

Protocols for High-Risk Pregnancies

To Barry, Juliana, Winston and my family for their dedication, support and encouragement and to my coeditor (JQ) who through his mentoring and friendship has inspired me to achieve more than I thought possible.

CYS

To Carrie and Susan who provided inspiration, guidance and support. For all this and much more, we thank you.

JQ and JH

I dedicate this clinical text to Peter Grannum, the consummate clinician and the ultimate class act. I am a better person for having known you.

JH

Protocols for High-Risk Pregnancies

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Preface

In light of the rapid advances in medicine and ready access to information, it is critical for health-care providers to have up-to-date guidance for the workup and management of high-risk pregnancies. Patients today are medically sophisticated and expect an optimal outcome for their pregnancy. Given the push by both managed care and the educated patient, the health-care provider needs guidelines for practical patient management. Most importantly, physicians want to do what is best for their patients.

Classifying pregnancies as “normal” or “high-risk” is an effective way to provide additional attention to patients with the greatest need. All pregnancies must be carefully evaluated to determine whether there are or will be risk factors. Some patients have factors at the beginning of pregnancy, such as diabetes or history of a premature delivery that place them in a high-risk category. Others start with normal pregnancies but subsequently develop risk factors, such as ruptured membranes or pregnancy-induced hypertension, which may develop suddenly; therefore, it is critical to be able to identify complications quickly and have a protocol for management.

Since the third edition of this book was published, advances in medical technology and new clinical knowledge have dictated changes in the diagnosis and therapy of “high-risk” patients. Thus, in this fourth edition, we have not only updated the original protocols but have also added many new protocols on topics such as vaginal birth after Cesarean delivery and West Nile virus. As with the prior editions, we have identified what we believe are the most important issues that confront the health care professional caring for high-risk patients and selected outstanding authors to discuss each topic. We asked each contributor to write a brief introduction and develop the protocol as if they were working up the patient and following her through the various stages of management. We asked for each protocol to be evidence-based to the degree that evidence is available, and where no data exists, we have asked the experts to describe their recommendations. There is some intentional overlap, as medicine

is an art as well as a science. All of these protocols represent the individual thoughts of the experts.

This edition, as with the others, was kept true to being practical and cost effective with a useful presentation: one that is easy to carry on rounds and consults.

We wish to thank Michele Prince, our dedicated editorial and administrative coordinator, and Stuart Taylor and Helen Harvey at Blackwell Publishing.

We realize that with the passage of time and continual updating of medical advances, new editions will need to be published in a timely fashion, thus we welcome your comments for future incorporation. We have designed this book to help you in your practice, make it your own!

John T. Queenan
John C. Hobbins
Catherine Y. Spong
2005

PART 1

*Hazards to
pregnancy*

Alcohol

Robert J. Sokol and Beth Nordstrom Bailey

INTRODUCTION

For over three decades, many in the medical community have recognized the negative consequences of maternal alcohol consumption for the developing fetus. Despite this, rates of pregnancy drinking have remained relatively stable, with 10% or more of women engaging in some level of alcohol consumption during pregnancy. A myriad of negative pregnancy, newborn, and long-term problems are associated with prenatal exposure to alcohol, and as many as 1 in 100 births are affected. Prenatal alcohol exposure is the most common cause of mental retardation and the leading preventable cause of birth defects in the USA. Armed with evidence-based clinical recommendations, healthcare providers working with pregnant women are now in a position to alter these statistics.

PATHOPHYSIOLOGY OF PRENATAL ALCOHOL EXPOSURE

Fetal alcohol spectrum disorder (FASD) is the latest term used to cover the range of outcomes associated with all levels of prenatal alcohol exposure. Fetal alcohol syndrome (FAS) represents the severe end of the spectrum and is characterized by specific facial dysmorphology, growth restriction, and central nervous system/neurodevelopmental abnormalities. However, even in the absence of full FAS, effects of prenatal alcohol exposure are evident. Hundreds of reports are now available, detailing outcomes associated with even low to moderate levels of exposure to alcohol prenatally. Low birth weight, prematurity, infant and childhood growth restriction, cognitive delay, hyperactivity and impulsivity, inattention, aggression, poor reaction time, memory deficits, difficulty with problem solving, and mood disorders have all been linked to exposure to alcohol during gestation, even at what appear to be moderate drinking levels.

DIAGNOSIS OF RISK DRINKING

How much drinking during pregnancy is too much? The short answers are that

no safe threshold has been identified, binge drinking is particularly harmful, and alcohol consumption during pregnancy should be avoided. Such are the recommendations of the US Surgeon General, the American College of Obstetrics and Gynecology (ACOG), and the National Institutes on Alcohol Abuse and Alcoholism. Drinking as little as twice weekly is associated with a 200-g decrease in birth weight, and binge drinking as infrequently as twice monthly has been demonstrated to double the likelihood of mental retardation, and to increase by 2.5-fold the risk of clinically significant child behavior problems. Thus, the threshold for risk drinking during pregnancy is much lower than what is considered risk drinking for other segments of the population. Not surprisingly, the developing embryo/fetus is more sensitive to the adverse effects of alcohol than is the adult woman. Generally, normal non-risk drinking for women is defined as not exceeding seven standard drinks per week, and never exceeding three standard drinks per day. A standard drink is, for example, a 12-ounce beer, a 5-ounce glass of wine, or a mixed drink containing an 80-proof jigger (1.5 ounces) of liquor. Using these standards, approximately 70% of American women do not engage in risky drinking patterns. However, risk drinking during pregnancy, defined as alcohol consumption at a level that could potentially damage the embryo/fetus, certainly involves a lower, but not well-defined threshold. Due to this, as well as differing susceptibilities, at risk drinking during pregnancy may include levels many clinicians would consider social drinking.

Identifying women who drink during pregnancy is not always an easy task. ACOG first recommended screening for alcohol use in pregnancy in 1977, several years before the Surgeon General's warning regarding pregnancy alcohol consumption was issued. Most recently, the Committee on Ethics in Obstetrics and Gynecology of ACOG released a policy statement informing clinicians they have an ethical obligation to screen for alcohol use during pregnancy, and to intervene when use is identified. Unfortunately, this recommendation is not yet universal policy. While a recent report reveals that 97% of women are asked about alcohol use as part of their prenatal care, only 25% of practitioners use standard screening tools, and only 20% know that abstinence is the only known way to avoid any possibility of alcohol-related pregnancy, delivery, and child outcome problems.

Because no reliable biomarker for alcohol use is available, clinicians must rely on self-report of maternal alcohol use during pregnancy. Under-reporting is common because of social desirability factors, so alcohol use histories must be sensitively elicited to yield accurate information. Debate continues over the best way to screen pregnant women for alcohol use in a clinical setting. An examination of the research literature, however, reveals some very specific evidence-based recommendations. Traditional tools are either too long for practical clinical use (MAST), or are not particularly reliable when used with women

(CAGE). An adaptation of the CAGE, the T-ACE, was developed for and validated with pregnant women, is simple to use, and is widely recommended. The T-ACE consists of four questions that may be asked verbally as part of the history, or included in the forms to be completed by the patient.

- 1 *T—Tolerance.* “How many drinks can you hold?” A positive answer, scored as a 2, is at least a 6-pack of beer, a bottle of wine, or six mixed drinks. This suggests a tolerance of alcohol and very likely a history of at least moderate to heavy alcohol consumption.
- 2 *A—Annoyed.* “Have people annoyed you by criticizing your drinking?”
- 3 *C—Cut down.* “Have you felt you ought to cut down on your drinking?”
- 4 *E—Eye opener.* “Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?”

These last three questions, if answered positively, are worth 1 point each. A score on the entire scale of 2 or higher is considered positive for risk drinking, and indicates that a woman is at risk to drink enough during pregnancy to potentially damage her offspring.

The T-ACE typically identifies 90% or more of women engaging in risk drinking during pregnancy. False-positives can be determined with follow-up questions. Since the development of the T-ACE, several other screening tools have been suggested for use with pregnant women, including the TWEAK, the Alcohol Use Disorders Test (AUDIT) and the Short Michigan Alcoholism Screening Test (SMAST). The AUDIT and the SMAST may not have adequate sensitivity (less than 20% in one recent validation study), and while the TWEAK has been found to have a reasonably adequate sensitivity in identifying pregnancy risk drinking, it is not better than T-ACE and includes five, rather than four questions. Thus, we recommend the T-ACE as the best tool to use to screen pregnant women for alcohol use.

While the T-ACE identifies who is at risk by asking questions about the effect of drinking on daily life, responses do not tell a clinician exactly how much alcohol is being consumed. Thus, when a woman screens positive on the T-ACE, follow-up should include questions about volume and frequency. A report of more than three drinks per week, or a single episode involving more than three standard drinks, should be considered an additional risk. Sensitive use of a combination of the T-ACE and frequency questions will identify over 90% of pregnant women who are drinking at risk levels during pregnancy, typically about 1 in 10 to 1 in 5 prenatal patients.

TREATMENT OF RISK DRINKING IN PREGNANCY

Once a prenatal patient is identified as an at-risk drinker, the clinician is in a position to intervene. Brief physician advice has been shown unequivocally to be powerful and feasible in the clinical setting. Brief behavioral counseling interventions with follow-up aimed at problem drinkers identified in the clini-

cal setting have been demonstrated to produce significant reductions in alcohol consumption lasting 12 months or longer. Thus, the physician can make a positive difference by engaging in a brief intervention. Some obstetricians and an increasing number of primary care physicians have obtained training in cognitive-behavioral therapy (CBT) or Motivational Interviewing. The basic principle is that communication from the physician is a powerful motivator, and can empower patients to make changes. In this empathic patient-centered counseling approach, the physician points out the importance of reducing or eliminating alcohol consumption, indicates that it may be difficult, but that the woman can do it, and provides education about why it is important. Follow-up is critical, and there is developing evidence that a series of such brief interventions is more effective than a single mention of stopping drinking. For example, a CDC-sponsored multicenter pilot study known as Project Choices identified reproductive-age, sexually active, heavy drinking women and targeted them for intervention. After a minimum of four motivational counseling sessions, nearly 70% were no longer at risk for an alcohol-exposed pregnancy 6 months later, with the most reduced risk among the heaviest drinkers. It should be noted that some patients chose not to decrease their drinking, but instead to use effective contraception or sterilization.

Brief interventions for pregnancy risk drinking generally involve systematic counseling sessions, approximately 5 min in length, which are tailored to the severity of the identified alcohol problem. Ideally, such interventions should occur preconceptionally, but it is never too late. The first time a brief intervention is conducted, the physician should state his/her concern, give advice, and negotiate abstinence or at a minimum a significant reduction in drinking by helping to set a goal. Educational “carry away” materials should be provided. Routine follow-up is essential and should involve encouragement, information, and re-evaluation of goals. While these steps are usually effective in reducing pregnancy drinking, lack of time in a busy clinical setting is often a major perceived barrier to implementation. Time can be saved by including alcohol-screening questions on intake forms, and by triaging patients. Those who do not meet criteria for risk drinking during pregnancy can receive brief targeted advice, while those with evidence of significant problems can receive more intense intervention. Finally, women who are actually alcohol-dependent may require additional assistance to reduce or eliminate consumption during pregnancy. For these women, referral for more intensive intervention and alcohol treatment is usually warranted.

Brief interventions for reducing or eliminating pregnancy alcohol consumption most often take the form of Motivational Interviewing. When implementing a motivational brief intervention, it is important to express empathy, manage resistance without confrontation, and support the self-efficacy of the patient. Techniques such as open-ended questioning, reflective listening,

summarizing, and affirming are most effective. Many women who may drink enough to damage the embryo/fetus do not perceive themselves at risk. In this common situation, Motivational Interviewing is particularly useful because it guides the individual to explore and resolve ambivalence about changing, increases the perceived discrepancy between current behavior and overall goals and values, and minimizes patient resistance to the intervention. Many resources are available to assist physicians with brief interventions and Motivational Interviewing with childbearing age and pregnant women consuming alcohol at risk levels.

In addition to utilizing brief interventions with alcohol consuming preconceptional and prenatal patients, we recommend that the following statements should be shared with all pregnant women and those considering pregnancy.

- *“If I were pregnant, knowing what I know today, I wouldn’t drink.”* This information is necessary to share based on the vast body of literature documenting adverse consequences of prenatal alcohol exposure.
- *“There is no evidence that an occasional drink during pregnancy will harm your baby”* and *“Do not worry about a few drinks earlier in pregnancy.”* While researchers and parents of affected children often cringe at such suggestions, they are scientifically accurate. While a physician should in no way advocate that pregnant women should have an occasional drink, it is reassuring to many women who had a few drinks before knowing they were pregnant, or who have consumed occasional drinks during pregnancy without realizing the dangers. They do not need to have an induced abortion!
- *“Certainly, don’t get drunk during pregnancy.”* This statement is warranted by evidence from animal studies of high circulating blood alcohol levels, and human studies of binge drinking. This research clearly demonstrates that alcohol consumed in quantity is much more likely to harm the fetus than the same amount of alcohol consumed over time.
- *“Even if you only drink socially, a few drinks in the evening throughout pregnancy could interfere with your baby’s development.”* Recent research has been documenting that persistent frequent drinking, even at relatively limited levels, is associated with FASD. A tiny minority of women in the USA drink daily during pregnancy, and this practice should be discouraged—it is a risk.
- *“You can help yourself have a healthier baby by cutting your drinking way down, or better yet, by quitting drinking completely.”* This is perhaps the key message that every woman should be told in the periconceptional period, and again during pregnancy.
- *“To avoid any possibility of FASD, any drinking during pregnancy is too much.”*

CONCLUSIONS

Alcohol consumption during pregnancy can have significant negative consequences for the fetus, with effects lasting throughout life. Exposure even at low levels, and particularly exposure to binge drinking, can be harmful. Armed with brief, well-validated screening tools and intervention approaches, the clinician has an opportunity and an ethical obligation to diagnose and treat pregnancy drinking.

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Developmental toxicology and teratology

James W. Hanson and Jan M. Friedman

INTRODUCTION

Exposures to potentially hazardous agents during pregnancy are common. Such agents include drugs (both therapeutic agents and abused substances), environmental chemicals, infectious agents, physical agents (radiation, heat, and mechanical factors), and maternal health conditions. Many of these exposures are not readily avoidable, as pregnancy is often not planned or recognized for an extended period after conception, or because there is a continuing need for maternal treatment for health conditions (e.g. epilepsy, infection, asthma, chronic cardiovascular disorders). Exposure to various agents in the home or workplace, or as a consequence of maternal lifestyles and self-medication is almost universal, and preconception planning only rarely provides an opportunity to identify exposures of concern. As a consequence, questions about the significance of such an exposure, whether stated or not, are often a source of concern to pregnant women or their care provider.

It is important to screen systematically for such concerns as early as possible in pregnancy. Ideally, such screening should be a part of a comprehensive risk factor analysis. This includes not only identification of risks related to developmental toxicants and teratogens, but also consideration of genetic risk factors (including maternal age), often identifiable through a careful family history.

Likewise, it is prudent to utilize opportunities to anticipate and educate non-pregnant women of reproductive age who are known to have, or are at increased liability for significant risk factors whenever possible. This approach can minimize maternal anxiety about adverse consequences of potentially hazardous exposures and can help to avoid inappropriate alarm, especially should abnormalities in the fetus or newborn be encountered. As the interaction of more than single genetic characteristics with each other, or in combination with environmental exposures, in the pathogenesis of adverse outcomes is understood, the need for comprehensive evaluation and preconception counseling and education will become increasingly imperative.

OUTCOMES OF EXPOSURE TO TERATOGENS AND OTHER DEVELOPMENTAL TOXICANTS

Not all developmental toxicants necessarily lead to permanent adverse outcomes for the fetus or newborn. Some agents may have at least partially reversible or transient effects if recognized early and appropriately managed. Examples include fetal growth restriction from tobacco smoking, or other functional disturbances in metabolism or physiology.

It is important to recognize that structural birth defects resulting from exposure to human teratogens are not the only manifestations of exposure to developmental toxicants. Fetal or postnatal growth disorders, functional developmental disorders including cognitive and behavioral deficits, abnormalities of placental function putting the fetus at increased risk, and death (embryonic, fetal, perinatal, or postnatal) are among potential manifestations of exposures. Furthermore, some adverse outcomes may not become apparent until many years later (e.g. reproductive consequences and cancer from exposure to diethylstilbestrol).

PATHOGENETIC FACTORS IN EVALUATION OF RISK FROM EXPOSURE TO TERATOGENS AND OTHER DEVELOPMENTAL TOXICANTS

When evaluating the likely significance of exposure to potentially hazardous agents, it is essential to consider the following issues in the context of the known or likely pathogenetic mechanisms for adverse fetal outcomes.

- 1 Dose and duration of exposure.** In general, the larger the dose, the more likely an effect, and the more likely the effect will be significant. Likewise, the longer the duration of exposure, the greater the chance is that susceptible periods of organogenesis and development will be encountered.
- 2 Timing.** Timing of exposure is a critical issue. Certain organ systems may have only a limited period of susceptibility for damage. Although it is commonly thought that damage can only result during the period of organogenesis, that is during the first trimester, this is not correct. Some organ systems (e.g. brain) still undergo important developmental processes later in pregnancy or can be damaged throughout the prenatal period.
- 3 Pathogenetic mechanism(s).** Teratogens and developmental toxicants produce their adverse effect by specific mechanisms. As these mechanisms are often important in multiple tissues and organs, it is not surprising that several specific types of damage can result. Those agents that affect basic morphogenetic processes are commonly related to first trimester exposures. However, those agents that act through mechanical pressures are likely to have the greatest impact during the third trimester, and those agents that produce necrosis through inflammation and/or hemorrhage can potentially destroy normally developing structures throughout pregnancy.

- 4** *Host susceptibility.* Variability in the genetic factors related to metabolism of certain drugs and chemicals may result in differential susceptibility of the host to adverse outcomes. However, it should be emphasized that these pharmacogenetic factors must be expressed at a relevant time in the tissue or organ system affected. It should also be emphasized that there are two potentially relevant “hosts” to be considered. Mother and embryo/fetus only share 50% of the genome. Thus, depending on the pathogenesis of the adverse outcome, maternal or fetal (or perhaps both) genotype may be more important.

It should also be understood that exposures to human teratogens and other developmental toxicants are commonly manifest across a wide spectrum of effects based upon the above factors. At the severe end of this spectrum, a clinically recognizable pattern of effects (a “syndrome”) may be identified. However, variability of manifestations within the scope of specific adverse outcomes comprising a syndrome is the rule. Among the population of exposed and affected infants, less severe and less pervasive manifestations are often more frequent. Thus, infants exposed to alcohol prenatally may have outcomes ranging from mild effects on cognition and behavior from smaller amounts consumed on a few occasions, to the full-blown fetal alcohol syndrome in infants of severe chronic alcoholics.

IMPORTANT HUMAN TERATOGENS

Information about the teratogenic or developmental toxicities of various agents is commonly woefully inadequate, especially for chemical agents in the environment where exposures are often of low intensity and multiple. Table 2.1 presents a list of agents, including therapeutic agents, for which substantial human data are available, establishing a risk for humans.

SOURCES OF INFORMATION

The list above is not comprehensive. It continues to grow as new research reveals more details about the magnitude and nature of risks associated with many of these and other newly recognized agents. Thus, it is important to check the current literature before counseling an exposed family. A variety of information resources, ranging from Internet-based computerized databases and commercially available information resources, to standard reference resources for further reading is listed in the suggested reading below.

For the clinician whose practice only rarely encounters these questions, or for those who encounter a question for which current data are limited or difficult to access, consultation with a specialist may be an appropriate option. Many states or academic centers have established “Teratogen Information Services” to help meet this need. Table 2.2 presents a current listing of these resources.

Table 2.1 Important human teratogens.

Agent	Dose	Susceptible period
Medications		
Acitretin	Usual therapeutic	1st trimester
Aminopterin	Usual therapeutic	1st trimester
Amiodarone	Usual therapeutic	12 weeks–term
Androgens (including danazol)	Usual therapeutic	Unknown
Angiotensin II receptor inhibitors (candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, valsartan)	Usual therapeutic	2nd and 3rd trimesters
Angiotensin-converting enzyme inhibitors (benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Usual therapeutic	2nd and 3rd trimesters
Carbamazepine	Usual therapeutic	1st trimester
Clonazepam	Usual therapeutic	1st trimester
Coumarin anticoagulants	Usual therapeutic	1st trimester
Cyclophosphamide	Usual therapeutic	1st trimester
Diethylstilbestrol	1.5–150 mg/day	1st and 2nd trimesters
Ethosuximide	Usual therapeutic	1st trimester
Etretinate	Usual therapeutic	1st trimester
Fluconazole	Chronic, parenteral, 400–800 mg/day	1st trimester
Indomethacin	Usual therapeutic	2nd and 3rd trimesters
Isotretinoin	Usual therapeutic (oral)	1st trimester
Lithium	Usual therapeutic	1st trimester
Methimazole	Usual therapeutic	1st trimester (malformations) 12 weeks–term (hypothyroidism, goitre)
Methotrexate	≥12.5 mg/week	1st trimester
Methythioninium chloride	Intra-amniotic injection	2nd trimester

Continued

Table 2.1 Continued.

