should be in place in each unit to deliver these cases as category 1 caesarean section.

- **Overall clinical picture and pattern evolution of CTG:** With baseline variability that is moderate (5–25 beats) acidosis described as a pH<7.15 is unusual. Once FHR variability is absent with atypical variable, late or prolonged decelerations severe acidosis (pH 7.0) is likely to develop if the pattern persists more than 60 minutes. This depends on the physiological reserve of the fetus and the CTG pattern. It is important therefore to be able to appreciate the CTG pattern evolution and recognize the gradual changes in FHR pattern tracing overtime. It must always be remembered that with any given CTG trace, the clinical actions and decisions will vary depending on the overall clinical picture.
- **Role of infection and inflammation:** Recently, the presence of infection/pyrexia has been found to be an important finding in fetuses that are destined to develop cerebral palsy. The fetal inflammatory response associated with maternal fever during labour, choriamnionitis and funisitis has been implicated as a cause of later cerebral palsy. This information needs to be factored in while managing cases with pathological CTGs in relevant clinical scenarios.
- **Team work and communication:** Effective intrapartum FHR monitoring requires good teamwork. All members of the maternity team (doctors, midwives, nurses) should be aware of how FHR traces are interpreted, which FHR patterns are associated with actual or impending fetal acidaemia and within what time frame the senior team member should be notified of abnormal FHR pattern.
- **Storage of CTG:** CTGs should be stored for at least 25 years and the hospital should make adequate provision for safe storage and easy retrieval.
- **Training in CTG interpretation and documentation:** It is essential that all maternity units provide a regular and structured programme on interpretation of CTGs for all midwives and doctors working on the labour ward. Participation in weekly case review meetings and discussions on CTG traces is one of the best ways of reinforcing knowledge.
- **Debriefing, audit and risk management:** The most senior member of the obstetric team should debrief the parents regarding the events surrounding the birth of their infant with HIE. This should occur as soon as practical after the birth of the baby. Incident reporting of adverse outcomes and audit of poor outcome (poor Apgar scores, cord arterial pH, need for assisted ventilation, admission for neonatal intensive care and HIE) are essential to find out whether there is a failure in education and training, induction of personal, supervision, inadequate staffing level or system failure. The role of clinical risk management is not to apportion blame but to improve the standard of clinical care and avoid adverse outcomes. Lessons learned from analysis of adverse obstetric events should be disseminated to all staff working on the labour ward.
- **Supervision and support:** Ensuring that staff is aware of when supervision is required and how to access a more senior opinion are important. Junior doctors and midwives must be supported by their senior colleagues in the development of their decision making processes and be confident enough to ask for assistance where necessary.

CONCLUSION

Birth asphyxia continues to be a cause for millions of deaths and disabilities all over the world. Many of these cases are preventable if prompt antenatal or intrapartum detection and management are offered for high-risk obstetric conditions. At the same time, it is important to minimize unnecessary interventions as the vast majority of babies will cope well with normal labour and hypoxia could be avoided. However, accurate identification of fetal hypoxia and metabolic acidosis still continue to pose a significant clinical challenge. Intrapartum fetal monitoring based on national guidelines, good communication and evidence based management are likely to be the key to successful outcomes and avoidance of litigations. Once a diagnosis of HIE has been made at birth – a multidisciplinary team effort involving radiologists and paediatric specialists is required for optimum treatment and assessment of long-term neurological development. Neurological injury due to asphyxia will depend on a number of factors (e.g., IUGR, infection, anaemia, the speed of onset and progression of hypoxia). Neuroimaging has helped us to understand the CTG patterns linked with injury. Newer modalities of treatment with medicines and brain cooling shows promise to reduce the number of babies who get affected or the severity of injury.

Therapeutic cooling can improve infant outcomes after hypoxic brain injury, however only 1 in 6 babies with encephalopathy will benefit from hypothermia therapy; many infants still develop significant impairment. While mild HIE is associated with good prognosis, cases with severe grade may suffer from significant long-term neurological impairment or disabilities.

Important Points

- Worldwide 1 million infants die and a similar number survive with long-term disabilities related to birth injury every year.
- Essential diagnostic criteria for hypoxic brain injury – (a) Profound umbilical artery metabolic acidaemia (pH <7.0 and base deficit (BD) >12 mmol/L), (b) Early onset of severe or moderate encephalopathy in infants >34 weeks, (c) Cerebral palsy of a spastic quadriplegic or dyskinetic type and (d) exclusion of other identifiable aetiologies, such as trauma, coagulation disorders, infectious conditions or genetic disorders.
- Umbilical cord arterial blood gas analysis at birth is an important part of diagnosis of intrapartum asphyxia. It should be performed in all deliveries where there was concern about fetal health during labour.
- Intrapartum CTG trace is central documentary evidence in obstetric litigations.
- *Neonatal encephalopathy* is clinically defined as a syndrome of disturbed neurological function occurring during the first week after birth characterized by difficulty in initiating and maintaining respiration, depression of tone and reflexes, altered level of consciousness and convulsions.
- A large proportion of asphyxial damage begins before labour and intrapartum surveillance and intervention may not benefit these babies.
- If asphyxia is suspected further investigations and involvement of a multidisciplinary team are required.
- Current management of neonates with birth asphyxia therefore focuses on (a) correction of haemodynamic and pulmonary disturbances, such as hypotension, hypoventilation and acidosis, (b) correction of metabolic problems (glucose, calcium, magnesium and electrolytes), (c) treatment of seizures if present and (d) other advanced/specific therapies.
- Moderate hypothermia (33–34°C) initiated within 6 hours of birth and maintained up to 24–72 hours in infants with moderate encephalopathy reduces the mortality and long-term disabilities.
- HIE grading (Grades 1–3 as described above) appears to be more useful in assessing long-term outcomes. Infants with grade 1 have a very good prognosis (most develop normally) whereas infants with grade 3 may die (50-70%) or have severe impairment.
- Half the infants with grade 2 have severe neurodevelopmental impairment while those with grade 2 for less than 5 days generally do well.
- Sequelae of HIE include mental retardation, epilepsy and cerebral palsy.
- Majority of medico-legal cases have similar problems which can be laid down to a few factors such as (a) inability to interpret FHR trace, (b) failure to incorporate the clinical picture, (c) inappropriate or delayed action, (d) technical aspects and (e) record keeping.
- The non-specific nature of variant CTG patterns as well as subjective element involved in the interpretation of the traces has made it necessary for additional tests of fetal well-being to be considered before interventions are undertaken in labour.
- The best defence against litigation is good clinical practice with adherence to evidence-based guidelines.
- It is important that all staff on labour ward receive regular mandatory training in the interpretation of CTG as well as support and/or supervision when necessary. There should be a mechanism for the rapid review of adverse obstetric events and dissemination of key learning points to all staff.

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Chapter 22

Operative Delivery

Hemantha Senanayake and Sabaratnam Arulkumaran

Chapter Outline

INTRODUCTION

Normal birth is the least traumatic way to be born. Normal presentation and position are the cornerstones of this wonder of nature. Failure to appreciate, diagnose and manage malpresentations and malpositions when there is lack of progress of labour can lead to maternal and neonatal morbidity and rarely mortality. This chapter deals with intrapartum operative procedures that are needed to provide the best outcome for the mother and baby when encountered with problems in labour. Safe operative delivery of the baby without compromising the mother should be our goal.

DEFINITIONS

Before malpresentations and malpositions are discussed it is important to consider some time-honoured definitions.

The part of the fetus that lies in closest proximity to the pelvic inlet is defined as the *presentation*. About 95% of fetuses present at term and during labour by the *vertex* and therefore it is considered the 'normal' presentation. The vertex is a diamond-shaped area defined by the two parietal eminences, anterior and posterior fontanels, and is best suited to the mechanism of normal labour. Any presentation other than a vertex presentation is classified as a *malpresentation*. These include breech, brow, face shoulder or cord presentations. The majority of malpresentations occur with no recognizable underlying abnormality of the mother or fetus. Contracted pelvis, large baby, polyhydramnios, multiple pregnancies, low-lying placenta, preterm labour, anomalies of the fetus (e.g. neck tumours) or uterus (congenital, e.g., unicornuate uterus or acquired, e.g., lower segment fibroids) can predispose to malpresentations.

Position is defined by the relationship of the denominator of the presenting part to fixed points of the maternal bony pelvis. The fixed points of the pelvis are the sacral promontory posteriorly, sacroiliac joint posterolaterally, ileopectineal eminences anterolaterally and symphysis pubis anteriorly. The denominator is the most definable peripheral point in the presenting part, for example occiput in vertex, mentum (the chin) in face and sacrum in breech presentation. The term malposition refers exclusively to abnormal positions of the vertex. Commonest position of the vertex at term (more than 90%) is the occipito anterior (OA) – (right, left or direct OA) position in the late first stage of labour. Hence it is referred to as the 'normal' position.

Almost all cases that present in an OA position have the head well flexed, making the vertex the presenting part. This has the shortest anteroposterior (suboccipito bregmatic) and transverse (biparietal) diameters (9.5 × 9.5 cm), making it the most favourable presentation for a normal delivery. As the head descends in an OA position, the parietal eminences lie at the same level in the pelvis (synclitism).

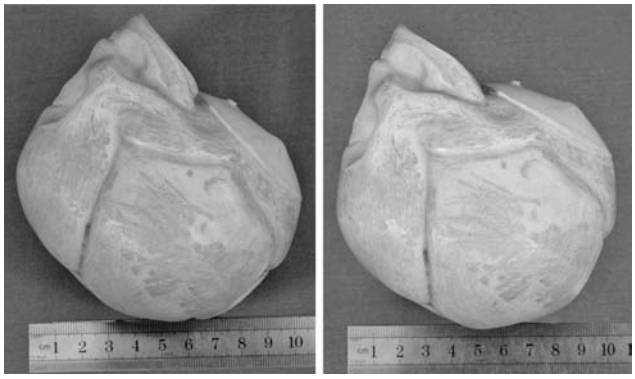

FIGURE 22.1 Deflexion of the head results in an increase in the anteroposterior diameters of the vertex. Suboccipitobregmatic in vertex presentation and occipitofrontal in a slightly deflexed head.

When the occiput lies in the posterior half of the pelvis they are considered as malpositions. They usually present with a slightly extended head, which makes the presenting anteroposterior diameter somewhat greater (occipitofrontal) of 11.5 cm (Fig. 22.1). They may also present with anterior or posterior asynclitism (parietal eminence in the anterior half of the pelvis and lying lower—anterior asynclitism and posterior—vice versa) and the sagital suture may be shifted more posteriorly or anteriorly (Fig. 22.2). Extension of the head with asynclitism presents a larger diameter and hence longer and difficult labour and operative deliveries ensue.

The vast majority of malpositions become occipitoanterior position with progress of labour due to flexion of the head at the atlantooccipital joint as the vertex meets the resistance of the pelvic floor musculature. This is promoted by the greater amount of forces on the forehead and due to the atlanto-occipital joint being connected to the head more posteriorly. Along with flexion of the head, when the occiput meets the pelvic musculature, a forward-facing V-shaped gutter, promotes its forward rotation. This 'anatomical' mechanism of labour promotes spontaneous deliveries in an occipitoanterior position. A minority of the occipitoposterior (OP) or occipitolateral (OL) positions will either have the occiput remaining in that position or rotate posteriorly to a direct OP position. The majority of OA and OL rotate anteriorly due to the mechanism described.

MALPRESENTATION (BREECH, FACE, BROW, SHOULDER) IN LABOUR

Breech Presentation

Incidence and Aetiology

Breech is the commonest malpresentation. The incidence of breech is higher at earlier gestations and reduces with progression of pregnancy; it is 40% at 20 weeks, 6–8% at 34 weeks and 3–4% by term.[1] In the majority of cases there is no identifiable cause for the breech presentation. Bicornuate uterus, uterine fibroids, low lying placenta, multiple pregnancies, polyhydramnios, oligohydramnios and congenital fetal malformations such as spina bifida or hydrocephaly can predispose to breech presentations.

Diagnosis

The commonest is an extended breech presentation where there is flexion at the hip and extension at the knees. The next common presentation is a flexed breech presentation known as complete breech where there is flexion at the hips and knees. Incomplete breech presents with one leg flexed and the other extended. The rare footling breech presents with both or one feet and at times with the knee (Fig. 22.3). The incongruence fit of the breech to the pelvis, predisposes to cord prolapse; about 10% with footling breeches. Antenatal diagnosis of breech presentation is easier in women with thin or lax abdominal wall, multiparare and with increasing gestation. In a small proportion of cases, the breech presentation is diagnosed in labour. Careful methodical palpation of the uterus including the fundus should be a routine. The fetus in the longitudinal lie with the hard globular head palpable as a spherical hard mass in the fundus confirms the diagnosis. The head may be felt to one or the other side under the hypochondrium and is tender on deep palpation. The breech, which is broader, is felt above or within the pelvis. When the extended breech descends into the pelvis, there is a greater chance of the diagnosis being missed. In earlier gestations, ballotment of the head provides additional information. 'A deeply engaged head may not be there at all' is an old adage in obstetrics. A deeply engaged head in a

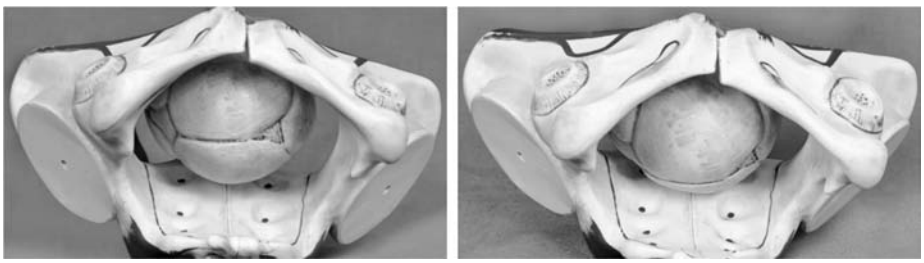

FIGURE 22.2 Normal synclitism (left) and anterior asynclitism (right). In the latter, the anterior parietal bone is more prominent and the sagittal suture is palpated posteriorly. This is a common situation in deep transverse arrest and occipitoposterior positions.

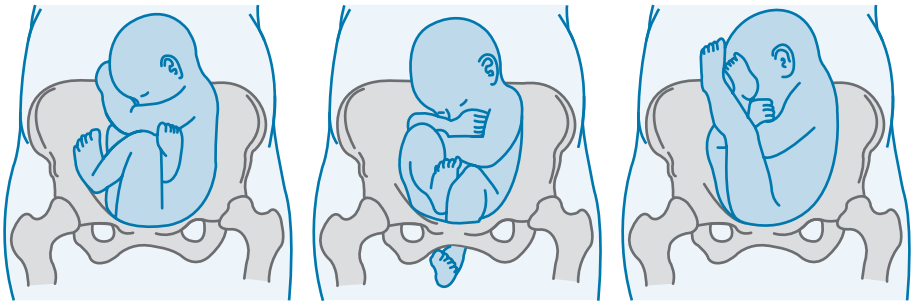

FIGURE 22.3 Types of breech presentation.

woman who is not in labour should arouse suspicion of a breech presentation. A vaginal examination and when in doubt an ultrasound examination will confirm whether it is the head or the breech. In a breech, auscultation with a stethoscope reveals the fetal heart to be above the umbilicus. A Doppler has the ability to pick up a heartbeat from afar and may mislead whether the heart is above or below the umbilicus and hence the presentation.

Management in the Antenatal Period

Perinatal mortality and morbidity is higher with breech presentation. Routine prenatal screening for congenital malformation and termination of lethal malformations has reduced perinatal mortality. Prematurity, birth asphyxia due to cord accidents and trauma are the main causes of morbidity. Current literature recommends elective CS for term breeches[2] but training in assisted vaginal delivery is still needed to deliver mothers who elect to have assisted breech deliveries. Injury to the fetus may still occur during CS. Delivery of a breech at CS needs the same technique and skills as for an assisted vaginal breech delivery. The large RCTs were for elective deliveries and did not address delivery of the breeches in established labour, those at preterm gestation and where the first fetus presents by a breech in multiple pregnancies. Breech presentation may be a reflection of an underlying pathology and the mode of delivery may have little influence on the final outcome.[3] The vast majority of breeches do not have abnormality. Delivery as a cephalic presentation after ECV or elective CS may reduce morbidity and mortality. Because of the need to deliver urgently should a complication arise with ECV and because the chance of spontaneous version to cephalic is 1 in 20 after 37 ECV is offered after 36 weeks.[1]

The procedure, success and failure rates and complications should be explained to the couple. Contraindications include placenta praevia, multiple pregnancies, and history of antepartum haemorrhage, intrauterine growth restriction, severe preeclampsia and hypertension. In those with uterine scars ECV is avoided and in those with a lower uterine scar are performed without force and with caution.

Facilities for urgent CS should be available if there is fetal compromise with ECV. To facilitate this, ECV is done in the delivery room after confirming breech presentation. Identifying the fetal back, type of breech presentation, fetal attitude, position of the placenta and the quantity of amniotic fluid helps with the ECV and can be identified by an ultrasound examination. Nonstress CTG prior to and after ECV is helpful to detect fetal compromise. Multiparity, flexed breech presentation, adequate liquor volume and a mobile breech above the brim favour the chance of success. Positioning the mother in the Trendelenberg position, intravenous hydration to increase amniotic fluid volume, use of vibroacoustic stimulation[4] and uterine relaxation with a short acting tocolytic have been reported to increase the success rates.[5] Forward or backward somersault is practiced after disengaging the breech and shifting it to the opposite side to where the head is moved. The success rate is about 60%.[5] ECV has the potential risks of cord accidents, prelabour rupture of membranes, feto maternal transfusion, placental separation, fetal compromise or death. Those mothers who are Rhesus negative should receive anti D. A Kleihauer-Betke test should help us determine the need for additional anti D. A reactive trace and no uterine irritability for 30–60 mins after ECV would be reassuring. The woman should observe for bleeding, leaking of amniotic fluid per vagina or uterine tenderness prior to and after discharge. A repeat attempt of ECV, an elective CS or assisted vaginal breech delivery are the options with failed ECV and should be discussed.

Management in Labour

Labour and delivery of a breech starts with careful selection, and full understanding of the risks and benefits. Frank and complete breech with normal fetal weights have fewer risks compared with footling presentations because of the increased chance of cord prolapse. Pelvic assessment by clinical examination is adequate. Various radiological pelvimetry has not been shown to be of benefit. The chance of

successful delivery is greater with spontaneous onset of labour. Induction of labour with breech should be avoided or should be in highly selected cases. In such situations, CS may be more appropriate.

Onset of labour with painful contractions or rupture of membranes should be a trigger for admission so that cord presentation or prolapse could be excluded. The conduct of labour is similar to that of a vertex presentation. The rate of cervical dilatation, descent of the breech and the fetal heart rate pattern should be normal/acceptable to allow progress. If cervical dilatation is slow, uterine contractions should be evaluated and if inadequate, a limited period of oxytocin augmentation could be permitted if there is no concern of feto pelvic disproportion. CS is preferable if there is no progress of labour in the first few hours of augmentation. Successful second stage depends on good uterine contractions and good bearing down efforts from the mother in addition to assistance by the accoucher. Epidural anaesthesia is good for pain relief and for assisted breech delivery.

Mothers have bearing down sensation early in breech presentation. Hence, cervical dilatation is checked before mother is encouraged to bear down. The cervix should be fully dilated and the breech should be in the perineal phase of the second stage. Mother should be in lithotomy only after the anterior buttock and anus of the baby come into view over the mother's perineum with no retraction. An episiotomy is not essential in multipara but is of great value in a primigravida. A regional block or pudendal block with local infiltration of the perineum is essential.

The fetus emerges in the sacrolateral position and up to the level of the umbilicus should be with contractions and maternal effort. Assistance for delivery is by lateral manipulation. Traction is used only for delivery of the head. Extended knees (frank breech) are delivered by slight abduction at the hip followed by flexion of the knees (Fig. 22.4). The body of the fetus is ideally kept with the dorsum facing upwards.

When the scapulae become visible, the arms are likely to be flexed. The flexed arms at the elbow are delivered by extending the arm at the elbow across the chest. When the upper arms are extended at the shoulder joint and then adducted to create space for the next maneuver. Then the upper arm is flexed and the forearm is flexed to bring it in front of the chest. This is followed by extension of the forearm at the elbow to bring it into the pelvis and outside the vaginal introitus. If the inferior angle of the scapula is not seen the descent may not be optimal due to extended arms. In such situations a 'Lovset manoeuvre' is useful. The posterior shoulder usually lies below the level of the sacral promontory. This is brought anterior and below the symphysis pubis by rotating the fetus in a clock or anticlockwise direction. Inappropriate handling of the fetal abdomen whilst performing this procedure could injure viscera of the fetus. To avoid such injury, the fetus is grasped with the thumbs on the sacrum and the index fingers on the anterior iliac spines; care taken to ensure that no part of the operator's hand goes above the ileac crests onto the abdomen (Fig. 22.5).

Now the shoulder that has been brought anterior exposes the arm and it can be delivered by flexing the shoulder and forearm. Then the fetus is turned in the opposite direction to enable descent of the opposite shoulder and the other arm is delivered (Fig. 22.6). After delivery of the shoulders, the dorsum of the fetus is kept facing upwards and baby is allowed to hang, the weight of which will make the head descend into the pelvis with uterine contractions. On vaginal examination, the face and chin of the fetus should be against the sacrum.

The fetus is gently supported till the nape of the neck is visible under the symphysis pubis. Appearance of the

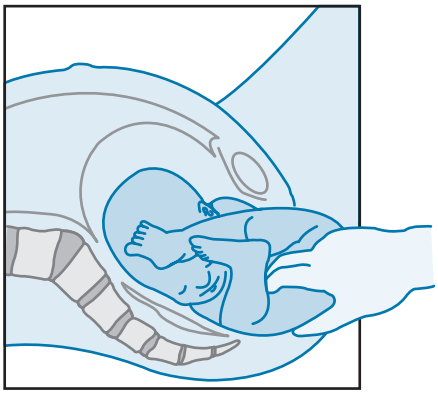

FIGURE 22.4 Delivery of the extended legs by slight abduction of the thigh and flexion at the knees. The thumb is pressed gently into the popliteal fossa while keeping the fore and middle fingers on either side for counter pressure.

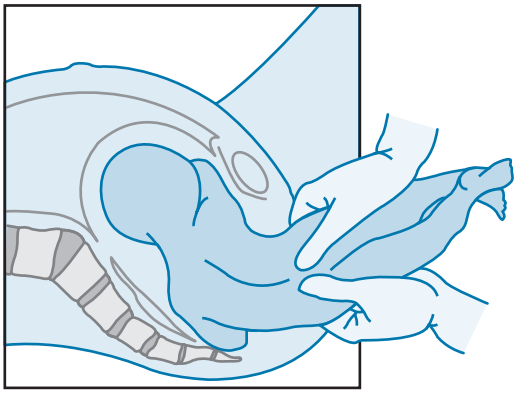

FIGURE 22.5 Correct handling of the baby whilst performing Loveset manouvere.

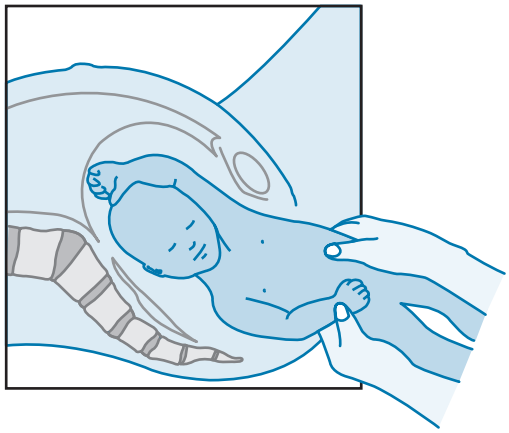

FIGURE 22.6 Delivery of the arm by rotation of the body so that the posterior shoulder which was below the level of the sacral promontory becomes anterior and below the pubic symphysis.

nape of the neck is an indication that the head is low in the pelvis.

The after coming head could be delivered by one of three methods:

1. Moving the trunk in an arc towards the maternal abdomen till the mouth and the nose of the fetus become visible.
2. Mauriceau-Smellie-Veit manoeuvre can be employed where two fingers are pressed over the maxilla to flex the head and delivery is accomplished by shoulder traction (Fig. 22.7).
3. A Piper or Neville Barnes Forceps can be applied from below whilst an assistant holds the baby just below the horizontal and traction is applied. Following any of the three methods, ironing the perineum beyond the forehead completes the delivery of the fetal head.

If the baby cries there is no need for suctioning. If it does not, the oropharynx followed by nasopharynx should be suctioned.

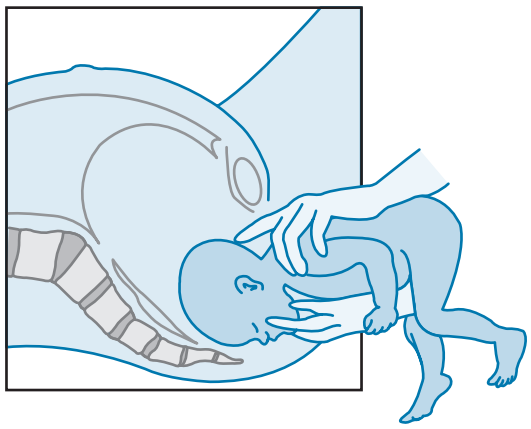

FIGURE 22.7 Delivery of the head by jaw flexion and shoulder traction.

Conclusion

Elective CS has become the norm for term breech presentation in many centers although the choice should be discussed with the mother. Mode of delivery for preterm breeches depends on the clinical situation; wish of the mother and experience of the caregivers, as there is no evidence for uniform recommendation. The outcome of the baby is dependent on the fetal maturity, estimated birth weight, the mode of delivery and the experience of the caregivers. Parents should have detailed counselling and consultation with the pediatricians in coming to an informed decision about the mode of delivery.

Mothers who prefer vaginal delivery and those admitted in advanced labour should be offered assisted vaginal breech delivery. The skills to accomplish a safe-assisted vaginal delivery should be acquired by assisting in breech deliveries, practicing assisted breech delivery at the time of CS and on mannequins. It is essential to have an accoucher with experience for assistance and reassurance for the learner to gain confidence without compromising the health of the mother or baby.

Brow Presentation

In brow presentation, the lower most palpable portion is the forehead but the next most definable portion of head are the palpable orbital ridges and the bridge of the nose; and hence called as brow presentation. The head is half extended; head presents the largest anteroposterior diameter (mento-vertical -13cm) to the pelvis. The incidence is rare and is about 1 in 1500 to 3000 deliveries.