Agent	Dose	Susceptible period
Misoprostol	Usual therapeutic	1st and 2nd trimesters
Penicillamine	Usual therapeutic	Unknown
Phenobarbital	Usual therapeutic	1st trimester
Phenytoin	Usual therapeutic	1st trimester
Primidone	Usual therapeutic	1st trimester
Quinine	≥2 g/day	Entire pregnancy
Tetracyclines (chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, tetracycline)	Usual therapeutic	1st trimester
Thalidomide	Usual therapeutic	41–54 days
Trimethadione, paramethadione	Usual therapeutic	1st trimester
Trimethoprim	Usual therapeutic	1st trimester
Valproic acid	Usual therapeutic	1st trimester
Agents of abuse		
Alcohol	Abuse	Unknown
Cigarette smoking	Risks greater with heavy smoking	Entire pregnancy
Cocaine	Abuse	Entire pregnancy
Toluene	Abuse (inhalation)	Unknown
Environmental exposures		
Methylmercury	Associated with maternal methylmercury concentration ≥0.1 µg/mL	Unknown
PCBs	Toxic exposure	Unknown
Infections		
Varicella	Primary infection (much smaller risk with recurrent infection)	Entire pregnancy (but higher in 2nd trimester)

Continued on p. 14

Table 2.1 Continued.

Agent	Dose	Susceptible period
Parvovirus B19	Primary infection (but higher in 2nd trimester)	Entire pregnancy
Cytomegalovirus	Primary infection (much smaller risk with recurrent infection)	Entire pregnancy (but much higher in first half)
Syphilis		2nd and 3rd trimester
HIV		3rd trimester, especially during labor
LCMV		Unknown
Toxoplasmosis	Primary infection	Entire pregnancy
Rubella	Primary infection (rarely secondary infection)	1st and 2nd trimester (but much higher in 1st trimester)
Maternal illnesses and conditions		
Maternal diabetes mellitus		1st trimester
Maternal autoantibodies (Rh, SLE, platelet)		2nd and 3rd trimester
Maternal endocrinopathies		Unknown
Maternal phenylketonuria	Untreated	Unknown
Maternal obesity	Risk greater with severe obesity than with mild obesity	1st trimester
Physical agents		
Chorionic villus sampling		<10 weeks
Early amniocentesis		<14 weeks
Ionizing radiation	>10–20 cGy	Entire pregnancy (but highest in 1st trimester)
Radioactive iodine	Therapeutic	12 weeks–term

HIV, human immunodeficiency virus; LCMV, LCM virus; PCBs, polychlorinated biphenyls; SLE, systemic lupus erythematosus.

Table 2.2 Teratogen information services in North America.

Alabama Birth Defects Surveillance (800) 423-8324 or (334) 460-7691
Arizona Teratogen Information Program (888) 285-3410 or (520) 626-3410 (in Tucson)
Arkansas Teratogen Information Service (800) 358-7229 or (501) 296-1700
CTIS Pregnancy Risk Information (800) 532-3749 (CA only)
IMAGE: Info-Medicaments en Allaitement et Grossesse Province of Quebec, Canada (514) 345-2333
Motherisk Program (416) 813-6780 Ontario, Canada
Connecticut Pregnancy Exposure Information Service (800) 325-5391 (CT only) or (860) 679-8850
Reproductive Toxicology Center District Of Columbia (MD) (301) 620-8690 or (301) 657-5984
Illinois Teratogen Information Service (800) 252-4847 (IL only) or (312) 981-4354
Indiana Teratogen Information Service (317) 274-1071
Massachusetts Teratogen Information Service (MaTIS) (800) 322-5014 (MA only) or (781) 466-8474
Genetics & Teratology Unit, Pediatric Service Massachusetts General Hospital (617) 726-1742
Missouri Teratogen Information Service (MOTIS) (800) 645-6164 or (573) 884-1345
Nebraska Teratogen Project (402) 559-5071
Pregnancy Healthline Southern New Jersey Perinatal Cooperative (888) 722-2903 (NJ) or (856) 665-6000

Continued on p. 16

Table 2.2 Continued.

Pregnancy Risk Network
(800) 724-2454 (then press 1) (NY only) or (716) 882-6791 (then press 1)

PEDECS
Rochester, NY
(716) 275-3638

NCTIS Pregnancy Exposure Riskline
1-800-532-6302 (NC)

North Dakota Teratogen Information Service
(701) 777-4277

Texas Teratogen Information Service
(800) 733-4727 or (940) 565-3892

Pregnancy RiskLine
Salt Lake City, UT
(801) 328-2229 or (800) 822-2229

Pregnancy Risk Information Service
800-531-9800 (VT only) and 800-932-4609

CARE Northwest
Seattle, WA
(888) 616-8484

West Virginia University Hospitals
(304) 293-1572

Wisconsin Teratogen Information Service
(800) 442-6692

Workplace Hazards to Reproductive Health
Madison, WI
(608) 266-2074

For information regarding the Teratology Information Service in your area, contact the Organization of Teratology Information Services (OTIS) at:
(866) 626-6847 or <http://www.otispregnancy.org>

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Computerized databases

REPROTOX (202) 687-5137.

TERIS (206) 543-2465.

Occupational hazards

George R. Saade

INTRODUCTION

In 1970, the Occupational Safety and Health Act was implemented and occupational medicine has been a growing science ever since. At the same time, there has been a surge of interest in the reproductive effects of working and the workplace. While an adult worker with an occupational exposure is best served by referral to an occupational medicine specialist, workplace exposures of pregnant women tend to be avoided by occupational physicians and the responsibility for these issues thus falls to the obstetrician. In their Guidelines for Perinatal Care, the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) include environmental and occupational exposures among the components of the preconceptional and antepartum maternal assessment and counseling. Help is available in the form of Teratogen Information Services, accessed through local health departments, and via the databases, such as REPROTOX (<http://reprotox.org/>) and TERIS (<http://depts.washington.edu/~terisweb/teris/>), which were set up to provide information to physicians and the Teratogen Information Services on potential teratogens from any source, including the workplace.

ERGONOMIC STRESSORS

The AAP/ACOG Guidelines for Perinatal Care state that a woman with an uncomplicated pregnancy usually can continue to work until the onset of labor, and that women with medical or obstetric complications of pregnancy may need to make adjustments based on the nature of their activities, occupation, and specific complaints. In its most recent update, the American Medical Association (AMA) did not include the recommendation made in the 1983 report that set a gestational age limit at which certain activities must be discontinued. The AMA's updated report concludes that the potential benefits and risks of occupational activities and exposures should be considered on an individual basis, and that physicians should work with patients and employers to define a healthy working environment. These include modifications in the work

schedule to accommodate breaks every few hours, with a longer “meal” break every 4 h; encouraging adequate hydration; regularly varying work positions; and minimizing heavy lifting, especially if associated with bending. All guidelines have been marred by the paucity of conclusive scientific evidence on which to base them. A multitude of studies have been carried out attempting to show an association between standing work, lifting, strenuous work, and length of work on preterm delivery rates and low birth weight infants. The greatest difficulty in evaluating the effect of work on reproduction is the vast range of activities that fall into the category of “work,” and the difficulty in controlling for confounding variables such as the work environment, socioeconomic stresses, and psychosocial factors (Table 3.1).

It is important to elicit a detailed account of the patient’s work activity. Although the studies on independent risk factors are reassuring, it is suspected that the heterogeneous nature of work may obscure important effects in women with particularly rigorous jobs. Clearly, a salesperson and a construction worker both stand for most of the working day, but other aspects of their jobs are markedly different. Studies that examine the additive effects of multiple risk factors (posture, machinery, exertion, stress, and environment) show an increase in prematurity and a slight decrease in birth weight. These same studies also demonstrate that defined rest periods during the working day, and each month, decrease the incidence of preterm birth in women with manual labor jobs. It is important to keep in mind that pregnancy affects the ability to lift a load safely. Compared with the woman’s ability before pregnancy, the maximum load should be reduced by 20–25% during late pregnancy.

There is a general consensus that some limitation of activity is indicated in women at risk for adverse pregnancy outcomes, such as women with repeated preterm birth or pregnancy loss, uterine or cervical anomalies, cardiac or pulmonary anomalies that may be exacerbated by activity or may limit activity, oligohydramnios, fetal growth restriction, multiple gestations, or preterm labor in the current pregnancy. However, there is no clear agreement as to the specific risk factors or the degree of activity restriction. It is of note that the most

Table 3.1 Impact of work on pregnancy.

Activity	Risks
Standing more than 5 h	Most studies show an increase in prematurity and no effect on birthweight
Lifting more than 12 kg	No studies show any effect on birthweight or prematurity
Strenuous work	Most studies show no effect on birthweight or prematurity

recent reviews in the Cochrane Library (<http://www.Cochrane.org>) concluded that there is not enough evidence to support a policy of routine hospitalization for bed rest in multiple pregnancy (most recent update November 2000), no evidence either supporting or refuting the use of bed rest at home or in the hospital to prevent preterm birth in singleton pregnancies (most recent update November 2003), and not enough evidence to evaluate the use of bed rest in the hospital for women with suspected impaired fetal growth (most recent update November 2002). Protocols for evaluating bed rest with or without hospitalization for hypertension during pregnancy and for evaluating bed rest for preventing miscarriage are still pending (most recent updates November 2001 and February 2002, respectively).

When discussing work in pregnancy, it is essential not to overlook work at home, which is often more strenuous and stressful than work away from home, and may actually increase if the patient is on leave from her job without adequate household help.

PHYSICAL AGENTS

Heat

The metabolic rate increases during pregnancy, and the fetus' temperature is approximately 1°C above the mother's. Because pregnant women have to eliminate the physiologic excess heat, they may be less tolerant of high environmental temperatures. Exposure to heat and hot environments can occur in many occupations and industries. Few studies specifically address the hazards of occupational heat stress in pregnancy. Data from animal studies and fever during pregnancy indicate that core temperature elevations of 38.9°C or more may increase the rate of spontaneous abortion or birth defects, most notably neural tube defects.

The National Institute of Occupational Safety and Health guidelines include ambient air monitoring, heat acclimation, medical surveillance, workload limits, hydration, and rest periods in cooler areas, heat shielding, ventilation, and worker education. If a question arises concerning heat or a pregnant worker complains of discomfort, worksite evaluation may be warranted and can be arranged through the local Occupational Safety and Health Administration office. It may also be necessary to consult with an occupational medicine specialist. Women with early pregnancy hyperthermic episodes should be counseled about possible effects and offered alpha-fetoprotein screening and directed sonogram studies.

Ionizing radiation

The effects of prenatal irradiation depend on the exposure dose and the timing of exposure during pregnancy as well as the repair capabilities of the developing organism. Information on the reproductive and developmental effects of

ionizing radiation derives from studies in animals, atomic bomb survivors, and those who have been medically irradiated. Preimplantation exposures are thought to result in an “all-or-none” phenomenon. Either the insult is great enough to destroy the embryo or, if sublethal, allows the totipotential cells to effectively repair the conceptus. Sensitivity to radiation is greatest during the late first and early second trimester.

Virtually all ionizing radiation exposures in the workplace are well below those expected to result in fetal loss or deficit. Occupational exposure most often occurs in the medical field, in mining, and in power plants. It is thought that while doses of less than 0.05 Gy might cause a genetic effect, this would be indistinguishable from the background burden of adverse developmental outcomes. According to the American College of Radiology, no single diagnostic X-ray procedure results in radiation exposure to a degree that would threaten the well being of a developing pre-embryo, embryo, or fetus.

Occupational exposure to radiation is regulated by a number of federal agencies. The current limit for whole-body radiation is 0.05 Sv. The Nuclear Regulatory Commission limits the total dose to the fetus at 5 mSv once pregnancy is established, not to exceed 0.5 mSv in any gestational month. The radiation dose can be limited by time, distance, and proper shielding. A pregnant worker must work with the physician to estimate the dose, frequency, and timing of exposure in gestation. All radiation worksites should have radiation safety personnel and availability of experts to provide quantitative estimates of the dose to the fetus. With exposures to the conceptus of less than 0.05 Gy, no intervention is recommended. If higher doses are documented, the patient must be counseled utilizing the data sets outlined above and offered sonogram screening for microcephaly. The normalcy of these tests cannot guarantee the neurologic status of the infant.

Video display terminals

There is no scientific evidence that pregnant women need to limit the use of video display terminals (VDTs) during pregnancy. VDTs do not emit ionizing radiation, but they do emit low-frequency electromagnetic radiation from the rear, and probably the sides of the device. The effects of these fields are not known.

The use of VDTs has been associated with carpal tunnel syndrome (CTS) resulting from improper keyboard angling. Because pregnant women are already predisposed to CTS because of fluid retention it would seem prudent to counsel women on appropriate placement of the keypad to minimize the likelihood of this occurrence.

CHEMICAL EXPOSURES

During prepregnancy counseling or at the first prenatal visit, attempts should be made to determine whether the potential for an adverse exposure exists.

Some jobs have known exposure potential, and these are discussed below. In eliciting a work history, the patient must be asked if she has any contact with chemicals, by inhalation, dermal exposure, or ingestion. If the patient does not know the chemical then material management data sheets can be requested from the place of employment. These contain the specific agents with which workers come in contact. After the agent is identified, a Teratogen Information Service or a reproductive toxicology databank can be accessed. Information may also be obtained from the employer's Health and Safety Office. A full listing of these services is available in Chapter 10 of Paul's guide for clinicians. Required and recommended exposure limits for some chemicals known or suspected to be associated with reproductive or developmental hazards are also available in the Appendices at the end of the Paul and Frazier & Hage textbooks included in the suggested reading below.

Hairstylists

Hair colorants and dyes contain aromatic amines that may be absorbed through the skin. These agents are mutagenic but are not teratogenic in rats and cause embryotoxicity in mice only at high doses that are also maternally toxic. Permanent wave solutions may cause maternal dermatitis but are not known to be teratogenic in animals.

There is no direct evidence that hair dyes and permanent wave solutions are teratogenic in human pregnancy, but very limited data are available. One study found a higher rate of spontaneous abortion among cosmetologists. Exposure to these agents should be minimized by the use of gloves and, if possible, reduction of chronic exposures in the first trimester.

Painters/artists

Organic and inorganic pigments may be used in paints. The raw materials for organic pigments may contain aromatic hydrocarbons, such as benzene, toluene, naphthalene, anthracene, and xylene. Inorganic pigments may contain lead, chromium, cadmium, cobalt, nickel, mercury, and manganese. Workers in battery plants and those involved in the removal of old paint are also exposed to lead salts.

Reproductive concerns about inorganic pigments is focused primarily on lead, which is readily transferred across the placenta. Inorganic lead salts have been associated with increased spontaneous abortion, infant cognitive impairment, and stillbirth rates in humans, and central nervous system (CNS) abnormalities and clefting in rodents. Women at risk of lead exposure should be monitored for blood lead levels before becoming pregnant. If blood lead concentration is greater than 10 $\mu\text{g}/\text{mL}$, the patient should be removed from exposure and chelation therapy considered before pregnancy. Chronically exposed workers will have significant bone lead stores and before attempting pregnancy

should remain in a lead-free environment until safe lead levels are reached. There is no consensus on how to manage elevated blood lead levels during pregnancy as chelation will at least temporarily elevate blood lead levels by releasing bone stores. Further, the chelating agent, calcium edetate, may cause developmental toxicity, by decreasing zinc stores.

Solvent workers

Some organic hydrocarbons may cause a fetal dysmorphogenesis syndrome comparable to fetal alcohol syndrome if ingested in large amounts. This has been evaluated for gasoline, in a group of individuals who habitually “sniffed” the fuel for its euphoric effects. An excess of mental retardation, hypotonia, and microcephaly was found in the offspring. The effects of lower levels of gasoline are not known. Similar effects were reported with toluene sniffing.

Ethylene glycol is another solvent used in a large number of industrial processes (paint, ink, and plastics manufacture). No human studies exist, but many studies in rodents report developmental, skeletal, and CNS abnormalities. If a woman has a considerable exposure level as determined by blood and urine levels or abnormal liver function tests, increased monitoring of fetal development is recommended.

Pesticide workers

Pesticides are often encountered in agricultural workers and landscape artists. Two common agents are carbaryl and pentachlorophenol. A suspected workplace exposure may be quantitated by urine levels. Human studies for these agents are not available but animal studies suggest that high doses, particularly those that produce maternal toxicity, may impair reproductive success and be responsible for skeletal and body wall defects. These outcomes may be related to maternal toxicity and may not be a specific developmental effect.

Exposure to inhalational anesthetics

The studies that have suggested an association between occupational exposure to inhalational anesthetics and adverse reproductive outcomes have been heavily criticized. The available scientific evidence, while weak, does lead to concern over occupational exposure to inhalational anesthetics in the trace concentrations encountered in adequately scavenged operating rooms. Recommending limitation of exposure may be reasonable in environments where scavenging equipment is not available, such as some dentists' offices.

OTHER OCCUPATIONAL HAZARDS

Air travel

The environment in passenger cabins of commercial airlines is maintained at the equivalent of 1500–2500m. While living at high altitude has significant

effects on maternal and fetal physiology, air travel has not been associated with harmful fetal effects because of the short duration of most flights. Adequate hydration is essential as the humidity is also reduced to less than 25% in most cabins. Intermittent ambulation and changing posture is recommended in order to prevent deep vein thrombosis. Reports indicate that flight attendants experience twice the incidence of first trimester spontaneous abortions as other women, but not other employed women. Most airlines restrict the working air travel of flight attendants after 20 weeks' gestation, and restrict commercial airline pilots from flying once pregnancy is diagnosed. Counseling for women with medical or obstetric complications should be individualized. It should be noted that air travel can contribute to background radiation. The magnitude of in-flight exposure to radiation depends on altitude and the solar cycle. A round trip between New York and Seattle can result in exposure to 0.06 mSv, well below the safe upper limit accepted by most experts. Because the effect may be cumulative, frequent flyers need to keep track of their exposure. Patients and physicians can consult the FAA's radiation estimation software (<http://jag.cami.jccbi.gov/cariprofile.asp>) to calculate the exposure and the National Oceanic and Atmospheric Administration (<http://www.sec.noaa.gov>) to check for solar flares.

Exposure to pathogens

For bloodborne infections, employers should comply with the regulations of the Occupational Safety and Health Administration (OSHA; <http://www.osha.gov/>). Vaccination for hepatitis B is not contraindicated during pregnancy. A number of occupations are at increased risk for exposure to viral or parasitic infections that carry a potential for fetal infection and harm, particularly infection with cytomegalovirus, parvovirus B19, varicella zoster virus, and *Toxoplasma gondii*. Women at increased risk for exposure to these pathogens, such as healthcare and daycare workers, should use precautions including use of latex gloves, hand-washing, and protection from respiratory secretions. Routine screening of pregnant women to determine risk status is not recommended, and may even lead to unnecessary intervention. However, women exposed or suspected of having any of these infections should be evaluated for prior immunity, and those with evidence of prior immunity can be reassured. For those without evidence of prior immunity, management is outlined elsewhere in this book (Chapters 42, 47, 51 and 52).

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Smoking

Jorge E. Tolosa and Surasith Chaithongwongwatthana

INTRODUCTION

Approximately 250 million women worldwide are daily smokers. The prevalence of smoking among women in developed countries is 22%, and 9% in developing countries. Although the percentage of women who smoke during pregnancy in the USA declined every year from 1990 through 1999, the prevalence of smoking during pregnancy remains high. In 1999, 12.3% of women giving birth reported smoking during pregnancy, with teenagers having the highest rate (17.5%). Smoking rates declined for all racial and ethnic groups in the 1990s. American Indian, non-Hispanic white, and Hawaiian women had the highest rates; 20.2%, 15.7%, and 14.7%, respectively. In general, black women smoke more than Hispanic women, but less than white women. The women most likely to smoke are the least educated and those with the lowest incomes. Smoking during pregnancy is associated with adverse outcomes as well as negative consequences for child health and development, and represents a significant public health problem. Perinatal mortality and low birth weight would be reduced by at least 10% if smoking was eliminated. Estimated smoking-attributable healthcare costs of complicated births range from 1.4 to 2 billion dollars annually.

PATHOPHYSIOLOGY

Tobacco smoke contains thousands of compounds that may have adverse effects on the human body. The major compounds suspected of causing harmful effects on the developing fetus are nicotine and carbon monoxide. Nicotine crosses the placenta and can be detected in the fetal circulation at levels that exceed maternal concentrations by 15%, while amniotic fluid concentrations of nicotine are 88% higher than maternal plasma. The actions of nicotine include vasoconstriction and decreased uterine artery blood flow. Carbon monoxide also crosses the placenta rapidly and is detectable in the fetal circulation at levels that are 15% higher than maternal ones. It has a higher affinity for hemoglobin than oxygen to form the compound carboxyhemoglo-

bin which shifts the oxygen dissociation curve to the left. Consequently, the availability of oxygen to fetal tissues is decreased. Levels of cyanide in the circulation are higher in smokers, a substance that is toxic to the rapidly dividing cells. In addition to the toxic effects of smoking, smokers frequently have other clinical characteristics that may account for some adverse pregnancy outcomes (e.g. poor nutrition, alcohol or drug abuse).