If diagnosed in early labour the brow may become the vertex by flexion or face by extension. If converted to vertex or face the mother could deliver vaginally without assistance. Brow presentation with no progress would not deliver vaginally and a better option for the mother and the baby is CS and not oxytocin with a view to cause flexion and correction to vertex. When diagnosed in early labour some time should be given to see whether flexion or extension would occur. This time could be used to prepare for CS should there be no change. A small preterm fetus may deliver as a brow or as vertex or face if flexion or extension takes place. A CS is preferred because of the concern of spinal cord injury even in a preterm where vaginal delivery looks plausible. Because of the incongruous fit of the presenting part to the pelvis there is a higher incidence of cord prolapse with membrane rupture. If labour is allowed despite poor progress, uterine rupture is a possibility. In cases of intrauterine fetal death and in those with lethal malformation in the extreme preterm period, where injury to the fetus is not a concern, labour may be allowed if there is good progress in anticipation of vaginal delivery. In current day obstetrics, destructive operations and vaginal delivery is not

encouraged in cases of fetal death or lethal anomaly at term for fear of genital tract trauma as the practitioners have little experience in these techniques; instead CS is advocated.

Face Presentation

Congenital malformations of the fetus especially anencephaly or thyroid goiter can give rise to face presentation in addition to congenital and acquired malformation of the uterus or low lying placenta. However in the vast majority, the fetus is normal in every aspect and it may be due to extension at the neck. The quoted incidence varies and is from one in 500 to 1000 deliveries. On abdominal examination, one may suspect face presentation if occiput is palpated more prominently and at a higher level on the side of the fetal spine. If additional attention is paid, one could palpate a deep groove may between the occiput and the back in a multigravida with thin abdomen. Feeling the contour of the hard gums which has no sphincteric action unlike the anus, followed by the identification of nose and eyes provides the clue of a face presentation. In early labour, when the membranes are not ruptured and the presentation is high the definitive diagnosis may be difficult. In established labour, the presence of facial edema can also cause difficulties in recognition of the face.

The transverse submentobregmatic diameter enters the pelvis and in most cases forward rotation takes place to a mentoanterior position. The chin would be behind the symphysis pubis and the presenting diameters are; transverse biparietal— 9.5cm and anteroposterior submentobregmatic— 9.5cm. These are similar to a well-flexed vertex presentation and favour vaginal delivery (Fig. 22.8). The mentum rotates anteriorly in the pelvis because of large space in the lateral sacral area can accommodate the larger part of the head. First the chin emerges under the pubic whilst the forehead sweeps over the perineum. Mentoposterior position is not conducive for vaginal delivery although the diameters are the same as mentoanterior. This is due to the lateral dimensions of the frontal bones cannot descend and negotiate the narrow retro pubic arch. CS is preferred for mentoposterior position especially with delay in the progress of labour. Failure to progress in the first stage even with mentoanterior or lateral position, are better dealt with by CS.

Forceps delivery can be performed for delay in the second stage of labour at the outlet, with mentoanterior or lateral position; there is no or minimal trauma when performed by an experienced person.

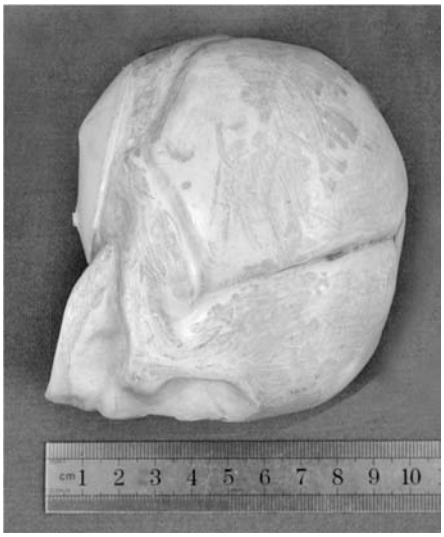

FIGURE 22.8 The submentobregmatic diameter of a face presentation is similar to the suboccipitobregmatic diameter of a vertex presentation.

Shoulder Presentation

The lax uterus in multiparous women can be the reason for shoulder presentation. Preterm, congenital fetal or uterine malformations, fibroids, placenta praevia and polyhydramnios are known associations. The incidence varies from series to series but at term it is about in 1:400. Increased muscular tone of the uterus with early labour helps to correct many transverse lie to longitudinal. Women with known transverse lie should come to hospital with rupture of membranes to confirm correction to longitudinal lie and to exclude cord prolapse, shoulder presentation and arm prolapse. In current practice version after 37 weeks and observation of a stable longitudinal lie for two days or stabilizing induction are practiced to avoid such complications.

If detected in early labour with the membranes intact, one could await spontaneous correction to longitudinal lie or if easy an external cephalic version could be performed and membranes ruptured to stabilize the lie. On admission if the membranes have ruptured, CS is best for a transverse lie to avoid injury to the fetus or the uterus. With an impacted transverse lie with the uterus contracted tightly over it, safe delivery of the fetus would be a challenge. Delivery should be via a longitudinal incision over the lower segment extended upwards as needed or a lower segment transverse incision with acute short acting tocolytic (e.g. 0.25 mg terbutaline in 5 cc saline given IV over 5 minutes).[6] If the uterus fails to contract despite oxytocics after the use of beta mimetics, PPH would ensue unless a small dose of beta blocker such as propranolol 1 mg IV is given to reverse the effect to enable the uterus to contract.[7] With transverse lie, labour and spontaneous vaginal delivery is possible in extreme preterm and macerated fetuses. The thorax flexes laterally and emerges followed by the limbs and head.

CEPHALOPELVIC DISPROPORTION

Labour is a dynamic process that alters the pelvic dimensions (widening of the symphysis pubis) and reduction of the cephalic dimensions by progressive flexion, rotation and

moulding. Cephalopelvic disproportion may be absolute (poor pelvic dimensions despite well flexed and LOA position with maximal moulding) or relative due to failure of flexion, rotation or moulding or asynclitism and is diagnosed after a well-conducted trial of labour. This distinction would determine whether CS is needed in subsequent pregnancies or whether a trial of labour could be offered. Failure of cervical dilatation despite optimal contractions with or without oxytocin, for sufficient length of labour (6–8 hours) with increasing caput and moulding, especially if associated with CTG changes is suggestive of absolute or relative disproportion. Appearance of fresh meconium may also be noted. Traditionally, one views the failure to progress due to problems with the passage, passenger and power.

Disproportion due to hydrocephalus, large baby or brow presentation can cause disproportion and augmentation is contraindicated. Congenitally, small pelvis due to Ricketts or maternal malnutrition is rare in current obstetric practice. Rarely the pelvis may be deformed with reduced dimensions due to an accident involving fracture of the pelvis. Women with good heights are expected to have adequate pelvis but some may present with disproportion and this may be due to an android or platypelloid pelvis.

Trial of labour in those with inadequate contractions needs augmentation to promote flexion, correction of asynclitism and increase moulding to enable a smaller diameter of the head. It can also increase the pelvic diameter by increasing the width of the symphysis pubis. Care must be taken to observe the fetal heart rate so as not to compromise the fetus due to too frequent contractions.

Poor descent of the head in the presence of good contractions in the second stage whilst there is increasing caput and moulding suggests disproportion. In the second stage, oxytocin augmentation could be used for a period of one hour with caution. If there is no descent to below spines despite adequate contractions with oxytocin infusion for one hour and then with bearing down efforts with contractions then a CS may be advisable. An instrumental vaginal (IVD) delivery should be preferred if there are concerns with the FHR and if the head is low. IVD could be attempted for poor descent due to malposition or asynclitism if the station is below spines.

INSTRUMENTAL VAGINAL DELIVERIES (IVD)

The incidence of IVD varies from country to country. In the UK hospitals, the incidence of IVD is quoted as between 6 and 12%. The commonest indications for IVD are universally the same and are delayed in the second stage of labour, poor maternal effort and concerns about the fetal status. Maternal illnesses such as severe cardiac, respiratory or hypertensive disease are preferably delivered by IVD to avoid maternal compromise due to strenuous bearing down efforts. Mothers with intracranial pathology like aneurysms. A/v malformations that has bled before or known increased intracranial pressure that may compromise maternal health with bearing down efforts are better delivered by CS in current practice.

The reasons for poor progress in the second stage (inadequate uterine contractions, poor expulsive efforts by the mother, minor disproportion or malposition) should be determined before deciding on IVD. Due to the absence of the reflex release of oxytocin in women with epidural (Ferguson's reflex—due to stretching of the upper vagina[8]), IVD are slightly increased. The use of oxytocin infusion helps to reduce IVD.[9]

IVD has its own hazards to the mother and the newborn and should be undertaken only if there is a proper indication and after consent. The explanation should include indication, advantages, disadvantages and alternatives and should be recorded. The mother and the fetus should be assessed for any contraindications and consent taken before embarking on IVD. Parents may be apprehensive and feel reassured when the findings and the plan of action and expected outcome are explained.

Mother should have adequate pain relief in the form of pudendal block and local perineal infiltration for low forceps or ventouse deliveries. Midcavity IVDs are usually trial of IVDs and are better performed with an epidural or spinal anaesthesia as this would easily facilitate proceeding to CS should the IVD fail. Fetal status should be established based on auscultation or cardiotocographic findings. The colour and quantity of amniotic fluid should be noted.

Cord prolapse, antepartum bleeding or prolonged deceleration dictates urgency and one should proceed to IVD immediately if conditions are favourable.

IVD should always be preceded by an abdominal examination to assess size of the fetus and fifth of head palpable. Uterine contractions should be optimal. If more than one-fifth of the head is palpable then IVD may not be advisable. If uterine contractions are inadequate, that is less than four in 10 minutes each lasting >40 seconds oxytocin can be used for an hour in the presence of reassuring fetal status. Bladder should be empty by natural voiding and if this is not possible by catheterization. Extra caution need to be taken to avoid prolonged period of traction and in cases of obese mothers, expected large babies and diabetics one should be prepared for possible shoulder dystocia especially if it was a delivery with malposition. Repeated attempts to deliver when there is no or poor descent of the head is likely to result in poor condition of the new born. Gentle traction over three contractions and maternal bearing down effort should result in descent of the presenting part. Failure of descent is better managed by caesarean section.

The basics before IVD, cervix should be fully dilated, absent membranes, vertex presentation, minimal to moderate

caput and moulding (+++ unable to reduce overlap by gentle pressure, ++ reduction with gentle pressure, + meeting of skull bones but no overlap). The position (e.g. LOA or LOT) and station (leading bony part of the skull in relation to ischial spines) and any asynclitism (parietal eminences at different levels) should be determined. The station below spines with descent of the head with contraction and bearing down effort is a favourable sign for successful IVD.

The fetal head at term fits into the three-dimensional size of a gynaecoid pelvis. Hence a head that is 0/5th palpable should have the station below ischial spines. In women who are obese and with occipitoposterior positions, palpation of the fifths may be difficult. With one or zero fifths of the head palpable above the brim if the leading vertex was above spines then the head palpated may have been the fetal chin due to the vertex being in occipitoposterior position.

The type of instrument to be used will be determined by position and station of the head that is determined by palpating suture lines, posterior fontanel and occiput. Inverted Y-shaped suture line due to overlapping of parietal bones over the occipital bone identifies the posterior fontanel. At times, it is difficult to identify due to its small size and excessive caput. Anterior fontanel is soft and diamond shaped, and is larger and is identified by following the sagittal suture.

In malpositions, the anterior fontanel is felt easily in the center of the pelvis suggesting a deflexed head. When the head is well flexed, the anterior fontanel faces the sidewall of the pelvis. Palpating and flicking the fetal ear provides confirmation of the position. Feeling the ear that is below the parietal eminences with maternal bearing down efforts suggests that the biparietal diameter of the head has descended below the mid cavity. With a well-flexed head the sagittal suture bisects the circumference of pelvis. The sagittal suture felt more in the posterior or anterior in the pelvis suggests asynclitism and can cause poor progress and difficult IVD. Descent and rotation of the head with contraction and bearing down effort are favourable signs for successful IVD.

Mother can be in the lateral or dorsal position with the legs flexed and abducted. Alternatively, mother can be in lithotomy position with the buttocks slightly beyond the edge of the bed. Good pain relief is essential for IVD and should be objectively checked before the procedure is done under antiseptic (vulva and perineum should be cleansed with antiseptic solutions and draped) and aseptic conditions.

Regional anaesthesia is preferred for mid cavity IVD, that is when the head is engaged but the station is above + 2 cm but below the ischial spines.[10] For low cavity IVD when the vertex is beyond + 2cm but not reached the pelvic floor, regional or pudendal block anaesthesia with local infiltration of the perineum is acceptable. Outlet IVD, that is when the head is on the perineum with the scalp visible without any separation of the labia, pudendal block anaesthesia and local infiltration of perineum should be adequate. In such cases, the vertex would have reached the pelvic floor and would be in the direct, right or left occipito anterior position needing no rotation or slight rotation of less than 45°.

Delivery by CS is preferred if the head is above spines. With the vertex below spines, IVD by different types of forceps and vacuum has been described depending on the position and station of the vertex. Comparisons of outcome with different instruments are better assessed with the procedures done at specific stations and positions, for example LOT at +1 or ROP at +2) at the time of instrumentation, instead of studying them as mid, low and outlet IVD.[11]

The Debate as to the Instrument for Safe Assisted Delivery

In the literature, descriptions of different designs of forceps and vacuum are available. However, the use of a particular instrument appear to be based on the training each obstetrician receive and what they are familiar with rather than a detailed study of the design or commercial pressure. Even within the specific instrument used, the safety of the procedure will depend upon the accurate determination of the position, station, caput and moulding of the presenting part. The Neville Barnes forceps is used for direct traction and is useful in occipitoanterior positions and direct occipitoposterior position if the head is 0 or 1/5'th palpable and the station is at or below spines with caput and moulding that is not excessive. A rotational forceps such as a Kiellands is useful with a occipitoposterior or lateral position as the absence of prominent pelvic curve and the sliding lock to correct for asynclitism enables one to accomplish the delivery after rotation. This results from the design of Keilland's forceps without the cephalic curve, which results in the toes of the forceps taking a smaller circle during rotational deliveries.

Vacuum devices such as silk, silastic or metal cup with the suction tubing arising from the dorsum of the cup, that is anterior cup can be used for an occipitoanterior position. The cup needs to be applied on the flexion point that is on the sagittal suture about 3 cm in front of the occiput. In occipito and lateral positions, the flexion point is very much posterior or lateral in the pelvis. Vacuum cup with the suction tube coming from the side is needed so that it can be slipped between the head and the vaginal wall to reach the flexion point. Special semirigid plastic and metal cups are available for this purpose (Fig. 22.9).

The concepts of the 'axis of the pelvis' (the path the centre of the head takes during its passage through the pelvis) and the flexion point are important in instrumental

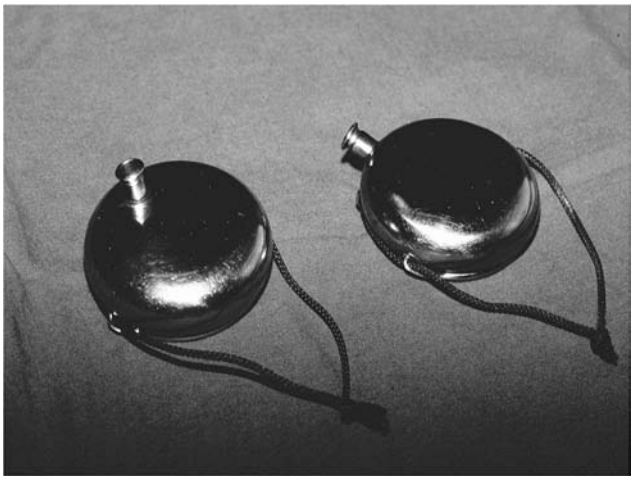

FIGURE 22.9 Metal cups with tubing on the side for application with OP or OL positions and on the dorsum of the cup for OA application.

deliveries. The descent of the fetal head must be along the axis of the pelvis to minimize perineal trauma. Too early extension of the head will increase the stretch of the perineum by presenting a larger diameter. The same may result if the ventouse cup is applied too anteriorly resulting in extension of the head.

Direct Traction Forceps Delivery

Forceps has been used to deliver babies for centuries. They have a standard design of handles, shanks to give some length to reach the head and the blades that grasp the head. Hence they have a cephalic curve, which grasps the head as a bimalar, bitemporal application so that the direction of pull would be along the flexion point (Fig. 22.10). The blades have a pelvic curve to negotiate the pelvis and are fenestrated to make the instrument light. A lock of varying nature constructed on the shank locks the handles. The Kielland's forceps has a sliding lock to allow for correction of asynclitism.

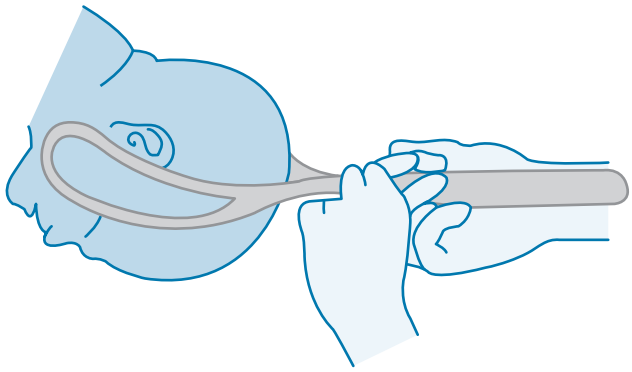

FIGURE 22.10 Forceps correctly applied—bimalar-biparietal application and the direction of the pull would be along the flexion point.

Before instrumental delivery, the woman should have an explanation of the procedure after informing the indication. Since number of forceps may be used on a day and whilst packing for sterilization blades from different pairs may have been packed wrongly. It is good practice to assemble the instrument to make sure that the left and the right side matches each other. It is convention for the left blade to be applied first by holding the left blade by the left hand almost parallel to the right inguinal ligament and for the right hand to be in between the head and the vagina so that the blade can be slipped to the side of the head using a curving movement to negotiate the cephalic and pelvic curve without inflicting trauma to the head or the vagina. The handle and the shank will sit in snugly in a horizontal position. The same manoeuvre is repeated using the right hand for the right side of the instrument. With good application the instrument would lock without difficulty. With such application the occiput would be 3–4 cm above the shanks, the sagittal suture would bisect the shank perpendicularly and only one finger can be inserted on either side between the heel of the blade and the head. If occiput is further up, the blades need to be slightly disengaged at the handle and the shank lifted to the appropriate position and locked again. This would facilitate traction along the flexion point.

It is useful to make use of the natural contraction of the uterus and maternal expulsion forces and hence traction is applied when mother pushes. First it is a downward traction to negotiate the pelvic curve and as the head descends and when the parietal eminence is about to be visible the direction of pull will be upwards and the head will be born by extension. An episiotomy may be necessary if there is a likelihood of a bad tear and could be judged when the head is crowning. A generous mediolateral episiotomy would avoid rugged tears and also injury to anal sphincter.

Rotational Forceps Delivery

Malpositions of occipitoposterior and lateral need rotational forceps or vacuum instrument if assisted vaginal delivery is a possibility. Kielland's forceps is designed with minimal pelvic curve, slightly longer shank and a sliding lock to help apply the blades and correct any asynclitism. The shank has two knobs on the same side to facilitate the application with the occiput in the direction of the knobs to identify the progressive rotation.

Abdominal examination should be done to have estimate fetal weight, assess the possible position based on the attitude of the fetal parts and how much of head is palpable abdominally. This is followed by vaginal examination to confirm full cervical dilatation, position, station, moulding, caput and synclitism. The uterine contractions should be optimal and mother able to assist the delivery by bearing down efforts.

Kielland's forceps can be applied directly to either side of the head to capture the bitemporal-bimalar area. Vaginal tissue and the head should be protected at the time of application. The handle of the forceps is held with fingers like holding a pencil to avoid forceful application that can inflict trauma to the mother or baby. Second method is called the wandering method where the anterior blade is applied to the side of the pelvis across the baby's face or occiput and wandered around to be placed in the bitemporal-bimalar position usually underneath the symphysis pubis. The posterior blade is directly applied in the roomy posterior pelvis and the handles locked and asynclitism corrected by sliding the handle on one another. The third is termed classical method where the anterior blade is passed underneath the symphysis pubis with the cephalic curve facing the pubis and pushed beyond the head and is rotated and brought down to a bitemporal bimalar application. The latter method is less practiced due to the fear of trauma.

Once applied and locked the rotation is carried out to have the occiput anterior. Once this is achieved, the three essentials of the flexion point 3 cm above the shank, sagittal suture bisecting the shank and one finger between the heel of the blade and the head is checked before applying traction with uterine contractions and maternal bearing down efforts.

Complications of Forceps Delivery

Maternal injury is mainly to the vagina and perineum. Very rarely it may be to the bladder or urethra. Third and fourth degree tears are more common than at the time of normal or vacuum delivery. Spiral vaginal tears with severe bleeding may cause maternal collapse and need to be tackled immediately and carefully. Suturing one side of the vaginal wall at a time and 'climbing up' the tear using the lower ones as stay sutures, good light and assistance are all extremely useful in these situations. Good regional anaesthetic and theatre conditions may be needed with difficult cases.

Fetal injury is usually in the form of minor abrasions or forceps marks. With bigger babies and malapplication facial nerve palsy may occur. Forceful locking and longer duration of traction may result in cephal hematoma and skull fractures. At times a depressed fracture and intra cranial bleeding could be lethal.

Vacuum-Assisted Vaginal Delivery

Vacuum or ventouse delivery is increasingly popular for assisted vaginal deliveries compared with forceps delivery. However there is a variation regarding the choice of instrument from unit to unit. The same conditions needed for forceps delivery should be satisfied for vacuum delivery, that is abdominally not a large baby, head 0 or 1/5'th palpable; vaginally the cervix is fully dilated, the station is at spines or below, the position and synclitism could be defined, there is no excessive moulding or caput and there is descent of the head with uterine contractions and bearing down effort.

The common indications for vacuum delivery are concern for fetal condition, poor maternal effort and prolonged second stage of labour.

The type of vacuum cup used would depend on the position of the vertex. For occipito posterior and lateral positions, a rigid plastic cup or metal cup with the suction tubing coming from the side of the cup ('posterior metal or omni cup') should be used to have the cup applied on the flexion point which is on the sagittal suture and 3 cm in front of the vertex.[12] Flexing median application provides the minimal diameter of the head transverse biparietal and anteroposterior suboccipitobregmatic diameters.

If the cup is placed in the mid line but closer to the anterior fontanel it is known as *deflexing median* application. If it is off the midline and closer to the anterior fontanel it is *deflexing paramedian* application. Deflexing applications are associated with larger diameters and these dimensions are further increased if they are paramedian applications (Fig. 22.11).

The best results with the use of the vacuum depend on accurate identification of the position of the head and to know whether the head is asynclitic so that the cup can be applied correctly over the flexion point. A 'posterior' cup is a must for occipito lateral and posterior positions. The suction tube is attached to the lateral aspect of the cup (posterior metal cup) or through a groove in the cup (e.g. posterior

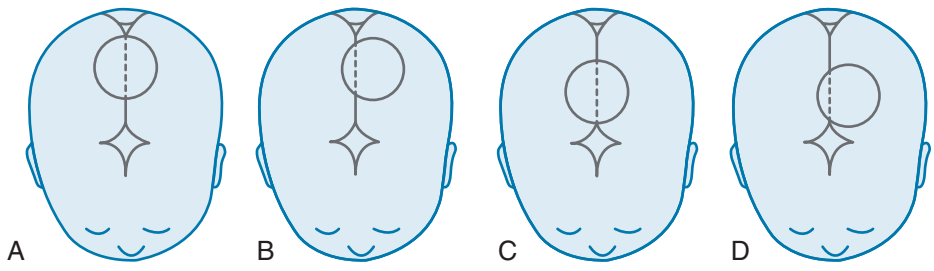

FIGURE 22.11 The figure shows the different applications of the ventouse. (a) Flexing median; (b) Flexing paramedian; (c) Deflexing median; (d) Deflexing paramedian.

rigid plastic cup—omni cup). This arrangement allows the cup to be inserted and moved between the vaginal wall and the head to reach the flexion point.[13] Soft silk, plastic or anterior metal cup where the tubing comes from the centre or dorsum of the cup is ideal for the occipitoanterior position as the flexion point is within reach when the labia are parted. The anterior or soft silk or cups where the suction tubing is on the dorsum of the cup are not suitable for occipitoposterior or lateral positions as the lateral vaginal wall would not permit the central stem or suction tubing to move the cup to the flexion point. The cup should be held firmly on the fetal scalp and vacuum created by a hand-held pump or a mechanical pump up to 0.2 bars or 150 mm Hg or 0.2 kg per sq cm negative pressure. The cup application on the flexion point should be checked and one should make sure that there is no vaginal or cervical tissue included within the cup. The negative pressure is increased to 0.7–0.8 bars or 500–600 mm Hg or 0.8 Kg per sq cm. The traction should coincide with uterine contractions and bearing down effort. Creation of the vacuum need not be in steps and there is no need to the release of the vacuum in between traction efforts. The direction of the traction should promote flexion of the head to expose the smallest diameter. This would promote descend of the head along the axis of the pelvis. Initially it is downward traction followed by changing the direction to follow the pelvic axis. With flexion and descent autorotation of the vertex in malposition becomes occipito anterior position.

The incidence of ventouse deliveries has increased due to the need for less pain relief needed and less perineal trauma including third degree tears.[14] The 'chignon' is the rounded and elevated soft tissue that was sucked into the cup; this swelling subsides in 48–72 hours. Minor neonatal injuries are not frequent and are scalp abrasions, retinal haemorrhages and neonatal jaundice. Hematoma confined to one of the skull bones is rare and subgaleal haemorrhage is extremely rare but can cause severe morbidity and mortality.[15] Babies born by outlet instrumental deliveries show normal physical and neurological outcome on long-term follow up.[14]

Vacuum is avoided in fetuses less than 34 weeks and those with known haemorrhagic conditions,for example hemophilia. Ventouse delivery prior to full dilatation is best avoided although it is possible in multiparae after 7–8 cm with good contractions in the hands of an experienced and skilled obstetrician. Where maternal bearing down efforts may worsen, their medical condition such as cardiac, respiratory or some neurological disease forceps may be preferable.[16]

Trial of Instrumental Delivery

Judgment to predict a safe instrumental delivery is at times difficult. In cases there is concern about fetal hypoxia and doubt exists as to the possible success of instrumental vaginal delivery, caesarean section is better.

Trial of instrumental delivery is best performed by the most senior obstetrician available or under his/her direct supervision. The procedure should be in the theatre under good regional anaesthesia. The theatre nursing team, anaesthetist and paediatrician should be present to facilitate conversion to CS without any hesitation. IVD should be abandoned when faced with difficulty. Prior to trial of IVD the mother and her partner should be aware of the possibility of a CS. A prior consent for CS is useful for smooth transition should the need arise.