COMPLICATIONS

Pregnancies among women who smoke have been associated with increased risks for miscarriage, ectopic pregnancy, intrauterine growth restriction, placenta previa, abruptio placentae, preterm birth, premature rupture of the membranes, and low birth weight. Overall, the perinatal mortality rate among smokers is 150% higher than in non-smokers.

The progeny of smoking mothers face additional risks during childhood. There is a strong association between maternal smoking and sudden infant death syndrome (SIDS), and a clear dose–response relationship has been demonstrated. Prenatal and postnatal tobacco smoke exposure has been associated with an increased risk of persisting reduced lung function, respiratory infections, and childhood asthma. A number of recent studies suggest that infants born to women who smoke during pregnancy may be at increased risk for childhood obesity. In addition, there is evidence suggesting a neurotoxic effect of prenatal tobacco exposure on newborn neurobehavior (i.e. being more excitable and hypertonic). The behavioral and cognitive deficits associated with *in utero* exposure to tobacco seem to continue into late childhood and adolescence, with increased risk for attention deficit hyperactivity disorder and conduct disorder.

TREATMENT

Smoking cessation

The benefits of smoking cessation during pregnancy are well documented. Smoking cessation interventions for pregnant women result in fewer low birth weight newborns and perinatal deaths; fewer physical, behavioral, and cognitive problems during infancy and childhood; and important health benefits for the mother. Women who discontinue smoking even as late as 30 weeks' gestation have infants with higher birth weight than those who continue smoking. In contrast, “cutting down” seems to improve fetal growth only slightly.

Smoking cessation interventions should be included as part of prenatal care. Women are more likely to quit smoking during pregnancy than at any other time in their lives. Clinicians can take advantage of this motivation by reinforcing the knowledge that cessation will reduce health risks to the fetus and there are postpartum benefits for both the mother and child.

Cessation counseling

An office-based cessation counseling session of 5–15 min, when delivered by a trained provider with the provision of pregnancy-specific educational materials, increases rates of cessation among pregnant smokers by 20%. The five-step intervention program (the 5 A's) is recommended in clinical practice to help pregnant women quit smoking and is found in the American College of Obstetricians and Gynecologists (ACOG) technical bulletin of September 2000.

- 1 *Ask* pregnant women about smoking status using a multiple-choice question method to improve disclosure.
- 2 *Advise* women who smoke to quit smoking, with unequivocal, personalized, and positive messages about the benefits for her, the baby, and family. Review the risks associated with continued smoking. Congratulate women who have quit and reinforce the decision by reviewing the benefits resulting from not smoking.
- 3 *Assess* the women's willingness to make an attempt to quit smoking within the next 30 days. If the woman wants to try to quit, the provider should move to the next step, Assist. For women who are unwilling to attempt cessation, the advice, assessment, and assistance should be offered at each future visit.
- 4 *Assist*
 - Provide self-help smoking cessation materials that contain messages to build motivation and confidence in support of a cessation attempt.
 - Suggest and encourage problem-solving methods and skills for cessation regarding issues that the woman believes might adversely influence her attempt to quit. Avoid "trigger situations."
 - Arrange social support in the smoker's environment by helping her identify and solicit help from family, friends, co-workers, and others who are most likely to be supportive of her quitting smoking.
 - Provide social support as part of the treatment. This means that the counselor is encouraging, communicates care and concern, and encourages the patient to talk about the process of quitting.
- 5 *Arrange* follow-up. Smoking status should be monitored throughout pregnancy providing opportunities to congratulate and support success, reinforce steps taken towards quitting, and advise those still considering a cessation attempt.

Pharmacologic therapies for smoking cessation

After a discussion of the risks of therapy compared with those of continued smoking, pharmacotherapy can be considered for pregnant smokers who have been unable to quit using psychosocial intervention, are highly addicted, and smoke more than 10–15 cigarettes daily. However, there are very limited data

on the safety and effectiveness of various pharmacologic treatments in pregnant women.

The FDA has assigned a Pregnancy Category C warning to nicotine gum (“risk cannot be ruled out”) and a Pregnancy Category D warning to transdermal nicotine (“possible evidence of risk”). However, the potential benefits of nicotine replacement medication may outweigh the risks from smoking among pregnant and lactating mothers. If used, doses should be delivered at the lowest effective range, blood levels of nicotine should be monitored, and an intermittent delivery system (such as gum) should be used. Although nicotine replacement therapy continues to expose the mother and fetus to nicotine, the duration of use and the total dose exposure to nicotine can be expected to be lower than with continued smoking. There is also a reduction in the exposure to numerous toxic substances in tobacco smoke, including carbon monoxide. To reduce fetal exposure to nicotine, it is advisable to avoid the longer acting nicotine replacement therapy, such as 24-h transdermal patches, and consideration has to be given for the potential of concomitant smoking. Further clinical studies are needed to determine the safety and effectiveness of nicotine replacement therapy, including the optimal dose, time, and route of administration.

Amfebutamone, a dopaminergic noradrenergic reuptake inhibitor, is the only drug available in this class and the only non-nicotine drug approved by the FDA for smoking cessation. FDA has approved amfebutamone SR marketed as Zyban® for this indication; it is also marketed for depression as Wellbutrin SR®, (Glaxo-Wellcome, Research Triangle Park, NC). Amfebutamone should be started 7–14 days before smoking cessation to allow for adequate CNS levels. It is used as two 150-mg doses daily for periods of 6–26 weeks. Amfebutamone is thought to increase the risk of seizures, but the slow release form has a lower risk, with a seizure incidence of 0.1%.

Prevention

It is essential to identify the pregnant woman who is a smoker, ideally at a pre-conceptional visit, when the risks associated with smoking in pregnancy should be discussed and the benefits of smoking cessation should be emphasized.

Follow-up

Cotinine, a metabolite of nicotine is an accurate assay for nicotine exposure and can be part of a cost-effective cessation program in some settings. Studies indicate higher success rates when participants are aware that biochemical tests for smoking will be obtained. Postnatal relapse rates are high, averaging 50–80% in the first year after delivery. Counseling should be continued at each postpartum visit including unequivocal, personalized, and positive messages about the benefits to the patient, her baby, and family resulting from smoking

cessation. If indicated, pharmacotherapy could be recommended to the lactating woman, after giving consideration to the risk for the nursing infant of small amounts of the medications passing through breast milk, compared with the increased risks associated with smoking for children such as SIDS, respiratory infections, asthma, and middle ear disease.

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Ionizing radiation

Robert L. Brent

INTRODUCTION

The responsibility of evaluating the risks of environmental toxicants to the pregnant patient and her embryo frequently resides with the obstetrician. When evaluating the risks of ionizing radiation, the physician is faced with several different clinical situations, as outlined below.

1 The pregnant patient presents with clinical symptoms that need to be evaluated. What is the appropriate utilization of diagnostic radiologic procedures that may expose the embryo or fetus to ionizing radiation?

A pregnant or possibly pregnant woman complaining of gastrointestinal bleeding, pain, or an abdominal or pelvic mass that cannot be attributed to pregnancy deserves the appropriate studies to diagnose and treat her clinical problems, including radiologic studies. Furthermore, these studies should not be relegated to one portion of the menstrual cycle if she has not yet missed her period. The studies should be performed at the time they are clinically indicated whether or not the woman is in the first or second half of the menstrual cycle.

2 The patient has completed a diagnostic procedure that has exposed her uterus to ionizing radiation. She now believes she was pregnant at the time of the procedure. What is your response to this situation?

Explain that you would have proceeded with the necessary X-ray diagnostic test whether she was pregnant or not, because diagnostic studies that are indicated in the mother have to take priority over the possible risk to her embryo, because almost 100% of diagnostic studies do not increase the risks to the embryo. At this time, obtain the calculated dose to the embryo and determine her stage of pregnancy. If the dose is below 0.05 Gy (0.05 Sv), you can inform the mother that her risks for birth defects and miscarriage have not been increased. In fact the threshold for these effects is 0.2 Gy.

3 A woman delivers a baby with a serious birth defect. On her first postpartum visit, she recalls that she had a diagnostic X-ray study early in her pregnancy. What is your response when she asks you whether the baby's malformation could be caused by the radiation exposure?

In most instances, the nature of the clinical malformation will rule out radiation teratogenesis. At this time, a clinical teratologist or radiation embryologist could be of assistance. On the other hand, if the exposure is below 0.05–0.1 Gy, it would not be scientifically supportable to indicate that the radiation exposure was the cause of the malformation. The threshold for malformations is 0.2 Gy. Dose, timing, and the nature of the malformation would enter into this analysis.

In order to respond to these questions appropriately and more completely, the obstetrician should rely on the extensive information that has accumulated on the effects of radiation on the embryo. In fact, there is no environmental hazard that has been more extensively studied or on which more information is available.^{1–7}

RADIATION RISKS TO THE EMBRYO

There is no question that an acute exposure to ionizing radiation above 0.5 Gy presents a significant risk to the embryo, regardless of the stage of gestation.⁴ The threshold dose for low linear energy transfer (LET) ionizing radiation that results in an increase in malformations is approximately 0.2 Gy. Although congenital malformations are unlikely to be produced by radiation during the first 14 days of human development, there would be a substantial risk of embryonic loss if the dose is high. From approximately day 18 to day 40 postconception, the embryo would be at risk for an increased frequency in anatomic malformations if the embryonic exposure is greater than 0.5 Gy. Up until approximately the 15th week, the embryo maintains an increased susceptibility to central nervous system (CNS) effects, major CNS malformations early in gestation, and mental retardation in mid-gestation. Of course, with very high doses, mental retardation can be produced in the latter part of gestation. While it is true that the embryo is sensitive to the deleterious effects of these mid-range exposures of ionizing radiation, the measurable effects fall off rapidly as the exposure approaches the usual exposures that the embryo receives from diagnostic radiologic procedures (less than 0.05 Gy). In fact, many studies indicate that the threshold for most embryonic radiation effects is in the 0.015–0.02 Gy range and that this threshold is raised by protraction of the radiation exposure; for example, following several clinical diagnostic radiologic procedures occurring over a period of days.⁴

That is why the recommendation of most official organizations, including the National Council on Radiation Protection and Measurements (NCRP),^{4,6,7} indicates that exposures of 0.05 Gy or less will not increase the risk of birth defects or miscarriage. The major risks of radiation exposure in the human embryo when the exposure exceeds the no-effect dose (0.02 Gy) are:

- Embryonic loss
- Growth retardation

- Congenital malformations
- Carcinogenesis (the magnitude of the risk is controversial)⁴
- Microcephaly and mental retardation
- Sterility

Because all of the above effects are threshold phenomena, except for carcinogenesis, radiation exposure below 0.05 Gy presents no measurable risk to the embryo. Even if one accepts the controversial concept that the embryo is more sensitive to the carcinogenic effects of radiation than the child, the risk at these low exposures is much smaller than the spontaneous risks.¹ Furthermore, other studies indicate that Stewart's estimate of the risk involved is exaggerated.⁸⁻¹⁰

Table 5.1 compares the spontaneous risks facing an embryo at conception with the risks from a low exposure of ionizing radiation (0.05 Gy). The hazards of exposures in the range of diagnostic roentgenology (0.2–50.0 mGy) present an extremely low risk to the embryo, when compared with the spontaneous mishaps that can befall human embryos. Approximately 30–50% of human

Table 5.1 Risk of 5 mSv exposure to embryo.

Risk	0 Gy exposure	Additional risk of 0.05 Gy exposure
Very early pregnancy loss, before the first missed period	350,000/10 ⁶ pregnancies	0
Spontaneous abortion in known pregnant women	150,000/10 ⁶ pregnancies	0
Major congenital malformations	30,000/10 ⁶ pregnancies	0
Severe mental retardation	5,000/10 ⁶ pregnancies	0
Childhood leukemia/year	40/10 ⁶ pregnancies/year	<2/10 ⁶ pregnancies/year
Early- or late-onset genetic disease	100,000/10 ⁶ pregnancies	Very low risk is in next generation and is not measurable increased with small populations
Prematurity	40,000/10 ⁶ pregnancies	0
Growth retardation	30,000/10 ⁶ pregnancies	0
Stillbirth	20–2000/10 ⁶ pregnancies	0
Infertility	7% of couples	0

embryos abort spontaneously. Human infants have a 2.75% major malformation rate at term, which rises to approximately 6–10% once all malformations and genetic diseases become manifest. In spite of the fact that doses of 0.01–0.03 Gy can produce cellular effects and that diagnostic exposure during pregnancy has been associated with malignancy in childhood, the maximum theoretical risk to human embryos exposed to doses of 0.05 Gy or less is extremely small. In my experience, when the data and risks are explained to the patient, the family with a wanted pregnancy invariably continues with the pregnancy.¹¹

The difficulty that frequently arises is that the risks from diagnostic radiation are evaluated outside the context of the significant normal risks of pregnancy. Furthermore, many physicians approach the evaluation of diagnostic radiation exposure with either of two extremes: a cavalier attitude or panic. The usual procedures in clinical medicine are ignored, and an opinion based on meager information is given to the patient. Frequently, it reflects the physician's bias about radiation effects or his/her ignorance of the field of radiation biology. We have patient records in our files of scores of patients who were not properly evaluated but were advised to have an abortion following radiation exposure. The following case history is a typical example.

CASE REPORT

A 27-year-old woman (gravida 3, para 2, abortus 0) called on a Friday afternoon because she was 8 weeks' pregnant and was scheduled for a therapeutic abortion on Monday morning. Her obstetrician and a pediatric genetic counselor had advised her to have a therapeutic abortion because at the time of conception she had had several X-ray examinations of the abdomen, and they were concerned that the embryo would be malformed. Dosimetry had not been performed, and an evaluation had not been initiated.

It took approximately 10 min on the telephone to determine that she became pregnant after the diagnostic radiation studies had been completed and that her two previous boys had developmental problems (hemangioma and pyloric stenosis). She canceled the abortion, and she delivered a normal full-term girl. She was adequately warned that we could not guarantee the outcome of the pregnancy—that there are 27.5 serious malformations per 1000 births as a minimum. She had another determining factor in that she had a serious problem with varicose veins and planned a tubal ligation after either the abortion or the delivery. This case history illustrates the inadequate amount of data that was collected by the physicians before counseling the patient. There was an added feature in this case. The paternal family was Catholic, and the consideration of an abortion was causing much dissension within the family.

EVALUATING THE PATIENT

Case histories similar to this are transmitted to our laboratory frequently. In most instances, the dose to the embryo is less than 0.05 Gy and frequently is less than 0.01 Gy. Our experience has taught us that there are many variables involved in radiation exposure to a pregnant or potentially pregnant woman. Therefore, there is no routine or predetermined advice that can be given in this situation. However, if the physician takes a systematic approach to the evaluation of the possible effects of radiation exposure, he/she can help the patient make an informed decision about continuing the pregnancy. This systematic evaluation can begin only when the following information has been obtained:

- Stage of pregnancy at the time of exposure
- Menstrual history
- Previous pregnancy history
- History of congenital malformations
- Other potentially harmful environmental factors during the pregnancy
- Ages of the mother and father
- Type of radiation study, dates and number of studies performed
- Calculation of the embryonic exposure by a medical physicist or competent radiologist
- Status of the pregnancy: wanted or unwanted

An evaluation should be made of the information, with both patient and counselor arriving at a decision. The physician should place a summary of the following information in the medical record. It should state that the patient has been informed that every pregnancy has a significant risk of problems and that the decision to continue the pregnancy does not mean that the counselor is guaranteeing the outcome of the pregnancy. The use of amniocentesis and ultrasound to evaluate the fetus is an individual decision that would have to be made in each pregnancy.

DIAGNOSTIC OR THERAPEUTIC ABDOMINAL RADIATION IN WOMEN OF REPRODUCTIVE AGE

In women of reproductive age, it is important for the patient and physician to be aware of the pregnancy status of the patient before performing any type of X-ray procedure in which the ovaries or uterus will be exposed. If the embryonic exposure will be 0.05 Gy or less, the radiation risks to the embryo are minuscule when compared with the spontaneous risks. Even if the exposure is 0.1 Gy, this exposure is far from the threshold or no-effect dose of 0.2 Gy. The patient will accept this information if it is offered as part of the *preparation* for the X-ray studies at a time when both the physician and patient are aware that a pregnancy exists or may exist. The pregnancy status of the patient should be determined and noted.

Because the risks of 0.05 Gy fetal irradiation are so small, the immediate medical care of the mother should take priority over the risks of diagnostic radiation exposure to the embryo. X-ray studies that are essential for optimal medical care of the mother and evaluation of medical problems that need to be diagnosed or treated should not be postponed. Elective procedures such as employment examinations or follow-up examinations, once a diagnosis has been made, need not be performed on a pregnant woman even though the risk to the embryo is very small. If other procedures (e.g. ultrasound) can provide adequate information without exposing the embryo to ionizing radiation, then they should be used. Naturally, there is a period when the patient is pregnant but the pregnancy test is negative and the menstrual history is of little use. However, the risks of 0.05 Gy or less are extremely small during this period of gestation (all or none period,⁴ first 2 weeks). The patient will benefit from knowing that the diagnostic study was indicated and should be performed in spite of the fact that she may be pregnant.

SCHEDULING THE EXAMINATION

In those instances in which elective X-ray studies need to be scheduled, it is difficult to know whether to schedule them during the first half of the menstrual cycle just before ovulation or during the second half of the menstrual cycle, when most women will not be pregnant. The genetic risk of diagnostic exposures to the oocyte or the embryopathic effects on the preimplanted embryo are extremely small, and there are no data available to compare the relative risk of 0.05 Gy to the oocyte or the preimplanted embryo. If the diagnostic study is performed in the first 14 days of the menstrual cycle, should the patient be advised to defer conception for several months, based on the assumption that the deleterious effect of radiation to the ovaries decreases with increasing time between radiation exposure and a subsequent ovulation? The physician is in a quandary because he/she may be warning the patient about a very low risk phenomenon. On the other hand, avoiding conception for several months is not an insurmountable hardship. This potential genetic hazard is quite speculative for humans, as indicated by the report by the NCRP and Committee on Biological Effects of Ionizing Radiation (BEIR) dealing with preconception radiation:^{1,6}

“It is not known whether the interval between irradiation of the gonads and conception has a marked effect on the frequency of genetic changes in human offspring, as has been demonstrated in the female mouse. Nevertheless, it may be advised for patients receiving high doses to the gonads (>25 rads [0.25 Gy]) to wait for several months after such exposures before conceiving additional offspring.”¹

Because patients exposed during diagnostic radiologic procedures absorb considerably less than 0.25 Gy, the recommendations made here may be

unnecessary, but it involves no hardship to the patient or physician. Because both the NCRP and the International Commission on Radiological protection (ICRP) have previously recommended that elective radiologic examinations of the abdomen and pelvis be performed during the first part of the menstrual cycle (10-day rule, 14-day cycle) to protect the zygote from possible but largely conjectural hazards, the recommendation to avoid fertilization of recently irradiated ova perhaps merits equal attention.

IMPORTANCE OF DETERMINING PREGNANCY STATUS OF PATIENT

If exposures less than 0.05 Gy do not measurably affect the exposed embryos, and it is recommended that diagnostic procedures should be performed at any time during the menstrual cycle, if necessary, for the medical care of the patient, why expend energy to determine the pregnancy status of the patient?

There are several reasons why the physician and patient should share the burden of determining the pregnancy status before performing an X-ray or nuclear medicine procedure that exposes the uterus:

- 1** If the physician is forced to include the possibility of pregnancy in the differential diagnosis, a small percentage of diagnostic studies may no longer be considered necessary. Early symptoms of pregnancy may mimic certain types of gastrointestinal or genitourinary disease.
- 2** If the physician and patient are both aware that pregnancy is a possibility and the procedure is still performed, it is much less likely that the patient will be upset if she subsequently proves to be pregnant.
- 3** The careful evaluation of the reproductive status of women undergoing diagnostic procedures will prevent many unnecessary lawsuits. Many lawsuits are stimulated by the factor of surprise and won on the basis of the double jeopardy of the defendant.⁸ In some instances, the jury is not concerned with cause and effect but with the fact that something was not carried out properly by the physicians.^{12,13} In this day and age, failure to communicate adequately can be interpreted as less than adequate medical care. Both these factors are eliminated if the patient's pregnancy status has been evaluated properly and the situation discussed adequately with the patient. Physicians are going to have to learn that practicing good technical medicine may not be good enough in a litigation-prone society. Even more important, the patient will have more confidence if the decision to continue the pregnancy is made before the medical X-ray procedure is performed, because the necessity of performing the procedure would have been determined with the knowledge that the patient was pregnant.

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Microwaves and ultrasound

Robert L. Brent

INTRODUCTION

Exposure to physical agents can present risks to pregnant and non-pregnant individuals, but these risks are related to the dose or amount of exposure and to the particular biologic effects characteristic of these agents. The physical characteristics of microwaves and ultrasound are listed in Table 6.1, and it is readily apparent that neither of these forms of energy has the capacity to produce ionization in tissue or, therefore, the potential to produce alterations in the DNA that would lead to mutation or carcinogenesis, or both, in surviving cells that were exposed.¹⁻⁵ This means that the biologic effects of these energy forms (hyperthermia for microwaves and hyperthermia plus mechanical changes in tissue for ultrasound) are threshold phenomena and, therefore, there are low exposures that do not produce significant or permanent damage.