SHOULDER DYSTOCIA

Definition, Incidence and Associations

Shoulder dystocia is difficulty in delivery of the shoulders after the head has been delivered and the incidence is about 1 in 200. Usually the anterior shoulder gets impacted above the symphysis pubis (anterior impaction) whilst the posterior shoulder is below the sacral promontory. The fetal neck is stretched and the head retracts against the maternal perineum (turtle neck sign) and external rotation does not take place. Rarely, there could be bilateral impaction when the posterior shoulder also gets impacted on the sacral promontory. This is more likely with mid cavity rotational instrumental deliveries. Shoulder dystocia can lead to permanent brachial plexus palsy in a small proportion of cases. Rarely, it is associated with fracture of the clavicle and/or humerus or birth asphyxia and its consequences. Immediate skillful management avoids such consequences. This is possible with good knowledge, help by experienced personal and practice of the procedures in a stepwise manner within clinical drill practice sessions.

Although it is mostly associated with macrosomia (9% of babies >4000g, 15% > 4500g, and 40% above 5700g) the condition is unpredictable as 50% of the incidence is with babies weighing <4000 g. Previous history of shoulder dystocia has a greater association followed by large babies with asymmetrical macrosomia on ultrasound, previous large babies, diabetic pregnancies, prepregnancy obesity, excessive weight gain in pregnancy, multiparity, clinically large babies and prolonged pregnancy. In labour, poor progress in the late first and second stage and mid pelvic cavity deliveries are associated with shoulder dystocia.

Diagnosis and Management

Failure of external rotation of the head, which is flushed against the perineum with little space to feel the neck and difficulty with delivery of anterior shoulder with uterine contraction, maternal bearing down effort and gentle traction on the head along the axis of the fetus suggests the diagnosis of shoulder dystocia.

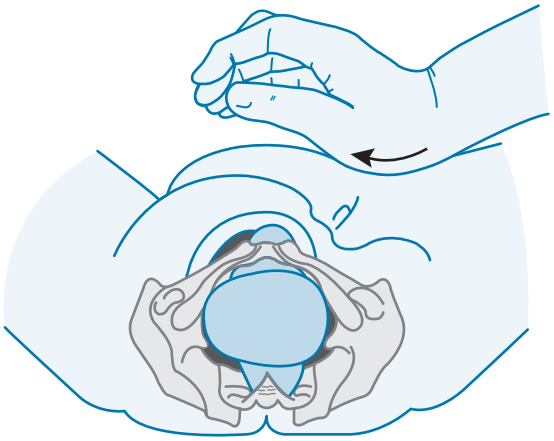

FIGURE 22.12 Application of directed suprapubic pressure.

A brief explanation to the couple should be followed by an immediate call for help. This should include two additional midwives, a paediatrician, an anaeshetist and where possible a senior colleague. Mother's legs should be slightly abducted and hyper flexed at 45° to the maternal abdomen (Mc Robert's position) and held in that position by two assistants.[17] The symhysis pubis rotates upwards and the sacral promontory flattens providing more space posteriorly and for the anterior shoulder to slip below the pelvic inlet. This can be further assisted by directed supra pubic pressure by an assistant applying pressure from behind the anterior shoulder to adduct the shoulders and rotate the biacromial diameter to the larger oblique diameter of the pelvis (Fig. 22.12). The hands are best held in a position similar to that used in adult cardiac massage. With these efforts delivery is attempted with the next uterine contraction and bearing down effort. Pushing on the uterine fundus may cause further impaction and should be avoided. Panic pulling and pivoting the fetal head towards the floor results in stretching of the brachial plexus or even may cause cervical cord injuries (Avoid four Ps—panic, push, pivot and pull).

If these external manipulations do not help, a generous episiotomy should be followed by fingers on the anterior aspect of the posterior shoulder and to rotate it in an effort to have the biacromial diameter into the larger oblique diameter of the pelvic inlet and with a 180° rotation, what was the posterior shoulder would be below the symphysis pubis and the anterior shoulder would be in the sacral hollow facilitating delivery (Wood's manoeuvre).[18]

If Wood's manoeuvre is difficult to perform, the posterior arm should be delivered by inserting the fingers along the back of the fetus and pushing the arm towards anterior chest wall followed by flexing the arm at the elbow and delivering the hand and the rest of the posterior arm (Fig. 22.13). This reduces the transverse diameter of the shoulder enabling the baby to be delivered. If difficulty still persists Wood's manoeuvre should be tried with one arm out with the patient still in the Mc Robert's position.

The last resorts are intentional fracture of the clavicle or symphysiotomy.[19] This need to be done by those who are more familiar with these procedures or else the injury to the fetus and mother may be considerable. Cephalic replacement into the pelvis and Caesarean section has been described (Zavanelli's manoeuvre).[20] It is done by rotating the head for the occiput to be below the symphysis pubis followed by flexion of the head. Delivery in all fours if necessary with delivery of posterior shoulder has been popular in some centers. The flexibility of the sacroiliac joint allows 1–2 cm increase in the sagittal diameter of the pelvic inlet in contrast to lithotomy position where the posterior mobility of the sacrum is limited.[20] Cutting one or both clavicles with strong scissors is useful in cases with an intrauterine fetal death.

The baby should be examined after delivery for possible brachial plexus palsy or fracture of clavicle or humerus. The couple should be informed of what happened, the need for various steps and the final outcome. Debriefing of the

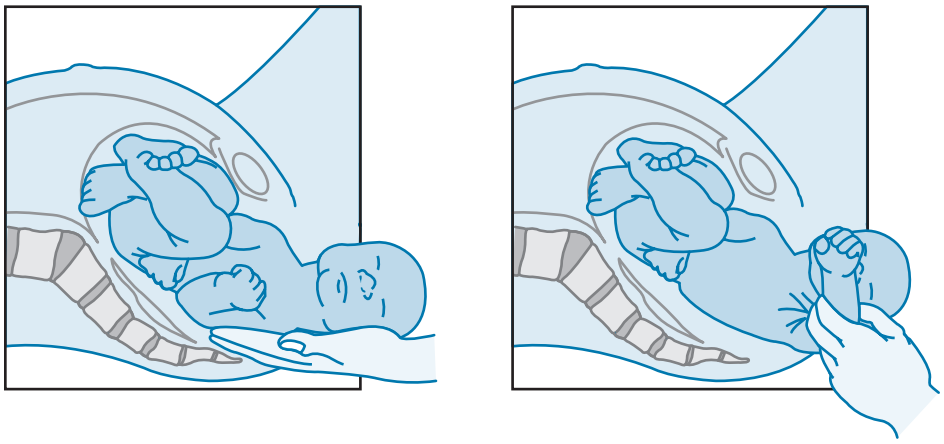

FIGURE 22.13 Delivery of the posterior arm.

staff is also useful to see whether there were any lapses in care in terms of anticipation or management. The position of the fetus must be entered in the records accurately, since damage to the brachial plexus could result in permanent disability. Accurate records are invaluable in case of legal action. Good practice, communication and record keeping are keys to avoid medicolegal issues.

CAESAREAN SECTION

The incidence of elective and emergency CS is on the increase. In developed countries, a minority are contributed by maternal request for nonmedical reasons.[22] Medicolegal, social convenience and monetary considerations may be other factors.[23] The incidence of CS in all countries is on the increase. In the United States and Brazil, figures beyond 33% are the norm. Fortunately, the maternal morbidity and mortality are minimal and should be attributed to asepsis, antisepsis, prophylactic antibiotics during procedure, antithrombotic measures taken and improved surgical techniques. Advanced anaesthetic techniques, availability of blood when needed and minimized risk with transfusion has played a major role to make this procedure safe.

Indications for CS

Based on the timing when a CS needs to be done, the indications are grouped under one of four categories.[24]

- **Category 1 or emergency CS** – There is an immediate threat to the mother or the fetus. Ideally, the CS should be done within the next 30 minutes. Some examples are abruption, cord prolapse, scar rupture, scalp blood pH <7.20 and prolonged fetal heart rate deceleration <80 beats per minute for > 9 minutes.
- **Category 2 or urgent CS** – There is maternal or fetal compromise, which is not immediately life threatening. Here the delivery should be completed within 60–75 minutes and cases are those with fetal heart rate abnormalities of concern.
- **Category 3 or scheduled CS** – There are number of indications in this category. These are cases where the mother or physician cannot wait to elect a date for delivery nor does it mean that a CS should be done on that day. In some cases, there may be a debate whether they should have a CS or an elective induction. Common examples are preterm IUGR, moderate to severe preeclampsia where continuation of pregnancy may cause morbidity to the mother or fetus but the timing when exactly cannot be pin pointed but waiting would increase the risks
- **Category 4 or elective CS** – Mother and staff elect the date and time of delivery. Malpresentations, previous CS where the mother request a CS, nonbleeding placenta praevia, HIV infection are some of the category 4 cases that are listed for elective CS. Where possible, it is done after 39 weeks to reduce the incidence of tachypnea of the newborn and admission to the special care baby unit.

With increasing incidence of repeat CS, the incidence of placenta accreta is not that uncommon. Interventional radiological assistance helps in internal iliac arterial balloons being appropriately placed so that they can be inflated after the delivery of the fetus or for embolization of uterine arteries at the time of CS should be considered where facilities exist. It is recommended that CS in cases of placenta accrete is performed before the completion of the 35th week, since there is a high chance of bleeding after that.

In other conditions, elective CS is preferred beyond 39 weeks to reduce the chance of tachypnoea of the newborn. Often medical or obstetric condition may dictate the gestation at which an elective CS should be carried out.

Types of Caesarean Section

Lower Uterine Segment Incision

Lower segment CS is the commonest procedure, where the uterine cavity is entered via a horizontal incision on the lower segment after reflecting the visceral peritoneum. Abdominal skin incision may be a low midline, paramedian or a Pfannenstiel— supra pubic horizontal incision. After opening the rectus sheath the parietal peritoneum is incised to enter the abdominal cavity. The visceral peritoneum is incised just above that attachment of the bladder and reflected down to expose the lower segment. Careful incision of the lower segment should expose the uterine cavity without injuring the fetus. The head or breech is delivered through the lower segment by lifting the presenting part to the incision. Forceps or vacuum is used at times to deliver the head.

After delivery of the placenta and membranes are delivered by controlled cord traction and checking the cavity is empty the uterine wound is examined for any extensions. Noncrushing hemostatic clamps are useful to identify the edges of the uterine wound and to reduce bleeding. Current literature appears to support two-layer closure of the uterine wound by an absorbable suture material. Once uterine hemostasis is achieved, the tubes, ovaries and the pelvis are checked for normality. Visceral and peritoneal closure is not necessary. Rectus sheath is closed with a continuous vicryl followed by skin closure using subcuticular dexon or clips or silk based on the surgeon's preference.

The short-term follow up of the CAESAR study did not show any differences in post CS outcomes. Long-term follow up is needed to reveal the benefit of these procedures on scar integrity. Prospective studies have shown that the incidence of rupture is less with two-layer closure.

Lower segment CS (LSCS) has the added benefit that it is thin, less vascular and easier to incise to deliver the fetus through the proximate incision. Approximation of the layers is easy with the lower segment because of the thin muscle layers. The peritoneal closure was thought to provide an advantage against infection but now it is not closed, as there appears to be no specific advantage. The blood loss and infection rate is much less with LSCS compared with an upper segment CS.

The uterine cavity should be cleaned and inspected so as to remove any retained tissue. Patency of the cervical os to allow drainage of blood should be checked. If necessary the cervical canal should be dilated digitally before closure of the uterus. Ovaries and tubes should be checked and documented. It is advisable to use prophylactic antibiotics to reduce infection and low molecular weight heparin to avoid thromboembolism. They are administered intraoperatively. Blood group of babies of Rhesus negative mothers should be tested and a dose of anti D should be given and a Kleihauer–Betke test performed to determine the adequacy of the dose of Anti-D if the baby is Rhesus positive. Postoperative care includes close observation and pain relief.

Midline Longitudinal Incision

The midline longitudinal incision could be in the lower or upper segment of the uterus. It is easier to make a small buttonhole incision in the lower segment till the uterine cavity is reached. Then two fingers are inserted facing upwards and knife or scissors can be used to extend the incision upwards. Upper segment incision is associated with increased blood loss and less than optimal approximation at closure. There is increased postoperative morbidity. A trial of vaginal delivery in the next pregnancy is associated with higher incidence of scar rupture and hence the midline incision is reserved for cases where LSCS is fraught with more difficulties. Examples include difficulty in approaching lower segment because of fibroids or anterior placenta praevia with large vessels in the lower segment. Others include preterm breech with poorly formed lower segment, impacted transverse lie with ruptured membranes, transverse lie with a congenital anomaly of the uterus or placenta accrete, where the incision is made over the upper part of the uterine body, superior to the upper margin of the placenta. Perimortem CS can be done via upper segment incision although it may be as easy to go through a lower segment incision. When delivery is difficult with a lower segment an inverted T incision is made.

Complications Associated with CS

Haemorrhage, anaesthesia-related problems and infection are the common complications. Rarely there may be injury to bowel, bladder, ureters or the fetus. Thromboembolism is extremely rare but could be fatal. Pre-, intra- and postoperative precautions are essential. Intraoperative pneumatic inflatable boots and prophylactic dose of heparin has become standard practice. Postoperatively, the use of heparin in adequate amounts based on BMI, graded elastic stockings, mobilization and chest and leg physiotherapy are helpful to reduce the incidence of DVT and PE.

Late complications are wound infection and rarely secondary haemorrhage. Vesico or uretero vaginal fistulae due to visceral injury are extremely rare. The incidence of placenta accrete is on the increase with increasing CS rate. The realization that an experienced anaesthetist is needed for obstetric anaesthesia and the ease of spinal or combined anaesthesia has made anaesthesia for CS as safe as possible.