The term radiation evokes an emotional reaction in many individuals because it is linked with ionizing radiation (X-rays, gamma rays, particle radiation, radionuclides). There is the concern that birth defects, cancer, and mutation can be produced by ultrasound and microwaves. While hyperthermic exposures of both of these forms of energy can interfere with reproduction, they do not have the biologic potential for inducing cancer or mutation as do mutagenic agents.

NON-IONIZING ELECTROMAGNETIC WAVES AT NON-HYPERTHERMIC EXPOSURES

Non-ionizing electromagnetic waves, such as radar, microwaves, radiowaves, frequency modulation (FM), and diathermy, involve electromagnetic waves, which range in frequency from 27.5 MHz (diathermy; 26,500 vibrations/s) to 10^4 – 10^5 MHz (microwave communications).¹⁻⁵ Diathermy electromagnetic waves have great penetration and can readily heat a human torso. Microwaves of 2450 or 915 MHz have less penetration but can also produce significant hyperthermia. Microwaves with frequencies above 10,000 MHz have minimal

Table 6.1 Comparative aspects of various forms of radiation. (From Brent 1986.²)

Type	Physical characteristics	Biologic effects
X-rays, gamma-rays	Short wavelength: electromagnetic waves, highly penetrating, with the capability of producing ionization within tissues and subsequent electrochemical reactions	Electrochemical reactions: can result in tissue damage at high exposures that results in cell death, mutation and developmental defects; these effects are dose-related
Microwaves, radar, diathermy	Longer electromagnetic waves with variable ability to penetrate but no ability to produce ionization within tissues	The primary biologic effect is hyperthermia, although the existence of non-thermal effects of these electro-magnetic waves is still being investigated; cataract development is the most widely known complication of high exposure to microwaves or radar
Ultrasound	Sound waves with a frequency above the audible range that produce mechanical compressions and rarefactions in matter, with no capability of producing ionization	If the energy is high enough, sound waves can cause tissue disruption by the production of cavitation and streaming as well as hyperthermia; none of these effects occurs with the energies utilized in diagnostic ultrasonography

penetration but could produce significant hyperthermia at the skin level if the flux were high enough.

Although a non-thermal effect has not been clearly demonstrated for these forms of electromagnetic irradiation, the matter of non-thermal effects is still being investigated. The organs most vulnerable to the thermal effects of microwave radiation are the eye and developing embryo because these structures have the least capacity to dissipate heat. There is no indication that these forms of electromagnetic energy have the capacity to produce mutations or malignancy; therefore the clinician can reassure patients that microwave ovens, properly handled, are reasonably safe.

Maximum permissible levels for occupational and medical exposures have been suggested for both these forms of energy. Persons working near FM radio

stations, radar, and microwave ovens are not exposed to the maximum permissible level.

With exposures below the maximum permissible level for long-wave electromagnetic waves, there is no measurable effect on the embryo. These exposures would occur from FM broadcasting, microwave communication systems, and microwave ovens. While the FM broadcasting electromagnetic waves can expose the fetus because of their depth of penetration, the population's exposure will be far below the hyperthermia dose.

The exposure to microwave ovens presents even less risks. A microwave oven generates 2450 MHz microwaves. This wavelength can produce hyperthermia above the 24-mW/cm^2 level with a penetration of several centimeters. There is no way to receive exposure from a microwave oven without bypassing several safety interlocks, and it is very easy to shield microwaves—a proper screen or thin metal foil is 100% effective in shielding radiation.

Theoretically, if a microwave oven had a door leak, one could expose oneself by placing a part of the body in direct contact with the area. In this way, it is conceivable that after several hours one might receive a significant exposure. However, because electromagnetic waves dissipate at a rate related to the square root of the distance, it is obvious that a leaking microwave oven would have no consequences several meters away unless it interfered with some electronic device that was sensitive to the wavelength of electromagnetic radiation (e.g. a pacemaker). Thus, the pregnant woman who operates a microwave oven does not place her embryo or fetus at risk, because:

- 1 Microwave ovens rarely expose the user to radiation above the maximum permissible dose
- 2 The 2450-MHz frequency used in microwave ovens does not have the characteristics to irradiate the human embryo within the uterus, because most of the radiation flux is absorbed in the first 3–5 cm below the skin
- 3 Microwave intensity, like all electromagnetic radiation, decreases according to the square root of the distance

Thus, a microwave oven with a door leak of 100mW/cm^2 at 1 cm from the door would expose an object 64 cm from the door to approximately 0.78mW/cm^2 , which is way below the threshold effect for any reproductive risks in small mammals and therefore in humans.

HYPERTHERMIC EXPOSURES FROM DIATHERMY, MICROWAVES, AND ULTRASOUND

Diathermy and ultrasound are utilized as a source of heat treatment. In these instances, local hyperthermia is produced (e.g. to the shoulder, neck, hip, back). Local hyperthermia to other than the pregnant uterus can be administered to pregnant women while reassuring the patient that the fetus is not at risk. Common sense would dictate that direct exposure of the embryo or fetus to

either penetrating electromagnetic radiation (diathermy, microwaves) or therapeutic ultrasound would not make sense, because it has been suggested that significant hyperthermia may be a risk factor for teratogenesis.

DIAGNOSTIC ULTRASOUND

The use of diagnostic ultrasound⁶⁻¹² has increased dramatically in the past 10 years.⁵⁻⁷ Although studies are still ongoing that deal with the effects of ultrasound, diagnostic levels of ultrasound appear to be without increased reproductive risks. Because ultrasound does not produce tissue ionization, the broader use of diagnostic ultrasound should reduce the necessity for many radiologic procedures using ionizing radiation.

The use of ultrasound for fetal monitoring and fetal diagnosis is rapidly expanding. Epidemiologic studies have so far indicated that diagnostic ultrasound does not have any measurable or significant biologic effects, but studies on the biologic effects of ultrasound are continuing, as well as epidemiologic studies of infants who are exposed *in utero*. There are some data on the biologic effects of ultrasound involving DNA repair, cytogenetic alterations, and teratogenesis.

While it is clear that the levels and types of medical sonography that have been used in the past have no measurable risks, it would be inaccurate to label the modality of ultrasound as totally safe regardless of exposure. Most agents have reproductive risks and even teratogenic risks if the exposure is raised sufficiently. Thus, the prudent use of sonography means that clinicians and designers of equipment have to maintain exposures far below the risks that have been demonstrated in animal studies and use the knowledge obtained about the physical changes that can be produced in humans as the absorbed dose is elevated. The reproductive risks are evaluated using five criteria:

- 1 Human epidemiology
- 2 Secular trend data
- 3 Animal experiments
- 4 Dose-response relationships
- 5 Biologic plausibility

The analysis reveals that diagnostic ultrasound does not represent a measurable risk to the developing embryo or fetus. Animal studies also indicate that diagnostic levels of ultrasound are safe and do not elevate the fetal temperature into the region where deleterious embryonic and fetal effects will occur. Because higher exposures of ultrasound can elevate the temperature of the embryo, the use of diagnostic procedures and the design of sonographic equipment should take into consideration the hyperthermic potential of higher exposures of ultrasound and the hypothetical additional risk of performing sonography on pregnant patients who are febrile. It would appear that if the embryonic temperature never exceeds 39°C, then there is no measurable risk.

At present, the results would indicate that the current exposures to diagnostic ultrasound present no measurable risks to the embryo or fetus. However, as diagnostic ultrasound procedures become more sophisticated and lengthy it is important not to ignore these concerns.

CELLULAR PHONES

Since the last revision of the "Protocols" there has been an exponential increase in the use of cellular phones.¹³ Case reports and some poorly performed epidemiologic studies have raised concerns that the use of cellular phones increases the risk of leukemia and brain tumors. Because the frequencies and energies used in cellular phones do not produce ionization in tissues or hyperthermia, only hypothetical etiologies can be provided to explain an oncogenic effect.

The suggestion that cellular phones cause cancer is being investigated by a large multinational study of phone users. A recent study of a rather large magnitude has not found any indication that cellular phones increase the risk of cancer. Boice *et al.*¹³ studied 420,095 cellular phone users in Denmark and were unable to demonstrate any increase in cancer risk in the population of cellular phone users. This negative result included leukemia, brain tumors, and salivary gland tumors. The author's conclusions are:

"The results of this investigation, the first nationwide cancer incidence study of cellular phone users, do not support the hypothesis of an association between use of these telephones and tumors of the brain or salivary gland, leukemia, or other cancers."

Because the cellular phone exposes the head and neck more than the abdomen, exposure of the embryo is much lower. In any event, reproductive effects are threshold effects and the exposures from cellular phones would have no potential for increasing the risk of reproductive effects.

CONCLUSIONS

Exposure of human embryo to long-wave, non-ionizing electromagnetic radiation (radar, diathermy, FM radiowaves, communication microwaves [cellular phones], microwave ovens) below the hyperthermic or maximum permissible exposure, or both, presents no measurable risk to the developing embryo. While hyperthermic exposures do not present a measurable risk to the embryo if the exposed area does not include the uterus, direct hyperthermic exposure to the pregnant uterus should be avoided.

The biologic effects of diagnostic ultrasound are continually being evaluated. At the present time, the available evidence indicates that the developing embryo or fetus is not at risk for permanent biologic effects, such as congenital malformations or permanent alteration of the central nervous system. This conclusion is based on the known physical and biologic effects of ultrasound at

diagnostic levels. If ultrasound procedures become lengthier or utilize higher intensities in the future, then ultrasonographers will have to be cautious and monitor these studies in order to prevent temperature increases that may result in an increase in reproductive risks.

In the past decade there has been an exponential increase in the use of cellular phones. Allegations that exposures from cellular phones increase the risk of cancer have only a hypothetical causal basis and a recent large study does not support a cancer risk. Reproductive effects, which are primarily deterministic or threshold effects, would be very unlikely because of the low exposure to the uterus and the manner in which cellular phones are used.

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Exercise—risks and benefits

James Clapp

INTRODUCTION

This chapter provides a brief review of exercise during pregnancy. It begins with a historic overview followed by a discussion of the interaction between the physiologic adaptations to pregnancy and the physiologic adaptations to exercise. The latter will emphasize that the overall interaction is beneficial for both mother and fetus. The risks, benefits, and potential preventive value of exercise during pregnancy is then addressed, followed by a brief set of recommendations.

OVERVIEW

Over the last 50 years the medical complications associated with a sedentary lifestyle have been well documented as have the health benefits of regular exercise. This first became common knowledge in the 1970s and immediately the general public's awareness about the value of maintaining an active lifestyle increased. As a result, running, weight training, and many health club activities (e.g. aerobics, stationary bike, swimming) became an integral part of many reproductive age women's lifestyle and most (more than 90%) planned on continuing their exercise regimen throughout pregnancy. Unfortunately, in the late 1970s and early 1980s, there was little or no information available to support that decision and there were many theoretical concerns that strenuous exercise might harm the fetus and/or the mother-to-be. By 1985, the American College of Obstetricians and Gynecologists (ACOG) decided that the benefits of regular exercise outweighed the risks for healthy women with normal pregnancies and published a set of logical guidelines for safe exercise during pregnancy. Although they provided badly needed standards for health-care providers to follow, they were based on theory and therefore necessarily conservative. Unfortunately, their multiple limitations and exclusions were not well accepted by many active women, which created conflict with their health-care providers and occasional guilt.

The lack of information, however, also stimulated research that eventually answered many of the questions and alleviated the concerns raised by health-care providers and recipients alike. It focused in two areas. First, an assessment of both maternal and fetal responses to an acute bout of exercise. Second, an evaluation of the effects of regular exercise on the course and outcome of pregnancy. Over the last 30 years the results have been generally positive and, as a result, ACOG revised and updated the guidelines for exercise during pregnancy in 1994 and again in 2002.¹

Currently, regular exercise during normal pregnancy appears to be beneficial to both mother and fetus. Beginning or continuing a structured exercise regimen is strongly recommended by both the American and Canadian Colleges of Sports Medicine and their respective Obstetrical Societies.² However, the type of exercise performed, its duration, its intensity, and its frequency remain somewhat controversial. These issues are now the subject of ongoing research as is the potential value of regular exercise in the prevention and/or treatment of pregnancy complications.

PHYSIOLOGIC RESPONSES TO EXERCISE DURING PREGNANCY

Maternal responses

The maternal physiologic responses to both acute exercise and exercise training (regular, sustained exercise) are modified by the physiologic adaptations to pregnancy. In addition, exercise training augments many of the positive physiologic adaptations to pregnancy and negates many of the negative ones. As a result, regular exercise during pregnancy appears to be physiologically protective to both mother and fetus.^{3,4} Important examples of the physiologic interplay are detailed below.

Thermal

Pregnancy drastically blunts the exercise-induced increase in body temperature; primarily by increasing the capacity for heat loss. It increases both skin blood flow and skin temperature, which dramatically increases the rate of heat loss through convection and radiation. Indeed, when a pregnant woman dressed in usual exercise apparel rests quietly in a thermoneutral environment, her core body temperature actually decreases because her rate of heat loss exceeds her heat production and, when she starts exercise, there is another abrupt decrease when the cooler peripheral blood returns to her core. Pregnancy also lowers the threshold for sweating, which improves evaporative heat loss further, blunting any exercise-induced rise in core temperature. These responses are further augmented in the trained recreational or competitive athlete. As a result, only prolonged, strenuous, endurance exercise (e.g. inter-

val training, Versa climbers, pleometrics) elevates maternal core temperature above 100.5°C.

Blood volume expansion, cardiac output, and vascular reactivity

Vascular reactivity decreases dramatically in early pregnancy which, in turn, increases peripheral venous pooling and decreases both venous return and functional blood volume during many types of hemodynamic stress. Thus, hypotension and tachycardia are common responses to hemodynamic stress during early pregnancy. These changes also trigger a rapid increase in blood volume, which progressively blunts these responses with advancing gestation. Exercise training also increases blood volume and alters vascular reactivity so women who exercise prior to pregnancy have a hemodynamic advantage, and the differential between them and their sedentary sisters is maintained throughout pregnancy if they continue to exercise.

In both sedentary and active women, however, heart rates during and immediately after exercise in early pregnancy are usually 20–40 beats higher than those present prior to pregnancy, and postural hypotension is common at rest in the upright position immediately after exercise. The magnitude of both responses is less in regularly exercising women and both decrease with advancing gestation. However, exercise that involves arm movement above shoulder level continues to accentuate the maternal heart rate response. Thus, one should avoid sudden cessation of exercise followed by quiet standing or sitting, and exercise heart rates are a poor index of exercise intensity during pregnancy. Indeed, heart rate monitoring is no longer recommended as a method for assessing exercise intensity during pregnancy.

During pregnancy the heart remodels, cardiac output increases, and splanchnic, uterine, and skin blood flows rise while blood pressure and total peripheral resistance fall. During exercise, the magnitude of blood flow redistribution away from the splanchnic and uterine beds to those in exercising muscle is undoubtedly buffered by these changes and is definitely reduced during late pregnancy in well-trained women. Again, this results from the additive effects of exercise training and pregnancy on blood volume, blood pressure, cardiac output, and flow redistribution requirements. An additional benefit is that many of these changes persist postpartum in exercising women, resulting in improved exercise capacity. Thus, pregnancy has a training effect in active women, which may explain the improved performance of elite women athletes after their index pregnancy.

Metabolic

Pregnancy is a growth process which increases oxygen consumption and glucose utilization, and decreases gluconeogenesis and insulin sensitivity. The latter shifts the balance of maternal substrate utilization towards lipid

oxidation which increases the availability of carbohydrate for fulfilling fetoplacental energy needs. The magnitude of these changes increases with advancing gestation. Exercise also increases oxygen consumption and glucose utilization while suppressing insulin secretion but increases sympathetic output and gluconeogenesis. The combined effects of exercise and pregnancy alter the glucose response to exercise from a hyperglycemic to a hypoglycemic one. The magnitude of the hypoglycemia increases with advancing gestation and is also augmented when exercise is performed in the 2-h postprandial period. Thus, the timing of exercise sessions relative to nutrient intake is an important consideration for the active pregnant woman as is the type and amount of nutrient intake during and immediately after an exercise session.

Concomitant progesterone-induced changes in the sensitivity of the respiratory center produce a respiratory alkalosis which augments oxygen transfer across the lung and into tissue both at rest and during exercise.

The effects of exercise training on the magnitude of these metabolic adaptations is unknown but the usual physiologic adaptations to exercise training in the non-pregnant state (greater reliance on lipid for energy, improved insulin sensitivity, and enhanced oxygen transfer) suggests that continuing exercise training during pregnancy should have similar beneficial effects. However, short-term exercise training in late pregnancy does not appear to change insulin sensitivity but does appear to reduce insulin requirements in gestational diabetics.

Muscle, ligament, and bone

The pregnancy-associated changes in muscle, ligaments, and bone are not well studied but it appears that the combination of maternal weight gain, protuberant abdomen, changing center of gravity, and ligamentous laxity alter posture, decrease mobility and balance, and increase musculoskeletal stress. Bone turnover is increased but bone density is unchanged; the effects of pregnancy on muscle mass is unknown. In sedentary women these changes make physical activity more difficult, often uncomfortable, and are associated with a high incidence of low back pain. Women who exercise regularly, however, gain less weight, experience very little change in posture, maintain their abdominal muscle tone, and feel much better than women who do not. Indeed, in Scandinavia, regular exercise sessions are used therapeutically to relieve low back pain and other musculoskeletal complaints with excellent success. Presumably, training effects on strength, muscle tone, balance, and joint stability are responsible for the difference.

Fetoplacental responses

Studies of the fetoplacental responses to acute maternal exercise and/or exercise training are necessarily limited but current knowledge suggests that they

are the same as those used by the fetoplacental unit to cope with other types of acute or recurrent stress. Their goal is simply to maintain nutrient delivery and ensure intact survival. The combined hemodynamic, respiratory, and metabolic responses are illustrated in the following paragraphs.

Response to decreased uterine blood flow

Direct measurement of uterine blood flow during or immediately after exercise is not yet available but indirect indices indicate that uterine blood flow falls significantly during exercise and, if the exercise is moderately intense and sustained for more than 10 min, fetal heart rate invariably increases. This is a manifestation of an acute fetal stress or sympathetic response to a small decrease in fetal PO_2 and the magnitude of the heart rate increase is directly related to the intensity and duration of the exercise and the muscle mass utilized. Other components of this acute stress response are an increase in fetal cardiac output and a change in the distribution of cardiac output which maintain adequate oxygenation of critical tissues (brain, heart, adrenal, and placenta). Transfer of oxygen into and carbon dioxide out of fetal tissues is improved by the concomitant shift in the oxyhemoglobin dissociation curve. Although not yet demonstrated in the human, improved perfusion–perfusion balance between the maternal and fetal placental circulations probably occurs in response to the exercise-induced decrease in uterine blood flow, which also enhances placental transfer function. In addition, the chronic pregnancy-associated increase in alveolar ventilation increases maternal arterial PO_2 and decreases PCO_2 , which further enhances placental transfer of both gases.

Whether the effectiveness of these normal stress responses are enhanced by regular maternal exercise is unknown but regular exercise does have several additional effects. First, it increases both maternal and fetal placental blood volumes and surface areas, which is estimated to improve placental transfer function by 20% or more. Second, regular exercise training during pregnancy augments the usual pregnancy-associated increase in maternal blood volume and cardiac output. This reduces the magnitude of the decrease in uterine blood flow by reducing the need for flow redistribution to supply the needs of exercising muscle.

How effective is this combined response to recurrent, sustained, exercise-induced decreases in uterine blood flow? In a normal singleton pregnancy, the answer is “very”, because these flow perturbations do not produce short- or long-term evidence of fetal distress or tissue hypoxia. The fetal biophysical profile does not decrease and the amount of time the fetus spends breathing and moving is either unchanged or increased. The incidence of meconium-stained amniotic fluid is actually decreased in fetuses born of women who exercised right up until the day of delivery and, at delivery, fetal cord blood and amniotic fluid erythropoietin levels are not increased. Both findings indicate

that fetal tissue oxygenation was well maintained during exercise in late pregnancy. Finally, the offspring of regularly exercising women experienced normal to superior neurodevelopment in various domains throughout the first 5 years of life.

However, it appears that, under specific circumstances, the combined response may not be entirely adequate. Several investigators report that episodes of bradycardia occurred in some of the fetuses of untrained women immediately after an acute bout of strenuous cycle ergometer exercise. This suggests that either severe fetal hypertension or hypoxic myocardial depression occurred. It is unclear, however, if this response was related to the exercise *per se* or to the effects of exercise plus the effects of superimposed maternal postural hypotension immediately after stopping exercise.

Response to decreased nutrient delivery

The fetus and placenta normally respond to a recurrent or chronic decrease in nutrient availability by decreasing their growth rate, which matches fetal demands to the supply available. As regular exercise sessions intermittently decrease both blood flow and glucose levels, one might expect that regular exercise would initiate a similar response. Detailed studies summarized elsewhere,⁵ indicate that the effects of regular exercise on fetoplacental growth vary depending on the type, frequency, duration, and intensity of the exercise, the total exercise volume performed at different times during pregnancy, and concomitant maternal carbohydrate intake. Thus, different exercise regimens and food intakes can increase, decrease, or not alter fetal growth, size at birth, and neonatal body composition.

Briefly, current evidence indicates that non-weight-bearing forms of exercise (biking, swimming) have no effect on size at birth. Continuing common weight-bearing types of exercise (running, aerobics classes, cross-country skiing) during pregnancy appears to stimulate placental growth while their effect on fetal growth varies with the effects of exercise on 24-h substrate availability. The latter is a function of maternal exercise volume and diet. Several examples follow. Women who start exercise in early pregnancy and eat to appetite have significantly larger babies than those who remain sedentary. Women who train hard or increase their exercise volume throughout pregnancy are delivered of offspring with normal, lean body masses who have experienced normal axial and head circumferential growth *in utero*. However, growth of their fat organ is restricted which, if it persists, may be of value later in life. Women who train hard in early pregnancy and then cut back have large infants with significantly increased fat mass suggesting overgrowth. Finally, women who exercise and eat a high-glycemic index diet deliver large infants (over 4 kg) while those who eat a low-glycemic index diet are delivered of fetuses who weigh approximately 3.2 kg.⁶

RISKS

Initial concern was that the effects of maternal exercise on body temperature, uterine blood flow, substrate utilization, catecholamine release, and shear stress placed the embryo, fetus, and/or placenta at risk for multiple complications. During pregnancy these included: spontaneous abortion, congenital abnormality, hypoxia, growth retardation, cord entanglement, preterm labor, placental insufficiency, premature membrane rupture, and placental abruption. There was also concern that the offspring might experience abnormalities in postnatal growth and neurodevelopment. The main risks for the mother-to-be appeared to be difficulty with conception, energy drain, and either acute or chronic injuries (e.g. arthritis, dislocation, hernia, diastasis). To date, it appears that neither these nor other unanticipated negative outcomes have occurred but there are many forms of exercise yet to be studied and risk may vary in women who lead different lifestyles or who experience a variety of complications during pregnancy.

BENEFITS

The major benefit of regular exercise during pregnancy is that it enhances the normal physiologic adaptations to pregnancy while negating many of their musculoskeletal side-effects. Additional maternal benefits of most forms of exercise studied to date include: an improved body image and sense of well being, improved productivity, a decrease in the incidence and magnitude of common pregnancy discomforts, a decrease in the incidence of situational depression both during and after pregnancy, and improved fitness. Specific fetoplacental benefits of most forms of maternal exercise have not been studied in detail. Thus, at present they are limited to the fetoprotective effects of the enhanced maternal adaptations to pregnancy and perhaps improved placental growth and function.

However, other specific maternal and fetoplacental benefits have been identified in women who continue moderate to high volume weight-bearing recreational exercise regimens throughout pregnancy.³ For the mother these include: limited weight gain and fat retention; shorter, less complicated labors; shorter recovery times after the birth; and improved maximal aerobic capacity. For the fetus, infant, and young child these include: a decreased incidence of clinically diagnosed fetal distress before or during labor; a decrease in the growth rate of the fat organ, which persists for the first 5 years of life; improved neonatal behavioral profile; and normal to superior cognitive development.

POTENTIAL PREVENTIVE VALUE OF EXERCISE

The enhanced physiologic adaptations to pregnancy suggest that regular exercise might be of value in women with a history of poor outcome (preterm labor, growth restriction, implantation abnormalities), and, when combined with

diet, its effects on fetoplacental growth could be of value. Its value in potentially improving insulin sensitivity remains controversial as is its value in the prevention and/or treatment of gestational diabetes mellitus. Its potential preventive value for pregnancy-induced hypertension is unknown. All warrant further study.

BRIEF RECOMMENDATIONS

It should be emphasized that currently these recommendations apply only to otherwise healthy women with clinically normal pregnancies.

- 1 A regular exercise regimen should be recommended as part of prenatal care.
- 2 The frequency of the exercise sessions should be three or more times per week with each session lasting 20–30 min or more.
- 3 The exercise should be continuous and conducted at a moderate to hard level of perceived exertion.
- 4 The overall weekly volume of exercise should be individualized based on a woman's exercise volume prior to pregnancy and her exercise tolerance. A beginner should start a moderate intensity regimen three times per week, increasing frequency and duration but not intensity over time. An athlete should avoid serious competition, limit interval training, and not exceed a weekly exercise volume equal to 120% of that performed prior to pregnancy. Chronic fatigue and/or other signs of overtraining suggest that overall exercise volume should be reduced.
- 5 Exercise sessions should occur 2 h or more after a meal and include a planned post-exercise snack.
- 6 Quiet standing or sitting immediately after exercise should be avoided and each individual regimen should include time for warm-up and cool-down.
- 7 Exercising in a hot, humid environment should be avoided, hydration encouraged, and interval training periods should be short.
- 8 Sanctioned guidelines view stationary biking and swimming as the best forms of exercise during pregnancy but, to date, experience with many other forms of weight-bearing exercise indicates that they are well tolerated and not associated with injury.
- 9 The exercise regimen should be re-evaluated and changed if clinical, pregnancy-related problems develop or local pain and tenderness occur.

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PART 2

*Antenatal
testing*

Routine antenatal laboratory tests and specific screening tests

Calvin J. Hobel

INTRODUCTION

Pregnancy provides a unique opportunity to assess a woman's general health. The objective of routine antenatal laboratory tests is to recognize an unknown condition. Pregnancy can initiate dramatic changes in various systems, and routine antenatal laboratory tests help detect alterations from what is considered normal for pregnancy. Ideally, routine laboratory and screening tests in the preconceptional period would help to identify the pregnancy at risk and provide an opportunity to institute preventive measures. The goal is to maintain the health of the mother in order to assure the optimal outcome for a pregnancy.

Routine laboratory tests and specific screening tests help clinicians to provide a more complete evaluation, identify the patient at risk, and provide counseling and therapy based on selected risk factors and laboratory tests.^{1,2}

ROUTINE BLOOD TESTS

Blood type and Rh factor

Every pregnant woman must have her blood type and Rh factor determined. Records of previous determinations have a 0.4–3.0 % error rate (either mislabeling, laboratory error, or a transcription error). If the patient's blood type is O or Rh-negative, or both, her husband's blood type and Rh should be determined. If the patient is Rh-negative and her husband is Rh-positive, there may be Rh incompatibility. If the patient's blood is type O and her husband's is A, B, or AB, there may be ABO incompatibility.

Antibody screen for sensitization

Every pregnant woman must have her serum screened for antibodies formed from exposure to major or minor blood group antigens. Exposure may have

occurred naturally or from a transplacental hemorrhage, abortion, or blood transfusion. If the screen is positive, the antibody must be identified and titered. Antibody screen should be repeated at 28 weeks' gestation in Rh-negative patients.

Hemoglobin and hematocrit

During pregnancy, the blood volume increases by 30–50%. Because plasma volume increases more than red cell volume, hemoglobin (Hb) and hematocrit (Hct) will fall. Mild anemia is defined as Hb less than 11 g/dL (Hct 27–33%); severe anemia is Hb less than 9 g/dL (Hct less than 27%).

Anemia during pregnancy is usually of the iron-deficiency type. A folic acid-deficient state may coexist with iron deficiency. Hemoglobin and hematocrit testing should be repeated at 28 weeks' gestation.

Leukocyte count

This test is used primarily as a screen to rule out leukemia and possible infection. Normal values may reach 16,000 in pregnancy.

Platelet count

This test is an automated part of the complete blood count (CBC) that can detect unrecognized thrombocytopenia. Thrombocytopenia (80,000–100,000) may be pathologic or a finding of minimal clinical significance.

Red cell count and indices

These tests help diagnose various types of anemias.

Differential smear

This test is performed primarily to identify the types of leukocytes, erythrocytes, cell abnormalities, and the adequacy of platelets.

Serology

This test is carried out to diagnose maternal syphilis, which can affect the fetus. VDRL (Venereal Disease Research Laboratory) is a screening test. If it is positive, the more specific fluorescent treponemal antibody (FTA) test is performed. Serology should be repeated in the third trimester in patients at risk.

Rubella titer

The purpose of the rubella titer screening test is to determine whether the mother is susceptible to rubella or is immune. If this test is performed during the preconceptional period, it does not need to be repeated. If the patient is not immune before pregnancy, vaccination should be advised and pregnancy avoided for 3 months.

Hepatitis B surface antigen and hepatitis C

All pregnant women should be screened for hepatitis B. The infants of hepatitis B surface antigen (HBsAg) positive mothers need immunoprophylaxis at delivery. Women at risk (drug abusers, homosexuals, healthcare workers) should be tested preconceptionally, and vaccination is advised. Women with high-risk behaviors should be tested for hepatitis C.

Glucose screening test

The glucose screening test (GST) is a 1-h test of blood sugar after the patient receives 50 g glucose. Because pregnancy may precipitate glucose intolerance, it is an ideal time to screen for diabetes. The following risk factors can be used to select patients for glucose intolerance screening at the first visit:³⁻⁵

- Age over 35 years
- Family history of diabetes
- Maternal obesity (more than 120% ideal body weight)

All patients are screened at 28 weeks' gestation. Patients with the following risk factors should be rescreened at 33–34 weeks:

- Prior abnormal 1-h value after 50 g glucose but normal glucose tolerance test (GTT)
- Prior 1-h abnormal value on a 3-h GTT

First trimester screening

Integrated sonography (fetal nuchal translucency) and biochemical markers (β -hcg and PAPP-A) are performed in the first trimester to detect trisomies 21 and 18 (see also Chapter 11). In addition, positive tests in the absence of trisomies may aid in the assessment of risk for other obstetric complications such as pre-eclampsia, abruption, preterm labor, and intrauterine growth retardation.¹²⁻¹⁴

Maternal serum alpha-fetoprotein

The maternal serum alpha-fetoprotein (MSAFP) test or the triple marker screen test should be performed on all pregnant women between 15 and 20 weeks' gestation to assess the risk for neural tube defect and trisomies unless the patient is undergoing genetic amniocentesis for advanced maternal age (see Chapter 17).

SPECIAL CONSIDERATIONS

Human immunodeficiency virus

Testing for human immunodeficiency virus (HIV) should be offered to all patients. Screening should be repeated at 36 weeks in the at-risk patient.

Illicit drug screening

Screening for illicit drugs should be offered to all patients.

Other screening tests

The following screening tests should be considered preconceptionally or in high-risk pregnant patients:⁶

- Toxoplasmosis.
- Cytomegalovirus.
- Tuberculosis skin test (some programs skin test all patients with a negative history of tuberculosis).
- Hemoglobin electrophoresis for patients at risk from sickle cell trait, thalassemia, or other hemoglobinopathies.
- Tay–Sachs screening for individuals of Jewish ancestry; if only one of the couple is Jewish, it is recommended that the Jewish partner be screened, and if he/she is a carrier, the other partner should also be screened.
- Cystic fibrosis.
- Thrombophilia screening. We are currently recognizing the association between several of the hereditary thrombophilias in patients with a history of severe pre-eclampsia, HELLP syndrome, intrauterine growth retardation, and abruption. Patients with a prior history of pulmonary emboli (while on the oral contraceptive pill) or a history of thrombosis in a family member may also be candidates for assessment.⁷
- Thyroid screening in women with history of hypothyroid or prior prescription for hyperthyroidism.
- See special considerations (in section on cervical–vaginal–rectal examination evaluation) for the assessment of risk for vaginal infection secondary to bacterial vaginosis (BV).

Ultrasound screening

Ultrasound screening for low-risk pregnancies should be performed for specific indications. The specificity for an anatomic survey in detecting fetal abnormalities is very good but sensitivity varies in different clinical settings.⁸

ROUTINE URINE TESTS

Urinalysis

Urinalysis must be performed on clean-catch specimens. The following tests can identify patients with asymptomatic kidney or bladder disease.

- *Microscopy*. Microscopic examination of a centrifuged specimen can identify bacteria, leukocytes, and erythrocytes, which may indicate infection. Casts or red cells, or both, may indicate chronic pyelonephritis. A complete urinalysis should be repeated at 28–30 weeks' gestation.

- *Glucose.* Glycosuria may occur in pregnancy because of increased glomerular filtration rate. However, it may also indicate carbohydrate intolerance. The test should be repeated; if positive (more than 1+), further testing should be carried out. Repeat this test at each visit.
- *Protein.* A value over 1+ is abnormal. The cause should be identified (e.g. urinary tract infection, pregnancy-induced hypertension, renal disease). This test should be repeated at each visit.
- *Leukocyturia.* The leukocyte esterase reagent test strip is helpful in identifying patients with significant leukocyturia.

Urine culture

A urine culture can be obtained on the first visit. However, some authorities consider the leukocyte esterase test as the first step and, if it is negative, the routine culture should be avoided.

CERVICAL–VAGINAL–RECTAL EXAMINATION EVALUATION

- *Papanicolaou smear.* The Papanicolaou (Pap) smear identifies cancer of the cervix, as well as cervical herpes and papillomavirus. A positive smear requires further evaluation.
- *Culture for gonorrhoea.* Culture for gonorrhoea is recommended at the initial visit. At 36 weeks' gestation, a repeat culture may be indicated in an at-risk patient. A positive culture requires treatment with appropriate antibiotics and a follow-up culture 2 weeks after therapy to assure a cure.
- *Culture for herpes.* Cultures should be performed only when a woman has active herpes to confirm the diagnosis. If there are no visible lesions at the onset of labor, vaginal delivery is acceptable.
- *Culture for group B streptococci* (2000 guidelines). Vaginal and rectal group B streptococci (GBS) screening cultures at 35–37 weeks' gestation for all pregnant women (unless patient had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease).⁹

Intrapartum prophylaxis indicated

- Previous child with GBS
- GBS bacteriuria during pregnancy
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery, in the absence of labor or amniotic membrane rupture, is performed)
- Unknown GBS status (culture not performed, incomplete, or results unknown) and any of the following:
 - Delivery at less than 37 weeks' gestation
 - Rupture of the membranes greater than 18 h
 - Intrapartum temperature 100.4°F or higher (38.0°C or higher)

Intrapartum prophylaxis not indicated

- Previous pregnancy with a positive GBS screening culture (unless a culture was also positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

Special considerations

Assessment for the risk of bacterial vaginosis

Because BV has become the most prevalent vaginal infection associated with preterm labor, assessment using either vaginal pH, the BV Blue test or the wet mount at 12–14 weeks and again at 20–24 weeks may be of value in certain high-risk populations.^{10,11}

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Assessment of gestational age

Lawrence D. Platt

INTRODUCTION

Assessment of gestational age is essential for proper management of every pregnancy. Traditional methods, based on the date of the last menstrual period, early pelvic examination, quickening, and fundal height measurement, remain major components of routine care. While last menstrual period has been shown to be the most effective of these, in many geographic areas up to 40% of patients present with uncertain dates because of irregular menses or recent discontinuation of oral contraception, or simply because they are unreliable historians. Obesity often makes an accurate early pelvic examination difficult. However, correct assessment of gestational age is an essential part of prenatal care where accuracy plays an important part in optimizing pregnancy outcome.

During the past 30 years, diagnostic ultrasound has become an understood part of obstetric care, especially its use to confirm last menstrual period. Although crown-rump length and biparietal diameter are probably the most common measurements, the advent of real-time scanning generated research in other parameters that have led to several new approaches to pregnancy dating. Whatever method or technique is used to assess fetal age, it is clear that normal, premature or postmature, and dysmature fetuses can only be identified when gestational age is known, and ultrasound is of great value for this purpose.

STANDARD METHODS

Gestational sac measurements

The measurements (e.g. diameter, area) of the gestational sac have been used but are not the most accurate, and there is no assurance that a viable pregnancy is present. They should be used only until such time that a fetus is visible and more precise measurements can be obtained.

Crown-rump length

Most authorities agree that this measurement, introduced by Robinson and conferred by numerous other investigators, is the most accurate ultrasonic

pregnancy dating method available today. It can best be obtained transvaginally (although the transabdominal approach is also reliable) to identify the longest axis of the fetus. The distance from the upper part of the fetal cephalic pole (crown) to the lower portion of the fetus (rump) is then measured. Many standard curves are available. 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 time. Multiplanar three-dimensional imaging is also helpful in aligning the fetus into a proper position.

Biparietal diameter

The biparietal diameter (BPD) is the oldest and most widely used method of assessing gestational age. Measurements are taken at the level of the thalamus. Consistent landmark identification is essential in order to reduce the error inherent in the technique. This method can be utilized from 12 weeks' gestation and is most accurate if performed before 28 weeks' gestation (but best if used before 20 weeks). Because growth of the fetal head slows from 4 mm/week to less than 2 mm/week after 32 weeks, to be accurate the clinician must recognize that the BPD is affected by head shape. Therefore, the cephalic index (which looks at the relationship of the occipital frontal in the BPD) has been shown to be useful in verifying the appropriateness of the BPD. The BPD may be unreliable for dating in certain conditions. For example, the BPD will be smaller in cases of microcephaly, symmetric intrauterine growth restriction (IUGR), or neural tube defects. It will be larger in cases of hydrocephaly. Cephalic index, a constant $78 \pm 4\%$, is obtained by dividing the occipital frontal diameter into the BPD.

Abdominal circumference

Studies have found the fetal abdominal circumference useful in assessing gestational age. This measurement is obtained by identifying the long axis of the fetus and then turning the transducer 90° to obtain a transverse section just below the fetal heart, at the level of the umbilical vein. This method is best utilized after 14 weeks' gestation.

Head circumference

This method is most commonly used for evaluating fetal growth or investigating evidence of fetal anomalies. However, it can be used for gestational age assessment when the head shape is abnormal (cephalic index is abnormal).

Fetal limb measurement

The fetal femur is also a reliable method for assessment of gestational age beginning in the second trimester. This measurement is accurate to ± 7 days. The

femur is best measured by first identifying the iliac crest, then positioning the transducer approximately 45° laterally. The largest view should be used for measurement. Measurement of the other long bones (humerus, radius, ulna, tibia, fibula) has also been shown to be reliable and can also be used for markers of genetic diseases such as skeletal dysplasia or Down syndrome.

Cerebellum

The use of transcerebellar diameters in the second trimester is another useful parameter. As a general rule, the diameter of a cross-section of the cerebellum in millimeters should be equal to the gestational age in weeks up to 26 weeks. The size of the cerebellum is least affected by IUGR.

Mean ultrasound age

Looking at a combination of parameters appears to improve the accuracy of dating the pregnancy. Using all measurements to derive a mean ultrasound is an easy and efficient manner to do this. This technique has proved useful in reducing the range of error, particularly in late pregnancy.

However, careful attention must be focused on excluding the measurements that are significantly different from the others. In the past, a score of investigators have suggested doing several studies weeks apart to derive an adjusted gestational age. These two methods of age assessment, growth-adjusted sonographic age (GASA) and mean projected gestational age (MPGA), are rarely used today.

Less frequently used ultrasound parameters for fetal age assessment

- Mandible length
- Maxilla length
- Foot length
- Inter/outer orbital distance
- Abdominal diameter
- Thoracic diameter or circumference
- Liver size
- Clavicle length
- Thigh diameter or circumference

TRADITIONAL METHOD OF ASSESSING GESTATIONAL AGE

Patients with good menstrual history

- 1 Obtain an accurate menstrual history.
- 2 Perform a pelvic examination to correlate uterine size with menstrual dates.
- 3 Measure fundal height at each antenatal visit after 14 weeks, using a tape from the top of the fundus to the superior board of the symphysis pubis.
- 4 Elicit timing of quickening.

- 5 Listen for fetal heart tones at each visit with a fetoscope (non-Doppler) after 16 weeks' gestation, or after a patient reports quickening.
- 6 Confirm any discrepancies with early ultrasound. Scanning is best performed before 20 weeks from the last menstrual period.

Patients with poor menstrual history, obesity, or recent discontinuation from oral contraceptives

Before 20 weeks

Perform an ultrasound scan at the first visit and, if the crown–rump length indicates a fetus of less than 12 weeks, plan to repeat the scan in 6–8 weeks to confirm dates. Plot the results against the median for that gestational age.

If the scan demonstrates the fetus to be between 12 and 26 weeks, perform a second scan 4–6 weeks after the first. At a minimum, the BPD, abdominal circumference, and femur length should be evaluated. Ideally, all three measurements should agree. If they do not, first consider a congenital abnormality. It is usual, for example, that the femur and humerus are smaller in trisomy 21. Extremely short limbs may indicate a skeletal dysplasia. Perform a third scan 3–4 weeks after the second to evaluate the fetus for growth abnormalities.

After 20 weeks or with fundal height above umbilicus

The reliability of any ultrasound method greatly diminishes as gestation advances. When patients present after 26 weeks, the reliability of any single ultrasound parameter is poor. If the patient has unreliable menstrual dates, plot the ultrasound measurements (BPD, abdominal circumference, femur length) against the 50th percentile for those measurements. Perform a repeat scan 3–4 weeks later and correlate results with the first to assess fetal growth. Any examination performed at or after the 36th week may be unreliable.