One of the disturbing complications is awareness under anaesthesia when she is paralysed. Vomiting at the time of induction and postoperative lung atelectasis following general anaesthesia are rare. Aspiration of gastric contents leads to Mendelson syndrome, and to reduce such an event gastric contents are neutralized with 20mls of 0.3 sodium citrate. Gastric emptying is promoted with metoclopramide 10mg IV. For elective CS, ranitidine 150 mg, an H2 agonist is administered two hours before surgery. Application of cricoid pressure to prevent stomach contents from regurgitating into the trachea via the pharynx is an essential safety measure in CS done under general anaesthesia.

Caesarean hysterectomy is rarely performed for uncontrollable postpartum haemorrhage, placenta accreta or uterine rupture and for cervical malignant disease. Maternal mortality is 0.33 per 1000 and is usually related to anaesthetic or haemorrhagic complications.

EPISIOTOMY AND PERINEAL LACERATIONS

Perineal lacerations can occur with normal deliveries but commoner with instrumental vaginal deliveries. Posterior vaginal and perineal tears are common compared with anterior vaginal or vulval tears and this is due to good flexion of the head at delivery. Posterior vaginal and perineal tears are less in a multipara and in spontaneous vaginal deliveries.

Perineal injuries are classified as follows:

- **1st degree** – only the vaginal epithelium is involved
- **2nd degree** – perineal muscles are damaged
- **3rd degree** – Anal sphincter is involved
  - **3a** = <50% external sphincter thickness
  - **3b** = >50% external sphincter thickness
  - **3c** = internal sphincter is involved
- **4th degree** – anal epithelium is torn

3rd and 4th degree tears are jointly referred to as obstetric anal sphincter injuries (OASIS).

Episiotomy

There is no role for routine episiotomy in obstetric practice. This intentional perineal incision after informed consent is to increase the soft tissue outlet dimensions and is performed with normal and mostly with IVDs. The rate of episiotomy varies and is mostly influenced by the center's and individual practitioner's philosophy than judgment of the caregiver as to whether it is needed.

It is performed when tearing in different places of the introitus is likely shown by multiple early perineal tears. Episiotomy helps to expedite delivery when there is fetal distress. It is almost routinely done with IVDs but the need is less with ventouse deliveries and where the perineum is lax. If vaginal delivery is delayed due to a rigid perineum, an episiotomy may help. Vaginal manipulations needed with assisted breech and shoulder dystocia may be made easier with an episiotomy. It is advisable in those who had a previous pelvic floor surgery for incontinence or third or fourth degree tears.

A midline episiotomy starting from the fourchette towards the anus is popular in some countries. A mediolateral episiotomy from the fourchette going laterally to 45º is preferable to avoid third and fourth degree tears. A sharp incision of about 3–6 cm is given and depends on the length of the perineum. The superficial perineal muscles are incised and are comparable to second degree tear. With normal vaginal delivery local perineal infiltration is adequate for making the incision. In women who already have epidural or spinal anaesthesia, local infiltration may not be needed. It is good practice to check whether pain is felt using a needle prior to the incision. This will help to provide the needed additional infiltration to avoid women feeling pain.

Midline episiotomies cause little bleeding, has less tension to repair and less postrepair pain. It heals well compared with the mediolateral episiotomy but with further tearing downwards has a tendency to cause more third and fourth degree tears.

The episiotomy is not given early to prevent more blood loss and to minimize loss it is given when the head crowns. For the same reason, an episiotomy or tear should be sutured as soon as possible.

Perineal Repair

Good pain relief prior to starting the repair, good light, optimal exposure and assistance when required are essential ingredients for a good repair. Difficulty with seeing the edges from the torn or incised vaginal skin can be facilitated by a tampon with a tail that can be clipped to an artery forceps. The tampon and all swabs should be removed after the repair and checked by having a swab count with an assistant. The descending branches of vaginal arteries attached to the vaginal skin might retract and continue to bleed. Hence it is important to start the suture above the apex of the tear or episiotomy. The suture of the vaginal skin should be at half to 1 cm intervals taking each vaginal wall in turn with a continuous locking suture. Synthetic suture material like 'vicryl rapide' is used. The technique used should provide haemostasis and prevent vaginal shortening. The distance between sutures in the medial side is shorter compared with the lateral vaginal wall to bring about good approximation. At the fourchette, the hymenal membrane and the junction of the pink vaginal skin to pigmented outer skin margin should meet as it was before the tear or the episiotomy.

The perineal muscles are sutured together by continuous or interrupted sutures. Subcuticular suture is preferred for the skin as it is associated with less pain and heals well. Continuous, loose nonlocking sutures to approximate perineal muscles and subcuticular skin closure causes less pain and avoids the need for removal of sutures.[24] Good approximation of the cut edges and good haemostasis should be checked by vaginal examination. A rectal examination should be carried out if there is concern about accidental suture through the rectum.

Needle and swabs count should be carried out followed by cleaning and placing a pad against the vagina. Documentation of every step taken during suturing is important including estimated blood loss. Postoperative care should include sufficient analgesics for pain relief.

After delivery of placenta and membranes and repair of episiotomy or perineal tears, mothers are kept in the labour room for one to two hours of observation to detect complications of bleeding or haematoma that may need medical or surgical intervention. Infection, break down of the repair, pain, scarring, dyspareunia and rarely fistula formation are late complications with progression of the postnatal period. If a woman complains of cyclical pain at the site of the episiotomy endometriosis of the scar is a possibility.

Third and Fourth Degree Tears

Third and fourth degree tear involves tear of the anal sphincter.

Only careful examination involving a rectal examination will reveal the extent of damage. For a good examination, it is important to clean the area of all blood using saline. Pressure anteriorly with the forefinger in the anal canal helps to recognize the sphincters. The torn external sphincter tends to retract laterally. The lateral reaches of the tear should be explored to identify the muscles. The third and fourth degree tears are best repaired in the operating theatre. Good light, experienced surgeon and assistance, appropriate instruments and adequate anaesthesia to relax the sphincter muscle are essential. Dissection and mobilization of the muscle is not possible without anaesthesia. Anal

epithelial tears are repaired with 3/0 vicryl rapide sutures with the knots on the side of the lumen. 3/0 PDS suture on a round-bodied needle is used for repair of the muscle. End to end or overlapping method can be used.[25] Accurate documentation helps to avoid misunderstanding of the adequacy of the repair.

Laxative, stool softener and antibiotics are used postoperatively. The patient must be told that symptoms may persist and the repair is not always successful. Patients are best followed up to evaluate the success of the repair and whether they have any symptoms; if present investigations such as endoanal ultrasonograpy or anal manometry studies can be offered if facilities are available. The help of experienced colorectal surgeon may be needed if symptoms persist and interferes with the woman's professional and social life.

CONCLUSIONS

Childbirth was in the realm of midwives for centuries. The need for operative delivery introduced the former barber surgeons who were mainly males into the field of obstetrics with the use of instruments to assist deliveries. The popularity of operative deliveries tends to wax and vane but they are here to stay. There have been better designs of the instruments used. A greater understanding of the application of the technique and the realization that training with mannequins, followed by under supervision would improve the outcome for the mother and newborn. In most postgraduate programmes, objective structure assessment of technical skills (OSATS) has become a norm to certify practitioners that they are fit to conduct an operative delivery independently. This is followed by maintaining a logbook or audit of their operative deliveries and morbidity outcomes. The WHO is undertaking a trial on the 'Odon device', which consists of two sliding plastic bags, which are slipped over the baby's head, and the head is delivered by the head in the inner bag being glided over the outer bag. The result of the trial is anxiously awaited.

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Chapter 23

Postpartum Haemorrhage

Sadia Muhammad and Edwin Chandraharan

Chapter Outline

INTRODUCTION

Postpartum haemorrhage (PPH) accounts for a quarter of maternal deaths worldwide[1] and its incidence in developed world is increasing.[2–4] According to the recent Confidential Enquiries into Maternal and Child health (CEMACH) Report, obstetric haemorrhage occurs in around 3.7 per 1000 births with uterine atony being the commonest cause.[5] Although in this triennium, there has been a significant reduction in the number of maternal deaths due to obstetric haemorrhage and PPH being the sixth leading cause of direct maternal deaths in the United Kingdom, it is a significant contributor of severe maternal morbidity and long-term disability including shock and organ dysfunction.[6-8] Worldwide, PPH continues to contribute to significant maternal morbidity and mortality mainly due to 'too little being done too late'.[9] A systematic approach using Algorithms such as HAEMOSTASIS to ensure timely and appropriate action may reduce morbidity and mortality. Recent advances include development conservative surgical techniques for placenta percreta, the use of topical haemostatic agents as well as use of tranexamic acid and changes in the ratio of blood:blood products.

DEFINITION

Primary PPH is classically defined as blood loss from the genital tract, exceeding 500 mL within 24 hours of vaginal delivery and 1000 mL during a caesarean section. PPH can be minor (500–1000 mL) or major (>1000 mL). Major PPH is further divided into moderate (1000–2000 mL) and massive (loss of 30–40% of a woman's blood volume) or more than 2000 mL resulting in changes in the haemodynamic parameters.

Visual estimation of blood loss (EBL) after birth is notoriously inaccurate. Average blood loss at delivery is approximately 500 to 600 mL. Genital tract bleeding >1000 mL after birth may be a more clinically useful definition of PPH because this corresponds to the 95th centile for blood loss associated with spontaneous vaginal delivery.[10]

Secondary PPH is defined as excessive blood loss from the genital tract after 24 hours following delivery, until 12 weeks post-delivery.

AETIOLOGY

The commonest cause of postpartum haemorrhage is uterine atony due to the failure of the myometrium to contract

and retract after the delivery of the fetus to stop bleeding from the raw placental site.[11] Common risk factors associated with PPH are listed in Table 23.1. Atonic PPH accounts for 80% of all cases of primary postpartum haemorrhage and other causes include genital tract trauma, retained placental tissue and rarely coagulopathy (Table 23.2).

Uterine Atony

It is the most common cause of PPH accounting for 70–80% of cases.[12-13] Normal physiological changes during pregnancy include an increase in maternal blood volume by approximately 50% (from 4 L to 6 L) and a concomitant increase in uterine blood flow which reaches up to 500–800 mL/min at term. This constitutes 10–15% of a woman's cardiac output. Branches of the uterine artery that supply the placental bed pass through myometrial fibres that are arranged in longitudinal, transverse and oblique directions. Following delivery, contraction and retraction of these 'criss-cross' myometrial fibres causes placental separation and kinking of blood vessels which in turn causes occlusion of blood flow. This 'criss-cross' arrangement of myometrial fibres surrounding uterine blood vessels that enables the uterus to 'clamp down' on blood supply to the placental bed immediately after childbirth has been referred to as the 'living ligatures' or 'physiologic sutures' of the uterus.[14] Uterine atony reflects a failure of this living ligature system to contract and retract immediately following the delivery of the fetus, leading to continued perfusion of the placental bed by the 'unclamped' uterine blood vessels.

Unlike other factors such as placental abnormalities that may be detected in antenatal period, occurrence of uterine atony is difficult to predict. Many risks factors associated with uterine atony have been reported in previous studies including uterine over-distension (e.g. multiple pregnancy, polyhydramnios), rapid or prolonged labour, oxytocin stimulation and obesity. In a recent study, maternal race/ethnicity, preeclampsia and chorio-amnionitis were consistent risk factors for uterine atony in women delivering vaginally that required treatment.[15] Increasing obstetric interventions such as induction of labour, caesarean sections and operative vaginal deliveries have also been implicated although the exact mechanism of this still remains unclear. It may be postulated that the reasons for operative delivery may be prolonged labour that can lead to atonic PPH in addition to increased risk of trauma to tissues during operative delivery.

TABLE 23.1 Risk Factors Associated with PPH

Placenta praevia
Abruptio placenta
Multiple pregnancy
Preeclampsia/hypertension
Asian ethnicity
Previous PPH
Obesity (BMI > 35)
Anaemia (Hb <9.0 gm)
Induced labour
Emergency/elective caesarean section
Mediolateral episiotomy
Operative vaginal delivery
Big Baby wt > 4 kg
Prolonged labour >12 hours
Age > 40
Pyrexia in labour

TABLE 23.2 The 'Four Ts': Causes of Postpartum Haemorrhage

Four 'T's Cause	Approximate incidence (%)
Tone—Atonic uterus	80
Trauma—Lacerations, haematomas, inversion, rupture	10–15
Tissue—Retained tissue	3–5
Thrombin—Coagulopathies	1–2

Genital Tract Trauma

The trauma to the female genital tract during spontaneous or assisted vaginal delivery or by caesarean section can also be substantial and can lead to significant disruption of soft tissue and tearing of blood vessels. Trauma accounts for 10–15% of causes of PPH and include genital tract lacerations, uterine rupture and uterine inversion. It is estimated that over 85% of women who have vaginal birth suffer some degree of perineal trauma and of these 60-70% will experience suturing.[16,17]

Amount of bleeding secondary to genital tract trauma may not be always visible due to the occurrence of paravaginal or broad ligament haematomas. Such haematomas should be suspected in the presence of severe pain or if the changes noted in the vital signs are disproportionate to the amount of blood loss. Haematomas can be confined to vulva or can involve infralevator and supralevator regions.

Retained Placental Tissue (and Membranes)

Retained tissue refers to blood clots, retained placenta, cotyledons and membranes. The mean duration of time from delivery of the fetus until placental expulsion is usually eight to nine minutes. If this duration increases, then the risk of postpartum haemorrhage may also increase as the uterus

is unable to contract and retract effectively in the presence of placenta and membranes. The risk of postpartum haemorrhage is estimated to double after 10 minutes. Retained placenta refers to a failure of the placenta to be expelled within 30 minutes after birth and this occurs in less than 3 per cent of all vaginal deliveries.