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Second trimester biochemical screening for neural tube defects and aneuploidy

John C. Hobbins

INTRODUCTION

Second trimester biochemical screening (BCS) started in the 1970s when it was found that fetal neural tube defects (NTDs) were associated with elevations of maternal serum alpha-fetoprotein (MSAFP). While the screening protocols for NTDs were being refined, it was noted that MSAFP tended to be low in fetal Down syndrome (DS). With a cut-off of 2.0 multiples of the median (MoM) 85% of NTDs would be screened in, and with a threshold of 0.5 MoM approximately 33% of DS fetuses would be screened in. With the addition of two other analytes, estriol (which is low in DS) and human chorionic gonadotropin (hCG) (which is elevated in DS), the sensitivity of biochemical screening for DS rose to approximately 65% across all ages at a 5% test-positive rate, and was over 85% in those above 35 years of age at a screen-positive rate of 19%. The most recent addition to the biochemical screening regimen, taking the above “triple screen” to a “quad screen,” is inhibin-A. This increases the sensitivity of the combined test by approximately 8%.

Algorithms allow laboratories to fold in the patient’s age, gestational age, and the levels of the individual hormones in MoMs so that the risk for an individual for DS and trisomy 18 can be quantified. This result can then be compared with her age-related risk (ARR) and the risk of amniocentesis.

SCREENING FOR NEURAL TUBE DEFECTS

Some laboratories quantify the risk of NTD based on the magnitude of the MSAFP elevation, but this is probably unnecessary. The recommended practice is to perform a detailed ultrasound examination in every patient whose MSAFP exceeds 2.0 MoM. The pertinent parts of this examination include:

- 1 Biometric establishment of gestational age. In approximately 30% of cases erroneous dates are the reason for the elevation of MSAFP.
- 2 Careful evaluation of the intracranial anatomy looking for:
 - The “lemon sign”—indentations in the temporal portion of the fetal skull will give the calvarium a lemon-like configuration in 75% of cases of open NTD.
 - Ventriculomegaly—the lateral ventricles are at least modestly dilated (past 1 cm at the level of the atrium) in 50% of NTD cases in the second trimester.
 - “Banana sign”—the cerebellar hemispheres are depressed into the foramen magnum, either because of the loss of cerebrospinal fluid through an open spinal defect into the amniotic fluid or tethering of the spinal cord, creating a banana-like configuration.
 - The cisterna magna is compressed. Because of the above Arnold–Chiari abnormality, which occurs in virtually all cases of open NTD after 16 weeks’ gestation, the fluid space representing the cisterna magna will be obliterated.

THE SPINE

In contrast to the evaluation of the fetal brain, pinpointing a spinal defect, especially if it is small and low, is sometimes difficult and is best performed by someone with considerable experience in this type of investigation. Therefore, the key to an NTD diagnostic regimen is to depend heavily on the status of the intracranial anatomy. If the usual transverse and sagittal views of the spine are normal and are coupled with normal intracranial findings, further investigation is unnecessary. However, if the posterior fossa is abnormal, compulsive investigation must be carried out. In NTD, the diagnostic goal is not only to make the diagnosis but also to characterize the size and level of the defect because this impacts on the quality of life for the fetus.

As the chances are almost 100% that a fetus with an open NTD will have intracranial findings, amniocentesis has been generally reserved for those with a very high suspicion (e.g. MSAFP more than 4.0 MoM), where findings are equivocal, or where the ultrasound information is difficult to obtain because of the patient’s body habitus. This would probably represent less than 5% of those with MSAFP elevations above 2.0 MoM.

Most recent data from experienced prenatal diagnostic centers indicate detection rates to be 100% with ultrasound.

OTHER AREAS TO EXPLORE

- 1 *Fetal cord insertion.* Ventral wall defects are associated with elevations in MSAFP.

- 2 Fetal kidneys.** Some kidney abnormalities, usually associated with oligohydramnios, have been reported with elevations in MSAFP. However, the rare Finnish congenital nephrosis is unlikely to be detected with ultrasound. Epidermolysis bullosa, a rare skin condition, would not be detectable with ultrasound.

SCREENING FOR DOWN SYNDROME

Although the greatest emphasis has been in women of advanced maternal age (AMA), it is generally accepted that all pregnant patients should be offered some form of biochemical testing in the second trimester. The reason that age 35 was arbitrarily chosen as a threshold above which the patient is considered to be AMA was based on the assumption that at this age the risk of amniocentesis was about the same as the risk of DS. This risk is also put into play when a laboratory reports a biochemical screen to be “positive” or “negative.”

CONTEMPORARY INTERPRETATION AND DIAGNOSTIC MANAGEMENT OF BIOCHEMICAL SCREENING

Screen negative

Every laboratory should quantify this result for a given patient.

- 1 Patients less than 35 years of age.** These patients should be reassured. The only exception would be, for example, an individual whose ARR is very low (approximately 1 in 1000) and who jumps to 1 in 300 by BCS. These patients might benefit from a detailed ultrasound examination.
- 2 Patients over 35 years of age.** The American College of Obstetricians and Gynecologists (ACOG) still indicates that these patients should be “offered” amniocentesis. However, many patients will weigh their quantified risk of DS by BCS against the risk of amniocentesis quoted by their provider. In our experience, only 20% of our screen-negative AMA patients opt for amniocentesis.

Patients should realize that the results of BCS are not 100% accurate in the detection of DS, as reflected in Table 10.1.

Screen positive

This simply means that the risk of DS is greater than the theoretical risk of amniocentesis. Many patients have the misconception that a positive test means that their fetus has DS. Counseling these patients is easier when the actual risk is quantified by the laboratory, but these patients should be offered an amniocentesis.

RISK OF AMNIOCENTESIS

Varying risks are quoted in the literature, but the only randomized trial to date in patients 34 years of age or less showed a procedure-related loss rate of 1%.

Table 10.1 Rates of detection of Down syndrome and false-positive rates according to maternal age and screening test. (Adapted from Wald *et al.* 1999.)

Maternal age* (years)	Triple test		Quadruple test	
	Detection rate	False-positive rate	Detection rate	False-positive rate
15–34	58	3.7	69	4.1
>35	88	19	91	17
<15	69	4.9	77	5.2

*All tests included maternal age and gestational age, estimated by ultrasonography. The risk cut-off levels were as follows: triple test, 1 in 250; quadruple test, 1 in 300.

Very recent data from a large DS screening trial (FASTER) shows only a modest increase in fetal losses in screen-positive women having amniocentesis versus screen-positive women declining this procedure.

The most commonly quoted literature-based loss rate attributed to second trimester amniocentesis is 1 in 200.

GENETIC SONOGRAM

This has emerged as a way to further lessen the risk of DS for any given patient. It consists of three parts:

- 1 Measurement of the fetal humerus and femur because these tend to be smaller in DS.
- 2 A fetal survey to rule out major abnormalities because 20% of fetuses with DS will have an anomaly.
- 3 A search for “markers” for DS, the most common components being the fetal nuchal skinfold thickness (NSFT), the nasal bone length, an echogenic focus in the heart, echogenic bowel, and fetal pyelectasis. Less commonly investigated areas include the fetal hands, ear, frontal lobe, the hip angle, and right heart predominance.

Many recent studies have shown that at least one positive finding is noted in approximately 75% of fetuses with DS. Therefore, if the scan is devoid of any of the above, a derived likelihood ratio would allow a patient’s chances of DS to be at least halved from their pre-ultrasound risk. A negative quad screen and a negative genetic sonogram result in a numerical risk for DS that is far below the risk of amniocentesis.

An isolated marker is seen in approximately 5% of normal fetuses and, with the possible exception of a positive NSFT, it should not appreciably raise the risk of DS, except in a patient with a high pretest risk.

A new “integrated” screening protocol has been developed, consisting of a first trimester ultrasound measurement of nuchal translucency, first trimester biochemistry, and a quad screen. This has a sensitivity for DS of over 90% in those over 34 years of age at a screen-positive rate of only 3.3%. The same concept should apply with a negative genetic sonogram in these patients.

SCREENING FOR TRISOMY 18

In this condition, the values for all biochemical markers generally are very low (below 0.5 MoM). For some reason, virtually all laboratories set a screen-positive rate for trisomy 18 at 0.5%, where the sensitivity for trisomy 18 is only 60%. Simply raising this to 2% will increase the sensitivity to above 85%.

Any patient found to be at risk for trisomy 18 by BCS would benefit appreciably from a genetic sonogram, because virtually 100% of fetuses with this condition will have at least one ultrasound clue. Whether or not to have an amniocentesis would depend upon the findings of the genetic sonogram.

BIOCHEMICAL SCREENING AND ADVERSE PREGNANCY OUTCOME

Elevated inhibin-A, MSAFP, and hCG have been associated with higher rates of pre-eclampsia, intrauterine growth restriction (IUGR), and preterm birth (PTB). Elevations of MSAFP have also been found in some patients with intrauterine demise. Elevations of any of the above analytes should prompt:

- 1 Careful attention to even modest elevations in maternal blood pressure
- 2 An ultrasound after 30 weeks' gestation to assess fetal growth (the rare MSAFP-associated fetal demise has almost always occurred in fetuses with IUGR)

At this time, the practice of scheduling weekly non-stress tests (NSTs) for these patients produces unnecessary concern in patients and is a time-wasting practice for patients with no signs of pre-eclampsia and a normally growing fetus.

There is new information suggesting that uterine artery waveform analysis may be useful in identifying or excluding patients with biochemical elevations who need further surveillance.

SUGGESTED READING

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Sonographic and first trimester detection of aneuploidy

Fergal D. Malone

INTRODUCTION

Fetal aneuploidy refers to an abnormal number of chromosomes, other than the usual diploid complement of 46 chromosomes. Presence of a single additional chromosome, known as trisomy, is an important cause of congenital malformations. The most common autosomal trisomies are Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and Patau syndrome (trisomy 13). Trisomy 21 is the most common of these chromosomal syndromes, and is one of the most important causes of congenital mental retardation, affecting approximately 1 in 800 to 1 in 900 live births. Trisomy 18 and trisomy 13 are considered lethal malformations, with 95% of trisomy 18 infants dying by 1 year of age, and almost all trisomy 13 infants dying by 3 months of age. The incidence of trisomies 18 and 13 is approximately 1 in 3000 live births and 1 in 5000 live births, respectively. Antenatal ultrasonography can be used to detect up to 80% of cases of trisomy 21, and 90–100% of cases of trisomies 18 and 13.

PATHOPHYSIOLOGY

The phenotype of trisomy 21 occurs when there is a triplication of genes at a particular part of chromosome number 21, known as band 21q22. Non-disjunction of the pair of number 21 chromosomes during egg or sperm meiosis accounts for 95% of cases of trisomy 21. In the vast majority of cases, the extra chromosome is maternal in origin, and there is a strong correlation between maternal age and the chances of fetal trisomy 21. In less than 5% of cases, the additional chromosome 21 material is a result of an unbalanced translocation, usually affecting chromosomes 14 and 21, but occasionally also involving chromosomes 15 or 22. Approximately 50% of such cases occur as *de novo* translocations and 50% are inherited from one parent who is a carrier of a balanced translocation. Rarer cases of trisomy 21 are mosaic, in which some cell lines carry three copies of chromosome number 21 while others are normal. Trisomies 18 and 13 are also caused by meiotic non-disjunction in

approximately 85% of cases, while 10% of cases are mosaic, and 5% result from a translocation.

DIAGNOSIS AND SCREENING PROTOCOL

Sonographic screening and diagnosis of autosomal trisomies is usually performed during antenatal care. Three options for screening for aneuploidy are now available: first trimester serum and sonographic screening, second trimester serum and sonographic screening, and combining different screens across both first and second trimesters.

First trimester screening

The ability to provide an accurate, patient-specific risk assessment for fetal trisomy 21 during the first trimester is potentially very attractive. This would allow patients the option of chorionic villus sampling (CVS) to confirm or exclude fetal aneuploidy, and the possibility of pregnancy termination, earlier in gestation. Techniques used to evaluate risk for trisomy 21 during the first trimester include nuchal translucency (NT) sonography, nasal bone sonography, Doppler sonography of the ductus venosus, as well as assay of the maternal serum markers-pregnancy-associated plasma protein A (PAPP-A) and either the free beta-subunit or the intact molecule of human chorionic gonadotropin (hCG). Additionally, first trimester cystic hygroma can also be used for trisomy 21 risk assessment, as it is the most powerful of all markers for fetal aneuploidy.

Nuchal translucency sonography

NT refers to the normal space that is visible between the spine and overlying skin at the back of the fetal neck during first trimester sonography (Figs 11.1 and 11.2). The larger this space, the higher the risk for trisomy 21, while the smaller the space the lower the risk for trisomy 21. Measurement of this NT space has been shown to be a powerful sonographic marker for trisomy 21, when obtained between 10 weeks and 3 days, and 13 weeks and 6 days' gestation. Table 11.1 describes the components of a standardized NT sonographic protocol.

NT sonography can be technically challenging to master initially, and requires considerable effort to maintain quality over time. Sonographers should be comfortable using both transabdominal and transvaginal approaches to NT sonography, as the latter approach may be required in up to 5% of cases. Additionally, in up to 7% of cases, adequate images of the NT space may not be obtainable, regardless of the sonographic approach. In such cases it may be reasonable to have the patient return in 1 week for remeasurement, provided she is still under 14 weeks' gestation or, alternatively, a risk assessment may be calculated based on serum assay results alone.

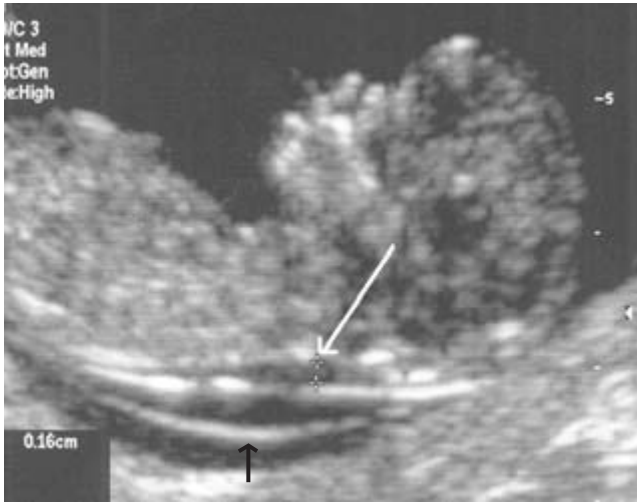


Fig. 11.1 Nuchal translucency (NT) ultrasound measurement at 13 weeks in a chromosomally normal fetus, measuring 1.6 mm. Various features of good NT ultrasound technique are evident in this image: adequate image magnification, mid-sagittal plane, neutral neck position, inner to inner caliper placement perpendicular to the fetal body axis (as indicated by white arrow), and separate visualization of the overlying fetal skin and amnion (black arrow). (From Malone and D'Alton, 2003.)



Fig. 11.2 Increased nuchal translucency measurement of 3.7 mm at 12 weeks in a fetus with Down syndrome. (From Malone and D'Alton, 2003.)

Table 11.1 Sonographic technique to optimize nuchal translucency (NT) sonography.

-
- 1 Nuchal translucency ultrasound should only be performed by sonographers or sonologists trained and experienced in the technique
 - 2 Transabdominal or transvaginal approach should be left to the sonographer's discretion, based on maternal body habitus, gestational age, and fetal position
 - 3 Gestation should be limited between 10 weeks 3 days and 13 weeks 6 days (approximate fetal crown–rump length 36–79 mm)
 - 4 Fetus should be examined in a mid-sagittal plane
 - 5 Fetal neck should be in a neutral position
 - 6 Fetal image should occupy at least 75% of the viewable screen
 - 7 Fetal movement should be awaited to distinguish between amnion and overlying fetal skin
 - 8 Calipers should be placed on the inner borders of the nuchal fold
 - 9 Calipers should be placed perpendicular to the long axis of the fetal body
 - 10 At least three nuchal translucency measurements should be obtained, with the mean value of those used in risk assessment and patient counseling
 - 11 At least 20 min may need to be dedicated to the nuchal translucency measurement before abandoning the effort as failed
 - 12 Nuchal translucency measurements for each sonographer should be monitored as part of an on-going quality assurance program to ensure optimal screening performance
-

In order to use an NT measurement to calculate a patient's risk for trisomy 21, a special software program is required to convert the raw millimeter measurement into a multiple of the median (MoM) value. Use of MoM values takes into account the normal gestational age variation in NT size, and allows integration of maternal age and serum results into the final risk assessment.

Nasal bone sonography

If a perfect mid-sagittal image can be obtained of the fetus at 10–13 weeks' gestation, with the fetal profile facing upwards, it may be possible to distinguish an echogenic line representing the fetal nasal bones (Fig. 11.3). It has been suggested that failure to visualize this echogenic line, suggesting absence of the fetal nasal bones, may be an independent marker for fetal trisomy 21. However, it should be noted that studies suggesting a role for this marker in the first trimester are derived from select high-risk populations, and more recent research has suggested that nasal bone evaluation may not be a useful tool for general population screening. At this time, first trimester evaluation of the fetal nasal bones for general population screening is not recommended.



Fig. 11.3 Nasal bone image of a euploid fetus at 13 weeks' gestation. Various features of good nasal bone technique are evident in this image: a good mid-sagittal plane, clear fetal profile, downward-facing spine, slight neck flexion, and two echogenic lines, representing the overlying fetal skin and the nasal bone. The white arrow represents the fetal nose bone, which loses its echogenicity distally. (From Malone and D'Alton, 2003.)

Ductus venosus Doppler sonography

Blood flow patterns in the fetal ductus venosus may be evaluated during the first trimester using Doppler ultrasound. Normally, this vessel shows a triphasic flow pattern, with forward flow reaching peaks during ventricular systole and early ventricular diastole. There should normally be forward flow even during the nadir, coinciding with the atrial contraction (Fig. 11.4). Absence or reversal of blood flow during the atrial contraction phase is considered abnormal, and has been suggested as an additional marker for trisomy 21 during the first trimester. However, to date there have been insufficient studies confirming the utility of first trimester ductus venosus flow assessment for population screening of trisomy 21.

PAPP-A and fetal beta-hCG

Maternal serum levels of PAPP-A are approximately 50% lower in trisomy 21 pregnancies compared with normal pregnancies at 10–13 weeks' gestation. By contrast, maternal serum levels of fetal beta-hCG are approximately twice as high in trisomy 21 pregnancies compared with normal pregnancies at this gestational age. When combined with maternal age, these two serum markers can be used to detect approximately 65% of cases of trisomy 21, for a 5% false-positive rate.

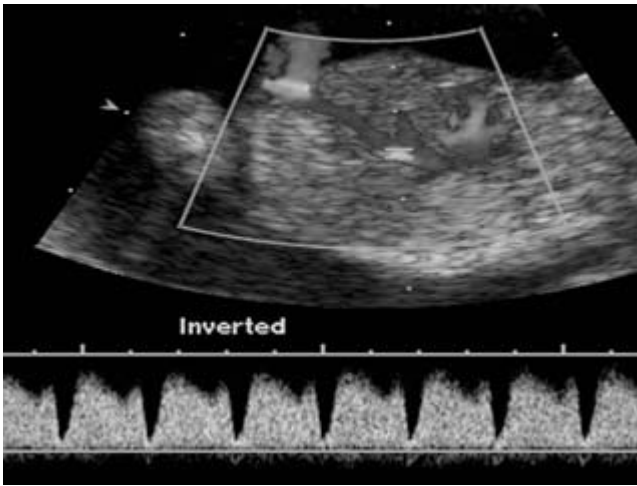


Fig. 11.4 Ductus venosus flow velocity waveform in a normal 13-week fetus. The Doppler gate is placed in the ductus venosus between the umbilical venous sinus and the inferior vena cava. Note that there is triphasic pulsatile flow with constant forward flow. The troughs of flow during the atrial contraction also demonstrate forward flow. (From Malone and D'Alton, 2003.)

Combined sonographic and serum screening

Because measurement of fetal NT is largely independent of maternal age and the serum markers PAPP-A and fetal beta-hCG, the most efficient method of first trimester screening for trisomy 21 involves a combination of these approaches. NT sonography, together with maternal age, PAPP-A and fetal beta-hCG will detect 85% of cases of trisomy 21, for a 5% false-positive rate, between 10–13 weeks' gestation. It is best to perform such combination screening earlier in the first trimester, as it has been shown to have trisomy 21 detection rates of 87% at 11 weeks', compared with 82% at 13 weeks' gestation, for a 5% false-positive rate.

Cystic hygroma

In approximately 1 in 300 first trimester pregnancies, during sonographic evaluation of the fetal nuchal translucency, the NT space will be found to be markedly enlarged, often extending along the entire length of the fetus, with septations clearly visible within the space. This condition is referred to as first trimester septated cystic hygroma and is the most powerful predictor of fetal aneuploidy yet described. In early gestation, this finding is associated with a 50% risk for fetal aneuploidy, with most being trisomy 21, and others including Turner syndrome, trisomy 18, trisomy 13, and triploidy. Of the 50% of such

pregnancies that are proven to have a normal fetal karyotype, almost half will be complicated by major structural fetal malformations, such as cardiac defects and skeletal anomalies. Less than 25% of all cases of first trimester septated cystic hygroma will result in a normal liveborn infant. Therefore, this finding should prompt immediate referral for CVS, and pregnancies found to be euploid should be evaluated carefully for other malformations.

Second trimester screening

The mainstay of risk assessment for fetal trisomy 21 for years has been second trimester serum and sonographic screening. Despite the growing popularity of first trimester methods of risk assessment, second trimester screening will remain necessary because many patients may not present for care sufficiently early to avail themselves of first trimester approaches, and also because many patients may be either wary of the safety of CVS or may not have access to a provider skilled in the performance of CVS. Techniques used to evaluate risk for trisomy 21 during the second trimester include sonographic detection of major structural fetal malformations, sonographic detection of minor markers, and maternal serum assay of alpha-fetoprotein (AFP), hCG, unconjugated estriol (uE3), and inhibin-A.

Sonographic detection of major malformations

The genetic sonogram is a term used to describe second trimester sonographic assessment of the fetus for signs of aneuploidy. The detection of certain major structural malformations that are known to be associated with aneuploidy should prompt an immediate consideration of genetic amniocentesis. Table 11.2 summarizes the major structural malformations that are associated with the most common trisomies. While the genetic sonogram can be performed at any time during the second and third trimesters, the optimal time is likely to be at 17–18 weeks' gestation, which is late enough to maximize fetal anatomic evaluation, yet early enough to allow for amniocentesis results to be obtained. When a major structural malformation is found, such as an atrioventricular canal defect or a double-bubble suggestive of duodenal atresia, the risk of trisomy 21 in that pregnancy can be increased by approximately 20- to 30-fold. For almost all patients, such an increase in their background risk for aneuploidy will be sufficiently high to justify immediate genetic amniocentesis.

Sonographic detection of minor markers

Second trimester sonography can also detect a range of minor markers for aneuploidy. The latter are not considered structural abnormalities of the fetus *per se* but, when noted, may be associated with an increased probability that the fetus is aneuploid. Table 11.2 also summarizes the minor sonographic markers that, when visualized, may increase the probability of an aneuploid

Table 11.2 Sonographic findings associated with trisomies 21, 18 and 13.

Trisomy 21	Trisomy 18	Trisomy 13
<i>Major structural malformations</i>		
Cardiac defects:	Cardiac defects:	Holoprosencephaly
AV canal defect	Double outlet right ventricle	Orofacial clefting
Ventricular septal defect	Ventricular septal defect	Cyclopia
Tetralogy of Fallot	AV canal defect	Proboscis
Duodenal atresia	Meningomyelocele	Omphalocele
Cystic hygroma	Agensis corpus callosum	Cardiac defects:
Hydrops	Omphalocele	Ventricular septal defect
	Diaphragmatic hernia	Hypoplastic left heart
	Esophageal atresia	Polydactyly
	Clubbed or rocker bottom feet	Clubbed or rocker bottom feet
	Renal abnormalities	Echogenic kidneys
	Orofacial clefting	Cystic hygroma
	Cystic hygroma	Hydrops
	Hydrops	
<i>Minor sonographic markers</i>		
Nuchal thickening	Nuchal thickening	Nuchal thickening
Mild ventriculomegaly	Mild ventriculomegaly	Mild ventriculomegaly
Short humerus or femur	Short humerus or femur	Echogenic bowel
Echogenic bowel	Echogenic bowel	Enlarged cisterna magna
Renal pyelectasis	Enlarged cisterna magna	Echogenic intracardiac focus
Echogenic intracardiac focus	Choroid plexus cysts	Single umbilical artery
Hypoplastic nasal bones	Micrognathia	Overlapping fingers
Brachycephaly	Strawberry-shaped head	Growth restriction
Clinodactyly	Clenched or overlapping fingers	
Sandal gap toe	Single umbilical artery	
Widened iliac angle	Growth restriction	
Growth restriction		

fetus. It should be noted that almost all data supporting the role of second trimester sonography for minor markers for aneuploidy are derived from high-risk populations, such as patients of advanced maternal age or with abnormal maternal serum screening results. It is still debatable whether the detection of such minor markers in lower risk patients from the general population is of any value.

Table 11.3 Likelihood ratios for trisomy 21 when an isolated minor sonographic marker is detected. The patient's a priori risk is multiplied by the appropriate positive likelihood ratio to yield an individualized post-test risk for fetal trisomy 21. (Adapted from Nyberg *et al.* 2001.)

Minor marker	Likelihood ratio	95% confidence intervals
Nuchal fold > 5 mm	11	6–22
Echogenic bowel	6.7	3–17
Short humerus	5.1	2–17
Short femur	1.5	0.8–3
Echogenic intracardiac focus	1.8	1–3
Pyelectasis	1.5	0.6–4
Any two minor markers	10	6.6–14
Any three or more minor markers	115	58–229
No markers	0.4	0.3–0.5

To counsel patients objectively following the prenatal diagnosis of a minor sonographic marker, likelihood ratios can be used to create a more precise risk assessment for the patient that their fetus might be affected with trisomy 21. Table 11.3 summarizes the likelihood ratios that can be used to modify a patient's risk for trisomy 21, depending on which minor marker is detected. If no markers are present, the patient's a priori risk can be multiplied by 0.4, effectively reducing their chances of carrying a fetus with trisomy 21 by 60%. The likelihood ratio values listed for each marker assume that the marker is an isolated finding. By contrast, when more than one minor marker is noted in the same fetus different likelihood ratios must be used, with the risk for trisomy 21 being increased by a factor of 10 when two minor markers are detected and by a factor of 115 when three or more minor markers are found. It should also be noted that the 95% confidence interval values for each marker's likelihood ratios are rather wide. These values should therefore be used only as a general guide for counseling patients, and care should be exercised to avoid implying too much precision in the final risk estimates. Accuracy of risk estimates, however, can be maximized by using the best available a priori risk value for a particular patient, such as the results of maternal serum marker screening, rather than maternal age, when available.

Nuchal fold

Sonographic measurement of the nuchal fold is performed by imaging the fetal head in an axial plane passing through the posterior fossa. Calipers should be placed on the outer aspect of the occipital bone and the outer aspect of the skin.

When measured between 15 and 21 weeks' gestation, a cut-off of 5 mm is commonly used to define an abnormally thickened nuchal fold. The finding of an isolated nuchal fold greater than 5 mm is associated with an 11-fold increase in background risk for trisomy 21.

Echogenic bowel

Sonographic visualization of bright bowel in the fetal abdomen is considered abnormal if the echogenicity is similar to that of fetal bone. A common pitfall with this minor marker is to overdiagnose the finding because of inappropriately high sonographic gain settings. When present, it is associated with a 6.7-fold increase in background risk for trisomy 21.

Humerus and femur length

The expected humerus and femur lengths can be estimated after a measurement of the fetal biparietal diameter (BPD) is obtained, and can be calculated using the formula $-7.9404 + 0.8492 \times \text{BPD}$ for the humerus, or $-9.645 + 0.9338 \times \text{BPD}$ for the femur. A ratio of observed to expected humerus or femur lengths less than 0.90 is considered abnormal. It is likely that separate norms will be needed to interpret long bone length in certain populations, as such biometry tends to be shorter amongst Asian fetuses. The isolated finding of a short humerus or a short femur is associated with a fivefold and a 1.5-fold increase in background risk for trisomy 21, respectively.

Echogenic intracardiac focus

Calcification of the papillary muscle in the intracardiac ventricles can be demonstrated by sonography as a discrete echogenic dot within the left or right ventricle. The majority of cases are present in the left ventricle, and care should be exercised in imaging the fetal heart from multiple angles to avoid overdiagnosis because of specular reflection. Additionally, echogenic intracardiac focus may be considered a normal variant in certain populations, being present in up to 30% of normal Asian fetuses. When an echogenic intracardiac focus is detected, the background risk for trisomy 21 can be increased by a factor of 1.8.

Pyelectasis

Sonographic measurement of the anteroposterior diameter of the renal pelves from 15 to 20 weeks' gestation should normally reveal a diameter of 3 mm or less. Bilateral pyelectasis, in which both renal pelves measure 4 mm or greater, is associated with a 1.5-fold increase in background risk for trisomy 21.

Nasal bones

Failure to visualize the nasal bone, on a perfect sagittal fetal profile during the second trimester, or visualization of hypoplastic nasal bones, has recently been

suggested as a powerful screening tool for trisomy 21. It is likely that this second trimester approach may not be as subjective as first trimester nasal bone evaluation. Very limited data exist to date assessing the strength of this association during the second trimester. It is possible that the absence or hypoplasia of nasal bones may increase the background risk for trisomy 21 by up to a factor of 8.

Choroid plexus cyst

Sonographic evaluation of the choroid plexus, using an axial view through the upper portion of the fetal head, can frequently reveal the presence of one or more discrete cysts. While debated extensively in the past, it does not appear that isolated choroid plexus cysts represent markers for trisomy 21, although they have been described as being associated with trisomy 18. It is possible that the detection of an isolated choroid plexus cyst might increase the background risk for trisomy 18 by a factor of 7. However, because the background risk for trisomy 18 is generally very low, it is unlikely that the finding of an isolated cyst in a low-risk patient is of any clinical significance. Additionally, it does not appear that the number, size, or evolution of choroid plexus cysts has any impact on trisomy 18 risk assessment.

AFP, hCG, uE3 and inhibin-A

Maternal serum levels of AFP and uE3 are both approximately 25% lower in pregnancies complicated by trisomy 21, compared with euploid pregnancies. By contrast, levels of hCG and inhibin-A are approximately twice as high in pregnancies complicated by trisomy 21. Maternal serum levels of AFP, uE3 and hCG tend to be decreased in pregnancies complicated by trisomy 18. The combination of AFP, uE3 and hCG, commonly known as the triple screen, can detect 70% of cases of trisomy 21, for a 5% false-positive rate. When inhibin-A is added to this test, commonly known as the quad screen, the trisomy 21 detection rate increases to 81%, for a 5% false-positive rate. Performance of serum screening tests can be maximized by accurate ascertainment of gestational age and, wherever possible, sonographic dating should be used instead of menstrual dating. It is optimal to provide serum screening between 15 and 16 weeks' gestation, thereby allowing the results to be available at the time of second trimester sonographic evaluation.

Combined first and second trimester screening

First trimester combination screening for trisomy 21, using NT, PAPP-A and fetal beta-hCG, has very similar performance characteristics to second trimester serum screening using AFP, hCG, uE3 and inhibin-A. In an effort to maximize the performance of both of these forms of risk assessment, it is possible to combine first and second trimester serum and sonographic screening

techniques. There are two approaches to combining different screening modalities across different gestational ages: integrated screening and stepwise screening.

Integrated screening

This form of risk assessment refers to a two-step screening protocol, with results not being released until all screening steps are completed. Sonographic measurement of NT, together with serum assay for PAPP-A, are obtained between 10 and 13 weeks' gestation, followed by a second serum assay for AFP, hCG, uE3 and inhibin-A obtained between 15 and 16 weeks' gestation. A single risk assessment is then calculated at 16 weeks' gestation. This "fully integrated" test has a trisomy 21 detection rate of 95%, for a 5% false-positive rate. A variant of this approach, referred to as the "serum integrated" test, involves blood tests only, including PAPP-A in the first trimester, followed by AFP, hCG, uE3, and inhibin-A in the second trimester. This latter test, which does not require an NT ultrasound assessment, has a trisomy 21 detection rate of 86%, for a 5% false-positive rate.

For some patients who are anxious to receive rapid screening results, or for those who might wish to avail themselves of a first trimester CVS, it is possible that such integrated screening tests might not be acceptable, as a delay inevitably exists between the time of first trimester screening measurements and release of results in the second trimester. However, for patients who may not be interested in, or have access to, first trimester CVS, the efficiency of being provided with a single trisomy 21 risk assessment result, which maximizes detection and minimizes false-positives, may make such integrated screening tests appear attractive.

Stepwise screening

In contrast to integrated screening, stepwise screening refers to multiple different trisomy 21 screening tests being performed, with risk estimates being provided to patients upon completion of each step. A key concept in performing stepwise screening is to ensure that each subsequent screening test that is performed should use the trisomy 21 risk from the preceding test as the new a priori risk for later screening. For example, if a patient with an age-related risk for trisomy 21 of 1 in 300, has a first trimester screening test resulting in a new trisomy 21 risk of 1 in 1000, it is better if a subsequent second trimester screening test uses the 1 in 1000 risk in its a priori risk calculation, rather than the original age-related risk of 1 in 300. If sequential screening tests are performed independently for trisomy 21, without any modification being made for earlier screening results, the positive predictive value of the later tests will inevitably deteriorate, and it is likely that the overall false-positive rate will increase.

A potential advantage of stepwise screening over integrated screening is that it allows patients in the first trimester to avail themselves of an immediate CVS, should their risk estimate justify this test, without having to wait until 16 weeks when the integrated screening results are provided. Patients could possibly get the benefit of early diagnosis associated with first trimester screening, as well as the higher detection rate for trisomy 21 associated with integration of both first and second trimester screening tests.

CONCLUSIONS

A wide range of screening tests for fetal aneuploidy, in particular trisomy 21, is now available in both the first and second trimesters. There is increasing integration of serum and sonographic screening tests across gestational ages, which will allow patients and providers access to a panel of risk assessment tools that can be tailored to suit individual patient's needs. Because of the huge array of available tests, and because of the potential for inefficient combinations of screening approaches, it would be ideal if all pregnant patients could be provided with formal pretest counseling to select the most appropriate risk assessment algorithm for their particular circumstances.

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Indices of maturity

Alessandro Ghidini and Anna Locatelli

INTRODUCTION

Surfactant is a complex substance containing phospholipids and apoproteins produced by type II alveolar cells. It reduces surface tension throughout the lung, contributing to its compliance, leading to alveolar stability, and reducing the likelihood of alveolar collapse. Neonatal respiratory distress syndrome (RDS) occurs when the lungs fail to produce an adequate amount of surfactant. RDS affects approximately 1% of live births and complications of its treatment are associated with an increased risk of serious acute and long-term pulmonary and non-pulmonary morbidities. Although the frequency and severity of RDS are worse for delivery remote from term, the pulmonary system is the last organ system to mature, and RDS can occur even near term. Indications for assessment of fetal pulmonary maturity include:

- preterm labor (as tocolysis is generally contraindicated in the presence of mature fetal lungs)
- iatrogenic preterm delivery
- need to plan delivery at term in the presence of unsure dates or obstetric complications affecting lung maturity

Several invasive and non-invasive tests are available to establish fetal lung maturity. Although all share a small rate of falsely mature results, they have different degrees of falsely immature rates and different costs.

INVASIVE TESTS

Given the outward flow of pulmonary secretions from the lungs into the amniotic fluid (AF), several tests can directly determine fetal pulmonary maturity from AF samples measuring the concentration of particular components of pulmonary surfactant or the surface-active effects of these phospholipids. (see Table 12.1)

Lecithin:sphingomyelin ratio

The lecithin:sphingomyelin (L:S) ratio for assessment of fetal pulmonary maturity was first introduced by Gluck *et al.* in 1971.¹ The concentrations of

Table 12.1 Accuracy and characteristics of available fetal lung maturity tests in non-diabetic women.

Test	Technique	Threshold	Predictive value mature test (%)	Predictive value immature test (%)	Difficulty/cost
L/S ratio	Thin-layer chromatography	2/1	95–100	33–50	High/high
PG	Thin-layer chromatography	Present	95–100	23–53	High/high
	Slide agglutination	Positive (>2%)			Low/low
Surfactant/albumin ratio	Fluorescence polarization	≥55 mg/g	96–100	47–61	Low/moderate
LB count	Cell counter	30,000–40,000/μL	97–98	29–35	Low/low
Amniotic fluid density at 650 nm	Spectrophotometric reading	OD ≥15	98	13	Low/low
FSI	Ethanol dilution	≥47	95	51	Moderate/moderate

these two substances are approximately equal until the middle of the third trimester of gestation, when the concentration of pulmonary lecithin increases significantly while the non-pulmonary sphingomyelin concentration remains unchanged. The measurement of sphingomyelin serves as a constant comparison for control of the relative increases in lecithin because the volume of AF cannot be measured reliably. Determination of the L:S ratio involves thin-layer chromatography after centrifugation to remove the cellular component and organic solvent extraction. The test requires time and expertise to perform and interpret. An L:S ratio of 2.0 or greater predicts the absence of RDS in 98% of neonates. With a ratio of 1.5 : 1.9, approximately 50% of infants will develop RDS. Below 1.5, the risk of subsequent RDS increases to 73%. Thus, the L:S ratio, like most indices of fetal pulmonary maturation, rarely errs when predicting fetal pulmonary maturity, but many neonates with an immature L:S ratio will not develop RDS.

A threshold value for prediction of lung maturity should be calculated in individual institutions by correlation with clinical outcome, as the variation within and between laboratories can be considerable. The sample should be kept on ice or refrigerated if transport to a laboratory is required. Improper

storage conditions can change the L : S ratio because AF contains enzymes that can be affected by temperature. Maternal serum has a L : S ratio ranging from 1.3 to 1.9; thus, blood-tinged samples could falsely lower a mature result but should not increase an immature result to a mature value. The presence of meconium can interfere with test interpretation increasing the L : S ratio by 0.1–0.5, thus leading to an increase in falsely mature results.

Phosphatidylglycerol

Phosphatidylglycerol (PG) is a minor constituent of surfactant which becomes evident in AF several weeks after the rise in lecithin.² Its presence indicates a more advanced state of fetal lung development and function, as PG enhances the spread of phospholipids on the alveoli. The original PG testing was performed by thin-layer chromatography and required time and expertise. More recently, enzymatic assay or slide agglutinations have been used successfully to determine the presence of PG. The results are typically reported qualitatively as positive or negative, where positive represents an exceedingly low risk of RDS. When reported in a quantitative fashion, a value of 0.3 is associated with negligible risk of respiratory distress. The test is usually immature when performed before 36 weeks' gestation. PG determination is not generally affected by blood, meconium, or vaginal secretion.

Surfactant: albumin ratio

The fluorescence polarization assay uses polarized light to evaluate the competitive binding of a probe to both albumin and surfactant in amniotic fluid.³ It provides a quantitative and automated measurement of the amniotic fluid surfactant : albumin ratio by the TDx-FLM analyzer and its subsequent modification, TDx-FLM II. The test is simple, rapid, objective, reproducible, and can be performed with equipment commonly available in clinical laboratories. It is independent of the AF volume. An elevated ratio is correlated with the presence of fetal lung maturity. A TDx-FLM value above 50–70 has similar predictive ability of pulmonary maturity as a positive PG test or L : S of 2 or greater. More recently, a surfactant : albumin ratio of 55 has been proposed as a better threshold to indicate maturity.⁴ A disadvantage of the TDx-FLM method is the large quantification scale. Values greater than 55 are regarded as mature; however, values of 35–55 are considered "borderline." There is controversy as to whether gestational age should be used in interpreting the TDx for determining the likelihood of RDS. In general, higher threshold values are needed at earlier gestational ages to determine lung maturity and lower thresholds are required at later gestational ages. Blood and meconium contamination can interfere with test interpretation. As for L : S ratio, red blood cell phospholipids may falsely lower the TDx-FLM result, but a mature test can reliably predict pulmonary maturity.

Lamellar body counts

Lamellar bodies (LB) are produced by type II pneumocytes and are a direct measurement of surfactant production because they represent its storage form. In 1989, Dubin⁵ described a method for quantifying lamellar bodies with a commercial blood cell analyzer that takes advantage of the similar size between lamellar bodies and platelets. The results can be obtained quickly, with a small fluid volume, and the test is less expensive than traditional phospholipid analysis. Moreover, the platelet counter is accessible in most hospitals, available 24-h, and requires no special training. Although initial studies employed centrifugation, it is now agreed that the sample should be processed without spinning as centrifugation reduces the number of LB. Values of 30,000–40,000/ μL generally indicate pulmonary maturity.⁶ The test compares favorably with L : S and PG, with a negative predictive value of a mature cut-off of 97.7% versus 96.8% and 94.7%, respectively.⁷ A meta-analysis calculated receiver-operating characteristic curves based upon data from six studies and showed the LB count performed slightly better than the L:S ratio in predicting RDS.⁸ Meconium has a marginal impact on LB counts, increasing the count by 5000/ μL . Bloody fluid can initially slightly increase the count because the platelets are counted as LB. Afterwards the procoagulant activity of AF produces an entrapment of both platelets and LB, causing a decrease of LB counts.

Amniotic fluid density

An indirect measurement of pulmonary maturity can be performed by measuring the optical density of amniotic fluid at a wavelength of 650 nm. It is based upon the concept that increasing opalescence is caused by increasing numbers of fetal squamous cells and LB, which are dependent on the total amniotic fluid phospholipid concentration rather than directly reflect it. An optical density of 0.15 or greater correlates well with a mature L:S ratio and the absence of RDS.⁵ Different authors report that a visual assessment of AF turbidity correctly classifies 87% of samples collected for assessment of fetal lung maturity by optical density, L:S, and PG, and has a 92% positive and a 87% negative predictive value for a mature TDx-FLM result.