One management option for retained placenta is to inject the umbilical vein with 20 mL of a solution of 0.9 per cent saline and 20 units of oxytocin. However, recent evidence has been shown that this approach does not reduce the need for manual removal of the placenta compared with injecting saline alone.[18] Manual removal of placenta (MROP) should be performed under suitable analgesia in theatre to arrest ongoing bleeding.

Coagulopathy

Coagulopathy refers to disorders of coagulation system and such coagulation abnormalities can rarely cause primary PPH. Coagulation defects should be suspected in patients who have not responded to the usual measures to treat primary post-partum haemorrhage, especially if the uterus is found to be well contracted.

Common causes of PPH due to coagulopathy include idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), von Willebrand disease (vWF) and haemophilia. Acquired coagulation abnormalities can develop in association with severe pre-eclampsia and HELLP (haemolysis, elevated liver enzyme levels, and low platelet levels) syndrome or secondary to disseminated intravascular coagulation (DIC). Disseminated intravascular coagulation may be seen with severe preeclampsia, amniotic fluid embolism, sepsis, placental abruption and a retained dead fetus.

Causes of Secondary Postpartum Haemorrhage

- Products of conception – retained placental tissue and membrane
- Endometritis
- Placental site trophoblastic tumour (gestational trophoblastic tissue)
- Arterio-venous malformations (e.g. pseudo-aneurysm of the uterine artery)

DIAGNOSIS OF POSTPARTUM HAEMORRHAGE

Visual Estimation of Blood Loss

Most clinicians visually attempt to estimate the amount of blood loss during PPH. However, it has been found to be notoriously inaccurate with wide inter and intra-observer variation. Its reliability decreases in large volumes of blood loss. Prasertcharoensuk et al[19] compared visual estimation of blood loss with direct measurement of blood loss during vaginal births. The incidence of PPH was underestimated in the visual estimation by 89%. Obstetricians estimate blood loss at delivery by visual estimation of blood collected in the obstetric drapes. Blood is often mixed with urine and surgical sponges/swabs. Visual assessment of blood loss has been shown to underestimate postpartum blood loss by 33% to 50% compared to an objective measurement of blood loss using photo spectrometry.[20]

Direct Measurement

It is one of the oldest methods of accurately determining blood loss. It requires several containers for collection and a graduated container for measuring the amount of blood. Women can give birth in any position or location. Again, the limiting factor is contamination with amniotic fluid and urine. Drapes, swabs and pads can be measured before and after splattered with blood, however, this needs to be done soon after birth to avoid drying and evaporation. Blood loss could also be estimated by weighing the pre-weighed swabs after they are used and calculating the amount of blood loss by changes in the weight of the swabs before and after use. This is often used by the operating theatre staff to estimate blood loss.

Shock Index

Shock index (SI) has been used in intensive treatment units (ITU) and trauma centres as a guide to estimate the amount of blood loss. It refers to heart rate (HR) divided by systolic blood pressure (SBP). The normal value is 0.5–0.7. Increase in the pulse rate and a fall in systolic blood pressure that is seen with significant haemorrhage, results in an increase in the shock index. It has been reported that if it increases above 0.9–1.1, intensive resuscitation may be required. Recently, attempts have been made to determine the normal and abnormal values of an 'Obstetric Shock Index' (OSI). A preliminary pilot study has suggested that the normal value in pregnancy is 0.7–0.8 and if OSI $>$ 1, then it indicated a massive blood obstetric haemorrhage that required blood transfusion in 80% of cases.[21]

Golden First hour and The Rule of 30

Severe PPH can lead to cardiovascular compromise, aggressive resuscitative measures should be deployed before the estimated blood loss is more than one-third of the woman's blood volume (blood volume [mL] = weight [kg] $\times$ 90 during pregnancy) or more than 1000 mL or a change in haemodynamic status. The 'golden first hour' is the time at which resuscitation must begin to achieve maximum survival before metabolic acidosis sets in. This has led to the concept of rule of 30 to recognize ongoing massive blood loss.

Rule of 30 is used to measure severity of shock resulting from at least the loss of 30% of blood volume leading to moderate shock. It is based on the fact that when a woman loses 30% of her blood volume, her systolic blood pressure (SBP)

is likely to fall by 30 mmHg, her heart rate (HR) is likely to increase by 30 beats/min, her respiratory rate is likely to be > 30 breaths/min and her haemoglobin or haematocrit is likely to drop by 30%. As a result of peripheral shut down, her urinary output is likely to fall < 30 mL/hour.

Signs and Symptoms

Degree of ongoing blood loss determines symptoms and signs observed during postpartum haemorrhage. Based on the amount of blood loss, different severities of shock have been described.[22] We have incorporated obstetric shock index (OSI) to illustrate that clinicans need to be aware of subtle increase in the pulse rate in mild degrees of shock. In addition, due to intense peripheral vasoconstriction to divert blood from nonessential organs to central organs, the diastolic blood pressure (DBP) may increase leading to a narrow 'pulse pressure'. We have proposed an 'Urgency Grid' for the managment of PPH based on Obstetric Shock Index (Table 23.3). We recommend that women scoring Grade 1 and Grade 2 (Shock Index > 1.5 indicating a fall in SBP in association with increasing pulse rate) should have immediate senior input.

MANAGEMENT

Management of postpartum haemorrhage should involve a logical and systematic approach to save lives. Confidential enquiries into maternal deaths have repeatedly highlighted 'too little being done too late' as an important contributor to maternal deaths due to postpartum haemorrhage. Therefore, treatment should focus on prompt recognition and management of the specific underlying cause of PPH, effective communication, assessment and involvement of a wider multidisciplinary team in the management, resuscitation and monitoring of a woman who has suffered a massive blood loss.

Chandraharan and Arulkumaran proposed a management algorithm 'HAEMOSTASIS' to aid systematic management of PPH (Table 23.4) and a recent study has suggested that use of this algorithm 'HEMOSTASIS resulted in a logical and timely approach for the management of PPH, can help to stop more than 90% of cases of massive postpartum haemorrhage.[23] In this study, the risk of peripartum hysterectomy in cases of massive postpartum haemorrhage was < 2%.

Communication includes multidisciplinary approach involving senior obstetric, midwifery staff, anaesthetists and haematologists. The woman and her family should also be kept informed as far as it is practically possible so that they could make an informed decision when radical, life-saving measures such as peripartum hysterectomy are contemplated.

Assessment of the general condition involves estimation of blood loss, identification of the cause of PPH and assessment of vital signs. Resuscitation involves ensuring ABC (ensuring an open airway and breathing by administering oxygen at 8–12 L/min via breathing mask regardless of woman's oxygen saturation level. If airway is compromised, anaesthetic help should be summoned immediately. Circulation should be maintained by establishing two 14 gauge IV accesses and at the same time taking 20 mL blood for diagnostic tests including full blood count, urea and electrolytes, coagulation screen and cross matching 4 units of blood. Blood pressure, pulse and respiratory rate should be recorded every 15 minutes. It is a good practice to have a 'PPH trolley' that has all the required drugs and equipment needed for initial management of PPH. If a massive postpartum haemorrhage (> 2 L) is suspected, a 'Massive Obstetric Haemorrhage Protocol' such as a 'Code Blue' should be declared.

Immediate measures should also include lowering head end of bed to improve venous return and cerebral circulation and avoiding hypothermia by using warmed air blankets and using pre-warmed resuscitation fluids.

Fluid Therapy

Aim of fluid therapy is to replace the blood volume, oxygen carrying capacity of the blood as well as to replenish

TABLE 23.3 Degree of Blood Loss and Clinical Findings in Obstetric Haemorrhage: The 'Urgency Grid'

Loss of Blood Volume Amount / % Blood volume	Blood Pressure Systolic (SBP)	Symptoms and Signs	Obstetric Shock Index	Degree of Shock/Urgency
500–1000 ml 10–15%	Normal SBP	Palpitation, mild tachycardia, dizziness	<1	Compensated Grade 4
1000–1500 ml 15–30%	Slight Fall in SBP (SBP= 80–100 mmHg) A rise in diastolic blood pressure leading to increased pulse pressure	Weakness, marked tachycardia, sweating	>1	Mild Grade 3
1500–2000 30–40%	Moderate Fall in SBP (70–80 mmHg)	Restlessness, marked tachycardia, pallor, oliguria	>1.5	Moderate Grade 2
>2000 >40%	Marked fall in SBP (50–70 mmHg)	Collapse, air hunger, anuria	>2	Severe Grade 1

TABLE 23.4 Management Algorithm for Postpartum Haemorrhage 'HEMOSTASIS'

H	Ask for **H**elp and **H**ands on uterus (uterine massage)
E	**E**stablish aetiology, **E**nsure ABC (Airway, Breathing & Circulation), **E**nsure availability of blood and **E**cbolics (drugs that contract the uterus)
M	**M**assage uterus
O	**O**xytocin infusion/prostaglandins IV/IM/per rectal
S	**S**hift to theatre-aortic pressure or anti- shock garment if considering transfer
T	**T**amponade balloon/uterine packing after exclusion of tissue and trauma /Consider **T**ranexamic acid 1 g i.v.
A	**A**pply compression sutures e.g. B-Lynch/modified
S	**S**ystematic pelvic devascularization-uterine/ovarian/quadruple/internal iliac
I	**I**nterventional radiology and, if appropriate uterine artery embolization
S	**S**ubtotal/total abdominal hysterectomy

depleted coagulation factors. Hence, the best replacement is blood and blood products but until these are available, a rapid infusion of pre-warmed crystalloids such as Hartmann solution (2 L) and colloids (1.5 L) should be administered.

If fully cross matched blood is still unavailable by the time 3.5 L of fluid resuscitation and if bleeding continues or haemodynamic parameters deteriorate, then uncross-matched group specific blood or O Rh D negative blood can be given if clinical situation demands so. British Committee of Standards in Haematology has recommended haematological parameters to be achieved in massive blood loss[24] and these are highlighted in Table 23.5.

Platelet concentrates should be given if platelet count < 50 and when 4 units of red cells have been transfused or if APTT or PT > 1.5, then 4 units of fresh frozen plasma (FFP) should be administered. However, recent evidence has suggested that use of red cells and clotting factors in 1:1 ratio as opposed to current 1:4 ratio may help reduce morbidity (please see What is new in the management of Postpartum Haemorrhage?)

If the blood loss exceeds 4.5 L and large volume of fluids have been given, deficiency of clotting factors that occur secondary to such 'Washout Phenomenon' can be replenished using 1 L of FFP and 10 units of cryoprecipitate in consultation with haematologist. Activated Factor 7 ('Novo-7') is currently not recommended in the routine management of postpartum haemorrhage due to thrombotic complications, including myocardial infarction that has been reported with its use.

TABLE 23.5 British Committee of Standards in Haematology Recommendations for Maintaining Coagulations Parameters on Massive Haemorrhage

- Haemoglobin > 8 g/dL
- Platelet count > 75 x 10^9
- Fibrinogen >1.0 g/L
- Prothrombin < 1.5 mean control
- APTT < 1.5 x mean control

Source: Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. *Br J Haematol* 2006;135:634–641.

Assessing the Cause

Whilst resuscitation is being carried out, the patient should be simultaneously examined to identify the specific cause of PPH so that definitive treatment could be instituted. Once a cause is established (Table 23.2) then timely and appropriate treatment should be instituted. The Algorithm 'HEMOSTASIS' is recommended to aid systematic management.

Mechanical Methods

If placenta has already been delivered and there is bleeding from the uterus that feels boggy (i.e. atonic), then massaging uterine fundus or bimanual uterine massage should be performed to stimulate contraction. This 'uterine massage' not only helps contraction and retraction of the uterus but also helps in expulsion of blood clots. If presence of large amount of blood clots were detected, then a vaginal examination should be performed with sterile gloves to remove these clots. An indwelling urinary catheter should also be inserted to empty the urinary bladder to promote contraction and retraction of the uterus.

Pharmacological Methods

Uterotonic Agents

Oxytocin (Syntocinon) 5 IU by slow IV injection is the first line of management in atonic postpartum haemorrhage. It may also be administered in combination of 0.5 mg of

ergometrine (syntometrine). Oxytocin stimulates the fundal myometrium to contract rhythmically, which constricts spiral arteries and decreases blood flow through the uterus. Alternatively, ergometrine 0.5 mg slow IV/IM injection can be given. This causes generalized, tetanic smooth muscle contraction of myometrium in both upper and lower segments of the uterus. Ergometrine can cause intense peripheral vasoconstriction and can increase the blood pressure. Therefore, it is contraindicated in hypertension.

If bleeding continues despite initial measures, then oxytocin (Syntocinon) infusion should be started using 40 IU syntocinon in 500 mL Hartmann at the rate of and starting at 125 mL/hour (10 units of oxytocin/hour). Prostaglandins enhance uterine contractility and cause vasoconstriction. The prostaglandin most commonly used is 15-Methyl Prostaglandin F 2α or carboprost (Hemabate). Carboprost 0.25 mg (250 mcg) can be administered intramuscularly and this dose can be repeated every 15 minutes eight times (maximum dose 2 mg). Carboprost has been shown to be effective in 87% of patients. It is contraindicated in bronchial asthma (can cause intense bronchoconstriction) and direct intramyometrial injection should be used with caution as inadvertent injection into uterine veins can result in maternal cardiac arrest.

Misoprostol is another prostaglandin that has been shown to be very effective in the treatment of atonic postpartum haemorrhage. However, it is associated with significant side effects (nausea, vomiting, diarrhoea) which may limit its use as the first line prostaglandin in the developed countries. It can be administered sublingually, orally, vaginally, and rectally. Doses range from 200 to 1,000 mcg; the dose recommended by FIGO is 800 mcg (4 tablets of 200 mcg each) administered orally. There is currently no evidence to support the use of carbetocin (long-acting oxytocin derivative) as the first line agent in postpartum haemorrhage.[25]

Shifting to the Theatre or Transferring to Tertiary Referral Centre

If the medical management of postpartum haemorrhage (primary measures: 'HEMO') fails then, senior input should sought as more specialized, secondary measures ('STASIS) are warranted to stop bleeding to save lives. The woman should be shifted to the operating theatre (if facilities are not available, should be stabilized and transferred to a referral centre preferably with the anti-shock' garment). Examination under anaesthesia should be performed to evacuate any blood clots, placental tissue and membranes. At the same time, the genital tract should be carefully examined to exclude trauma in a systematic manner in the lower vagina and perineum, side walls of the vagina, upper vagina and cervix as well as the uterus and the broad ligament.

Tamponade Test

Intrauterine balloon tamponade has been quite widely used as a second-line procedure in the management of massive PPH, and is an integral part of the algorithm 'HEMOSTASIS'. This involves the inflation of a mechanical device such as a balloon (Sengstaken-Blakemore, Rush, Bakri or just a condom catheter) in uterine cavity to create mechanical compression of the placental bed to have a 'tamponade' effect. Tamponade test identifies those who will or will not need laparotomy.[26] Positive test has sensitivity of 87% which, indicates that if the balloon is inflated and the bleeding stops, then no further surgical measures would be necessary in 87% of women. The balloon is usually left inflated within the uterine cavity for 4–6 hours prior to deflation and removal. In a low-resource setting, if uterine balloons are not available, a condom catheter (a condom tied to a nasogastric tube) or uterine packing with gauze can be used.

Haemostatic Uterine Compression Sutures

Use of uterine sutures to compress the anterior and posterior uterine wall so as to compress the placental site can be lifesaving. Brace sutures were described by B Lynch et al for atonic postpartum haemorrhage.[26] However, several modifications (vertical and horizontal compression sutures) are technically easier to perform and hence various new techniques such as 'Hayman's sutures' have been described.[27-33]

The main aim of compression sutures is to stop bleeding from placental site by opposing anterior and posterior uterine wall together. In addition, direct compression of the placental bed may also be attempted by over-sewing.

In a recent study conducted by the United Kingdom Obstetric Surveillance System (UKOSS) rate of application of uterine compression sutures were 18 per 100,000 deliveries (95% CI) with 25% failure rate seen and no difference observed with regard to suture techniques.[34] However, UKOSS reported that a prolonged delay of 2–6 hours between delivery and uterine compression suture was independently associated with a fourfold increase in the odds of hysterectomy. This emphasizes the importance of timely and appropriate management in PPH to improve the outcomes and to reduce morbidity and mortality.

Systematic Pelvic Devascularization

If bleeding continues despite application of compression sutures, a systematic pelvic devascularisation should be attempted. It includes ligation of uterine artery, tubal branch of ovarian artery and internal iliac artery ligation, in that order. The latter requires an in-depth knowledge of anatomy of the lateral pelvic wall to avoid damage to neighbouring structures (ureters, internal iliac vein, external iliac

artery and vein). A recent study has suggested that internal iliac artery ligation seldom affects the next pregnancy and childbirth.[35]

Interventional Radiology

Pelvic arterial embolization should be considered when there is active bleeding in a woman who is haemodynamically stable, when the primary measures have failed. Rarely, it may be indicated when the primary cause of PPH is not amenable to surgery (e.g. uterine arteriovenous malformation, broad ligament haematoma). The WHO Guidelines concluded that uterine artery embolization, if available, may be offered as a second-line treatment of PPH due to uterine atony. Although quality of evidence to support this is very low and therefore, the strength of this recommendation was weak.

Reported success rates of pelvic arterial embolization ranges from to 86% to 100%.[36,37] Uterine artery embolization (UAE) is associated with several adverse effects which include endometritis, and formation of intrauterine synechiae as well as rare but potentially serious complications such as migration of the embolus, uterine or bladder wall necrosis, vaginal fistula. Other procedure-related complications include perforation of the internal iliac artery and inadvertent occlusion of external iliac artery leading to ischaemia of lower limbs. It is noteworthy that despite the reported incidence of uterine synechiae of 11.7% with uterine artery embolization in a series of 68 women, it appears that future fertility may not be significantly compromised.[38]

Peripartum Hysterectomy

Peripartum hysterectomy is a lifesaving procedure in massive postpartum haemorrhage. However, it could only be lifesaving if it is attempted at the right time. Conversely, if it is attempted when conservative measures were attempted, it could result in more harm (increased maternal morbidity and mortality and future loss of fertility). It is, therefore, recommended that a second consultant should be involved in making a decision to perform peripartum hysterectomy.[39]

In a recent systematic review, the most common causes of hysterectomy were abnormal placentation 38%, uterine atony 29% and uterine rupture 12%.[40] A subtotal hysterectomy is technically easier and faster to perform. However, a total hysterectomy is preferred in cases where the precipitating factor for PPH is located in the lower uterine segment (placenta praevia, lower segment uterine rupture and cervical trauma) or in cases of morbidly adherent placenta.[41]

Women Refusing Blood Transfusion

A woman may refuse transfusion of blood or blood products for religious (e.g. Jehova's Witness), social, cultural or personal reasons. Management of woman refusing blood transfusion remains a challenge in current obstetric practice and in the last two confidential enquiries into maternal deaths, there were two deaths reported in each instance in this group. A recent report from Netherlands indicated a three to fourfold increase in the risk of maternal deaths in these women. According to Royal College of Obstetricians and Gynaecologists (RCOG) guidance, these women should be seen jointly by consultant obstetricians and consultant anaesthetists in antenatal period and the woman's family and religious advisers should be aware of the implications of their refusal for blood products. Senior obstetricians should be involved in their delivery and cell salvage should be available where appropriate. Anaemia in antenatal period should be corrected with aim of $>$ 10.0 g/dL of haemoglobin. In cases of very high risk caesarean section (e.g. with abnormal placentation), delivery should be conducted in referral units where facilities for interventional radiology, cell salvage and surgical, anaesthetic and haematological expertise are readily available.

What is New in the Management of Post-Partum Haemorrhage?

Transfusion Strategies

Fluid replacement is the initial resuscitating step of PPH to normalize blood volume and current recommendation is to infuse crystalloids and colloids. However, this significantly worsens existing coagulopathy and enhances fibrinolysis.[42,43] Therefore, there is a drive to rapidly correct coagulopathy by increasing the ratio of FFP units to red blood cell (RBC), to increase the chances of survival.[44] This retrospective study analysing patients receiving massive blood transfusion concluded that survival rate improved with a high platelet to RBC ratio ($>$ 1:2) relative to patients with low platelet to RBC ratio ($<$ 1:2). A ratio of FFP:platelets:RBC 1:1:1 was associated with a significant reduction in mortality (40% versus 60%) as compared to the traditional 1 unit of FFP, 1 unit of platelets for every 4 units of blood transfused (1:1:4 ratio). Based on this emerging evidence, our transfusion strategy for massive PPH is very likely to change in the future with platelets and FFP administrated simultaneously with every unit of packed call (RBC) transfusion to correct ongoing coagulopathy.

Massive Transfusion/Trauma Exsanguination Protocols

The morbidity and mortality associated with massive PPH is often accompanied by a triad of hypothermia, acidosis and coagulopathy. This has led to the development of predefined protocol driven early transfusion of RBC, platelets, FFP and crystalloid solutions which may allow significant improvement in outcomes. These massive transfusion protocols or trauma exsanguination protocols should be closely

monitored for appropriate use. Staff should be educated and quality improvement processes should be in place when they are utilized.[45] Usage of these protocols in obstetric patients has not been studied in detail. However, it is anticipated that their usage in obstetric practice will be more widespread in future.

Use of Fibrinogen

Massive transfusion occasionally causes fibrinolysis and decreases fibrinogen level that may worsen ongoing PPH. It is debatable whether administering fibrinogen alone is beneficial since it could increase the risk of thrombotic episodes. Currently a randomized controlled trial is underway to answer this question.[46]

Thromboelastograph (TEG)

Conventional laboratory-based coagulation tests are of limited use due to delayed availability of results, poor predictive power for massive transfusion, inability to quantify clot propagation versus clot lysis or overall clot strength.[47] The role of TEG and rotational thromboelastometry (ROTEM) in acute traumatic coagulopathy is fast gaining popularity. These devices examine clot formation and dissolution in whole blood and identify reduction in clot strength within 5–10 minutes and can be used to predict need for rapid transfusion with accuracy of 71%. TEG has been shown to correlate well with the level of fibrinogen. An observational study concluded that clot amplitude (CA) and maximum clot firmness (MCF) as assessed by TEG showed a CA of 12 mm in PPH group versus 16 mm in controls and a MCF of 14 mm in PPH group versus 19 mm in control group. These corresponded to the level of fibrinogen was 3.4 g/L in PPH group versus 5.1 g/L in control group.[48]

Tranexamic Acid

Although, the role of tranexamic acid (TXA) in surgical and trauma patients has been extensively studied, its role in obstetric haemorrhage is still under evaluation. A recent French study reported that the use of TXA was associated with a lower median blood loss (173 mL versus 221 mL), increased likelihood of stopping bleeding within 30 mins (63% versus 46%) and less chance of progressing to severe PPH (27 versus 37 women) in women undergoing vaginal delivery when compared with controls.[49] Similar results were seen in patients undergoing caesarean sections with lower intra-operative and post-operative blood loss as well as with the use of oxytocin.[50,51] There are no studies comparing the effectiveness of TXA in absence of other uterotonics. Adverse effects include nausea, vomiting and catheter-related thrombosis. The role of TXA in postpartum haemorrhage is currently evaluated by multicentre RCT.[52]

Recombinant Factor VII a

The role of Recombinant factor VII a is well established in haemophilia. However, its role in uncontrollable life-threatening obstetric haemorrhage is still uncertain. Available data is limited to case reports and series only.[53] Activated factor VII a acts by binding with tissue factor to augment the intrinsic clotting pathway by activating factor IX and X.[54] Recommendation associated with its use warrants the correction of hypovolemia, acidosis and thrombocytopenia prior to its use.[55] Complications include thromboembolic events, and hence, further studies are required before its widespread usage can be advocated.

Triple P Procedure

The Triple P procedure for placenta percreta has been developed as a conservative surgical alternative to peripartum hysterectomy for morbidly adherent placenta.[42] It involves three steps: **p**eri-operative placental localization and delivery of the fetus via transverse uterine incision above the upper border of placenta; **p**elvic devascularisation and **p**lacental non-separation with myometrial excision and reconstruction of the uterine wall (Fig. 23.1). Limitations of this technique include when placenta percreta invades the broad ligament in which case lateral myometrial excision may not be feasible because of increased vascularity and involvement of ureters. A recent case series involving first 16 cases reported a mean blood loss of 1.44 L with no cases of peripartum hysterectomy in women with placental percreta.[57]

Role of Monitoring

The recent confidential enquiry into maternal deaths in the UK concluded that in three out of five women who died due to PPH, there was lack of routine postoperative measurements of BP, pulse, oxygen saturation and respiratory rate. It is recommended that all women should have regular observations of these vital signs recorded on Modified Early Obstetric Warning Score (MEOWS) chart for the first 24 hours after a caesarean section. This should not only be for recording the parameters but also guiding the health care providers to act upon on abnormal readings. Obstetric Shock Index (OSI) may also help clinicians to recognize ongoing massive postpartum haemorrhage and thereby, help institute timely and appropriate action.

Important Points

- Postpartum haemorrhage is the leading cause of maternal mortality worldwide.
- Timely and appropriate interventions are needed to improve outcomes.
- A systematic approach using algorithms such as 'HEMOSTASIS' may help save lives.
- New interventions such as the Triple P procedure, changes in ratio for replacement of coagulation factors and the use of tranexamic acid may help improve outcomes.

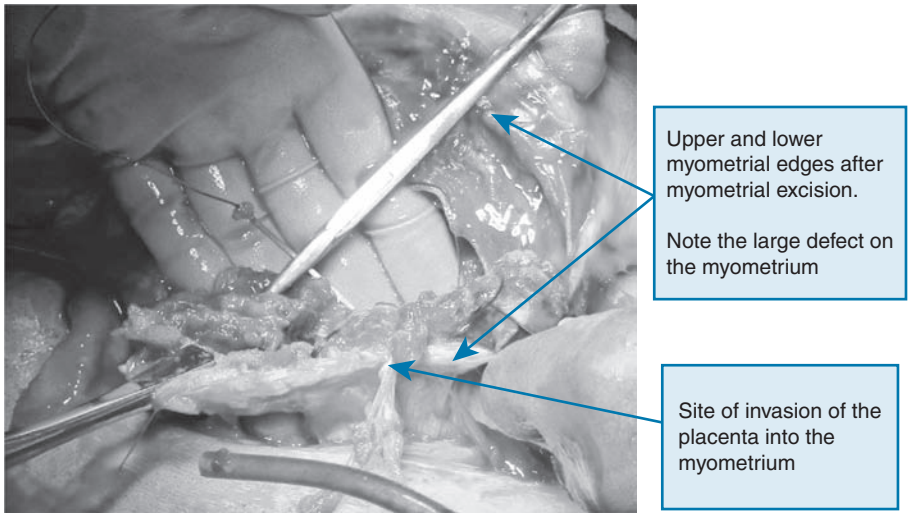

FIGURE 23.1 Triple P procedure showing uterine reconstruction following placental non-separation and myometrial excision.

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