Foam stability index

The foam stability index (FSI) is a simple and rapid predictor of fetal lung maturity based upon the ability of surfactant to generate stable foam in the presence of ethanol. After centrifugation ethanol is added to a sample of AF to eliminate the contributions of protein, bile salts, and salts of free fatty acids. The mixture is shaken for 30 s and demonstrates generation of a stable ring of foam if surfactant is present in the AF.

The FSI is calculated by utilizing serial dilutions of ethanol to quantitate the amount of surfactant present.

RDS is very unlikely with an FSI value of 47 or higher.

A positive result virtually excludes the risk of RDS; however, a negative test often occurs in the presence of mature lung. AF samples should not be collected in silicone tubes as the silicone will produce “false foam.” Contamination of the AF specimen by blood or meconium interferes with the FSI result.

Multiple tests or cascade?

Faced with different assays for fetal lung maturity, some laboratories perform multiple tests simultaneously, leaving the clinician with the possibility of results both indicative and not of pulmonary maturity from the same AF specimen. In general, any “mature” test result is indicative of fetal pulmonic maturity given the high predictive value of any single test (5% or less of false-mature rates). Conversely, the use of a “cascade” approach has been proposed to minimize the risk of delivery of an infant with immature lungs, while avoiding unnecessary delay in delivery and costs. According to this approach, a rapid, easy to perform, and inexpensive test is carried out first (e.g. LB count or FSI), with follow-up tests (e.g. L:S ratio or PG) performed only in the face of an immature result. However, a recent study showed that L:S ratio does not add any significant information to that already provided by LB count and PG.⁶

Special conditions

Several maternal/fetal clinical or non-clinical circumstances can affect the risk of RDS and modify the predictive value of pulmonary maturity tests:

- *African American race*: lung maturity is achieved at lower gestational ages and at lower L:S ratios (1.2 or greater) than in white people
- *Female gender*: associated with acceleration of lung maturation
- *Intrauterine growth restriction and pre-eclampsia*: associated with an acceleration of fetal lung maturity
- *Maternal diabetes and Rh-isoimmunization*: associated with a delay in fetal lung maturation. Some authors have recommended the use of higher thresholds of L:S ratio (e.g. a cut-off ratio of 3) to establish pulmonic maturity in these conditions. Presence of a lamellar body count $\geq 50,000/\mu\text{L}$ has similarly been recommended to indicate mature fetal lungs in diabetic women.⁹ Presence of PG is commonly considered as gold standard for documentation of fetal lung maturity with diabetes or Rh-isoimmunization. Despite initial suggestion that higher cut-offs be required also for TDx-FLM, it is currently felt that the cut-off needs not be adjusted for the presence of these pathologies.

For the above reasons, in twin gestations it is commonly recommended that the sac of the male twin or the larger twin be sampled at amniocentesis. The reasoning is that if the sampled twin has mature pulmonic results, the other twin is even more likely to be mature.

NON-INVASIVE TESTS

Amniocentesis performed under ultrasonographic guidance in experienced hands is associated with low rates of failure or of bloody fluid collection, and less than 1% risk complication, such as emergent delivery.¹⁰ The assessment of fetal pulmonary maturity can be obtained from vaginal pool specimens in presence of premature rupture of membranes. Blood, meconium, and mucus can alter the results. In the absence of these contaminants, vaginally free-flowing collected fluid can be evaluated for determination of L:S ratio, PG, and LBC, yielding results similar to those observed with samples obtained by amniocentesis.

None of the proposed ultrasonographic indicators of fetal maturity are specifically predictive of pulmonic maturity. The proposed parameters are in general predictive of gestational age.

INDICATIONS FOR ASSESSING PULMONARY MATURITY AND ROLE OF GESTATIONAL AGE

The American College of Obstetricians and Gynecologists has recommended that fetal pulmonary maturity should be confirmed before elective delivery at less than 39 weeks' gestation unless fetal maturity can be deduced from any of the following criteria:¹¹

- Fetal heart tones have been documented for 20 weeks' gestation by non-electronic fetoscope or for 30 weeks by Doppler
- Thirty-six weeks have elapsed since a serum or urine human chorionic gonadotropin-based pregnancy test was reported to be positive
- Ultrasound measurement of the crown-rump length at 6–11 weeks' gestation or other ultrasound measurements (e.g. biparietal diameter, femur length) at 12–20 weeks' gestation support a clinically determined gestational age ≥ 39 weeks.

Fetal lung maturity assessment in non-elective delivery is more controversial. Pretest probability of RDS is highly dependent on gestational age. After 37 weeks' gestation the risk of respiratory distress syndrome is very low, thus testing is not indicated if prolonging pregnancy will place the mother or fetus at significant risk. Prior to 32–34 weeks, the prevalence of neonatal morbidity is sufficiently high that knowledge of fetal lung maturity does not substantially modify obstetric management. Between 32 and 36 weeks' gestation, fetal pulmonary maturity assessment is most useful in managing pregnancies with the above indications for delivery.¹²

CONCLUSIONS

Several methods can be used to establish fetal lung maturity by testing for components of fetal lung secretions in amniotic fluid (Table 12.1). Fetal pulmonary maturity should be viewed as a probability that is a function of gestational age,

amniotic fluid analysis, and clinical maternal/fetal conditions. Most methods have similar diagnostic indices, and the predictive value of a mature test ranges from 95% to 100%. On the contrary, the risk of RDS for an immature test varies from 5 to 100%, depending on gestational age and result of the test.¹³ The choice and the sequence of tests should be based upon availability, presence or absence of contaminants, and physician and laboratory personnel preference.

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Clinical use of Doppler

Henry L. Galan

INTRODUCTION

Doppler depends upon the ability of an ultrasound beam to be changed in frequency when encountering a moving object such as red blood cells (RBC). The change in frequency (Doppler shift) between the emitted beam and the reflected beam is proportional to the velocity of the RBC and dependent on the angle between the ultrasound beam and the vessel. Pulsed wave Doppler velocimetry provides a flow velocity waveform from which information can be obtained to determine three basic aspects of blood flow that are useful in obstetrics: velocity, resistance indices, and volume blood flow. Doppler velocimetry is primarily useful for diagnostic fetal echocardiography and antenatal surveillance of three high-risk obstetric conditions:

- 1 intrauterine growth restriction (IUGR)
- 2 rhesus alloimmunization (isoimmunization)
- 3 preterm labor (tocolysis with indometacin)

PATHOPHYSIOLOGY

Normal fetal circulation

The umbilical vein brings oxygen and nutrient-rich blood to the fetus. The umbilical vein enters the umbilicus and travels anteriorly along the abdominal wall diving into the liver becoming the hepatic portion of the umbilical vein. The umbilical vein then becomes the portal vein and gives off branches in the following order throughout the portal sinus starting with the left inferior and superior portal vein, the ductus venosus, and the right portal vein. The ductus venosus carries approximately 50% of the blood that comes through the umbilical vein to an area under the diaphragm that is referred to as the subdiaphragmatic vestibulum. In the subdiaphragmatic vestibulum, blood coming back from the liver via the right, middle, and left hepatic veins and the inferior vena cava joins that of the ductus venosus and the process of preferential streaming is initiated. Blood from the ductus venosus and the left and middle hepatic veins are preferentially shunted across the foramen ovale into the left atrium and left ventricle so that the heart and the head receive the most oxy-

genated and nutrient-rich blood. Blood coming from the inferior vena cava and the right hepatic vein are preferentially shunted into the right atrium and right ventricle and then out of the pulmonary artery and shunted across the ductus arteriosus which then delivers this blood to the descending aorta. Blood leaving the fetus does so via two umbilical arteries arising from the hypogastric arteries. The umbilical arteries course around the lateral aspects of the bladder anteriorly and cephalad exiting the umbilicus returning back to the placenta.

There are three primary shunts in the fetus that require closure after delivery in order for the normal postnatal circulation and subsequent adult circulation to take place. The ductus venosus shunts blood from the hepatic portion of the umbilical vein and portal sinus towards the heart. The ductus arteriosus shunts blood from the main pulmonary artery to the descending aorta, thus taking approximately 90% of the blood from the main pulmonary artery to the systemic circulation, and leaving only 10% of the blood to travel through the fetal lungs. The third shunt is the foramen ovale which is maintained in a patent state *in utero* to allow the process of preferential streaming to occur from the right atrium to the left atrium. Failure of any one of these shunts to close properly may result in adverse cardiopulmonary transition in the newborn.

Intrauterine growth restriction

Fetuses that fail to reach their genetically determined growth potential because of uteroplacental dysfunction may develop abnormal resistance to blood flow in the placenta. This abnormal resistance is caused by numerous placental vascular abnormalities (poor villous capillarization, reduced number and branching of stem arteries, luminal reduction and wall hypertrophy) and can be detected with Doppler velocimetry in the umbilical artery located upstream from the placenta. Progression of placental disease with concomitant worsening of blood flow resistance may lead to additional Doppler velocimetry changes in the precordial venous system or in the heart. Once the fetus decompensates to that level, acidemia is nearly always present.

Rh alloimmunization

In Rh disease, a fetal RBC antigen enters the maternal blood stream and stimulates antibody production against that RBC antigen. An amnestic response may occur in a subsequent pregnancy if the same antigen is present on the fetal RBC, which may lead to a series of events that include fetal anemia, extramedullary hematopoiesis, hydrops fetalis, and fetal death. Historically, the degree of fetal anemia and need for RBC transfusion to the fetus involved an amniocentesis to determine the amniotic fluid ΔOD_{450} to assess the degree of RBC-derived hemoglobin breakdown products and to estimate the extent of fetal anemia. If moderate to severe anemia is suspected, the fetus should undergo a fetal blood sampling and transfusion if the hematocrit is $<30\%$.

Preterm labor

Although the pathophysiology of preterm labor is still largely unknown, tocolytic use is widespread. Use of agents that inhibit prostaglandin synthesis can result in premature closure of the ductus arteriosus and oligohydramnios. Doppler velocimetry is useful in these circumstances.

Cardiac abnormalities

Fetuses with known cardiac abnormalities including congenital or structural heart disease, arrhythmias, and congestive failure may have intracardiac and outflow tract flow velocity abnormalities that can be detected with Doppler velocimetry. Depending on the nature of the abnormality, this can affect other flow velocity waveforms including those of the ductus venosus, hepatic veins, inferior vena cava, and the umbilical vein.

DIAGNOSIS

Doppler techniques and measurements

Pulsed wave Doppler velocimetry can be used to obtain the following basic information from a flow velocity waveform:

- 1 *Velocity of the blood*: requires that the angle of insonation is 0° between the transducer and the vessel of interest (Fig. 13.1)
- 2 *Resistance indices* (S:D ratio, resistance index, pulsatility index): these are angle-independent measurements such that the value obtained for any one of these indices is not dependent upon the angle between the transducer and the vessel being interrogated (Fig. 13.2)

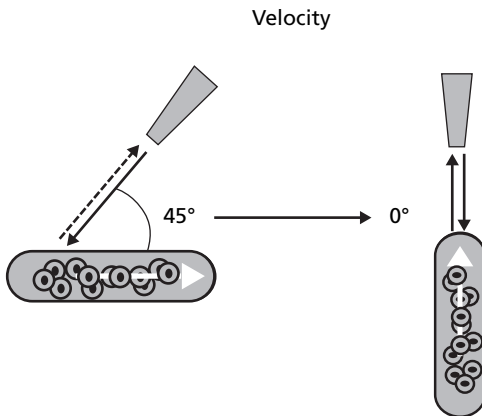


Fig. 13.1 Schematic representing 0° angle of insonation between the Doppler transducer and the vessel of interest.

- 3 **Volume blood flow** (milliliters per minute); this is obtained by obtaining the velocity of the blood and multiplying it by the cross-sectional area of the vessel (obtained by two-dimensional ultrasound) $\times 60$ s (Fig. 13.3)

Cardiac flow velocities

Normal values and blood flow velocity patterns have been previously reported for cardiac Doppler velocities. More specifically, blood flow velocity values and patterns have been described for the pulmonary and aortic outflow tracts, ductus arteriosus, ductus venosus, tricuspid and mitral valves, and the inferior vena cava. Any fetal structural cardiac abnormality or precordial or postcor-dial vascular abnormality can affect the blood flow velocity and waveform of the aforementioned vessels and valves. Further discussion of detailed fetal echocardiography is beyond the scope of this chapter.

Intrauterine growth restriction

The blood flow velocity waveform obtained by pulsed wave Doppler velocimetry changes throughout gestation. There is a progressive increase in diastolic flow velocity across gestation which reflects a decrease in the resistance within the placenta. Depending on the definition used, IUGR of placental etiology can affect up to 10% of all pregnancies. A characteristic of IUGR is an increase in

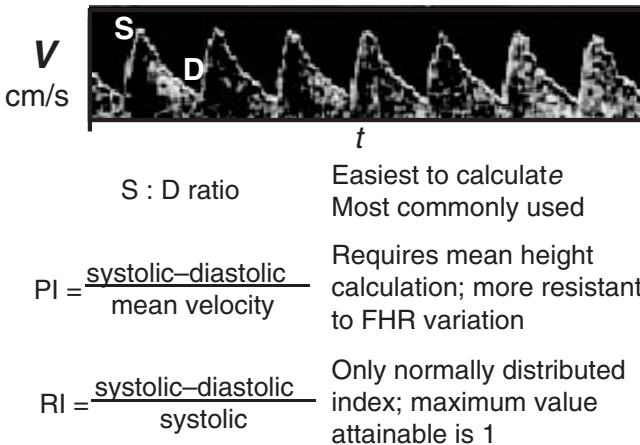


Fig. 13.2 Flow velocity waveform of the umbilical artery and definitions for the different Doppler indices of resistance. FHR, fetal heart rate.

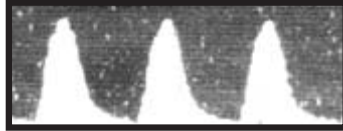
$$\text{Volume flow (mL/min)} = \text{velocity (cm/s)} \times \text{cross-sectional area (cm}^2\text{)} \times 60 \text{ s}$$

Fig. 13.3 Equation for calculation of volume blood flow.

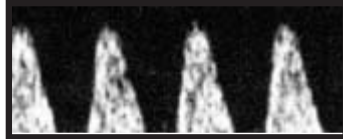
Normal



Abnormal
High resistance



Abnormal
Absent EDF



Abnormal
Reverse EDF

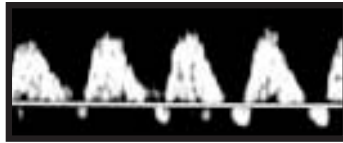


Fig. 13.4 Normal and abnormal flow velocity waveforms in the umbilical artery. EDF, end-diastolic flow.

blood flow resistance within the placenta. This increase in blood flow resistance can be detected in the upstream umbilical arteries with Doppler velocimetry. If the placental disease progresses, the increase in placental resistance can be sensed across the cardiac structures and into the venous (precordial) circulation such that the flow velocity waveforms within the inferior vena cava, the ductus venosus, and the hepatic veins become abnormal.

Umbilical artery Doppler velocimetry was first introduced into clinical use in the late 1980s and subsequently approved by the American College of Obstetricians and Gynecologists as an adjunct to antenatal testing for the management of IUGR. The use of umbilical artery Doppler velocimetry reduces mortality by approximately one-third when used in surveillance of the growth-restricted fetus. Figure 13.4 shows a normal flow velocity waveform in the umbilical artery and then several abnormal flow velocity waveforms. Reverse end diastolic flow in the umbilical artery is associated with obliteration of more than 70% of the placental arteries. Absent or reverse end diastolic flow is also associated with a high rate (more than 60–70%) of fetal hypoxia and acidemia. If the disease process worsens in IUGR, flow velocity waveforms in the precordial aspects of the fetus can become abnormal. More specifically, the flow velocity waveform in the inferior vena cava, ductus venosus, and hepatic veins can become abnormal showing increased resistance and possibly reversal of blood

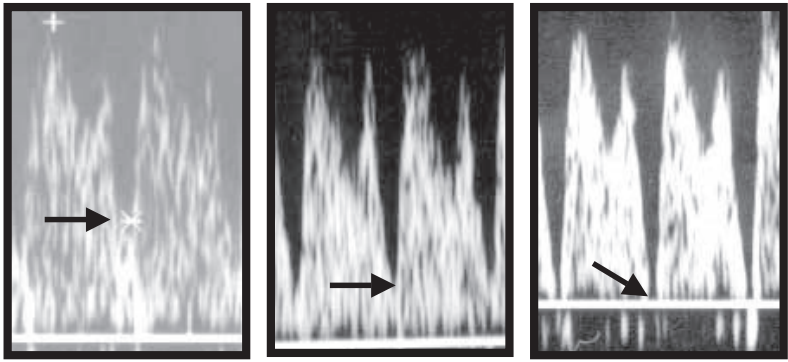


Fig. 13.5 Ductus venosus flow velocity waveform deterioration from normal to abnormal as indicated by a decrease in flow at the atrial kick (arrow).

flow. If the disease process worsens further, abnormalities may become apparent in the umbilical vein flow velocity waveform. Studies published in 2001 and 2002 showed that the decompensating fetus will proceed to have flow velocity waveform abnormalities in a sequential fashion across different fetal vessels in approximately 50–70% of cases. When flow velocity waveforms are assessed in the decompensating fetus, the first vessels to show abnormalities are the umbilical artery and the middle cerebral artery. The umbilical artery abnormality first noted is an increase in resistance such as an increase in the S:D ratio. Abnormalities in the middle cerebral artery show a decrease in resistance which represents an effort on the part of the fetus to spare its brain by increasing the delivery of blood. Abnormalities then typically proceed in the following sequence: absent end diastolic in the umbilical vein, an increase in resistance in the ductus venosus, reverse flow in the umbilical artery, and abnormalities in the outflow tracts of the heart. Figure 13.5 shows normal and abnormal flow velocity waveforms in the ductus venosus. Additional information regarding management of IUGR can be found in Chapter 69.

Rh sensitization

Fetal anemia resulting from Rh sensitization is detected by amniocentesis and assessment of $\Delta OD450$ and then confirmed by fetal blood sampling. One of the resultant pathophysiology features present in Rh disease is a reduction in the viscosity of the fetal blood. The decrease in viscosity results in an increase in the velocity of blood flow which can be detected by pulsed wave Doppler velocimetry. One of the vessels branching off the circle of Willis is the middle cerebral artery (MCA). The MCA is first identified with the use of color flow Doppler. With an angle of insonation of 0° , pulsed wave Doppler velocimetry is used to obtain the flow velocity waveform. From the flow velocity waveform,

one can place the calipers on serial peaks of the systolic component, and from this a mean systolic peak velocity of the MCA flow waveform can be determined. Nomograms are available for peak systolic velocity and the MCA across gestation. When the MCA peak systolic velocity rises above 1.55 multiples of the median (MoM), there is a high risk of moderate to severe anemia in the fetus. The cut-off of 1.55 MoM has a sensitivity of 100% and a negative predictive value of 100% for moderate to severe anemia. Once this value is surpassed, the fetus should undergo blood sampling to determine the actual fetal hematocrit and from that one can determine if a transfusion is necessary. Using Doppler to assess peak systolic velocity of the MCA and identifying anemia in the fetus in this fashion avoids the invasive procedure risks of amniocentesis.

MANAGEMENT

Congenital heart disease and arrhythmia

A number of clinical scenarios may warrant fetal echocardiography (Table 13.1). The ideal time to obtain a fetal echocardiogram is between 18 and 22 weeks' gestation. Counseling of the patient with a congenital heart defect is largely dependent on a variety of factors including karyotypic status of the fetus, religious disposition of the patient, and the presence of extracardiac abnormalities. Management of a patient with congenital heart disease should involve a collaborative team approach involving the perinatologist, pediatric cardiologist, neonatologist, and pediatric surgeon.

Fetal arrhythmias are typically first detected by routine fetal heart rate Doppler assessment in a prenatal clinic visit or by external electronic fetal monitoring. Further identification of the specific type of arrhythmia requires the use of M-mode cardiography and full assessment of cardiac structure and flow velocities.

Table 13.1 Indications for fetal echocardiography.

Family history of congenital heart disease
Maternal diabetes
Drug exposure
Teratogenic exposure
Other fetal abnormalities
Chromosomal abnormalities
Rhythm abnormalities
Non-immune hydrops
Maternal phenylketonuria

Intrauterine growth restriction

Once the fetus has been diagnosed by ultrasound to be growth restricted, a full assessment of the fetus should be performed to exclude fetal anomalies, possible karyotypic abnormalities, and congenital infection. Particular attention should be paid to the symmetrically growth-restricted fetus to exclude karyotype abnormalities and congenital infection. In cases where these additional abnormalities have been excluded, treatment should consist of placing the patient on modified bed rest, increasing fluid intake, and avoiding tobacco use.

Surveillance of the growth-restricted fetus includes the use of fetal activity count, serial assessment of fetal growth with ultrasound (every 2–3 weeks), non-stress testing and/or biophysical profile, and Doppler velocimetry. Figure 13.6 shows an algorithm as a guideline for the management of the IUGR fetus

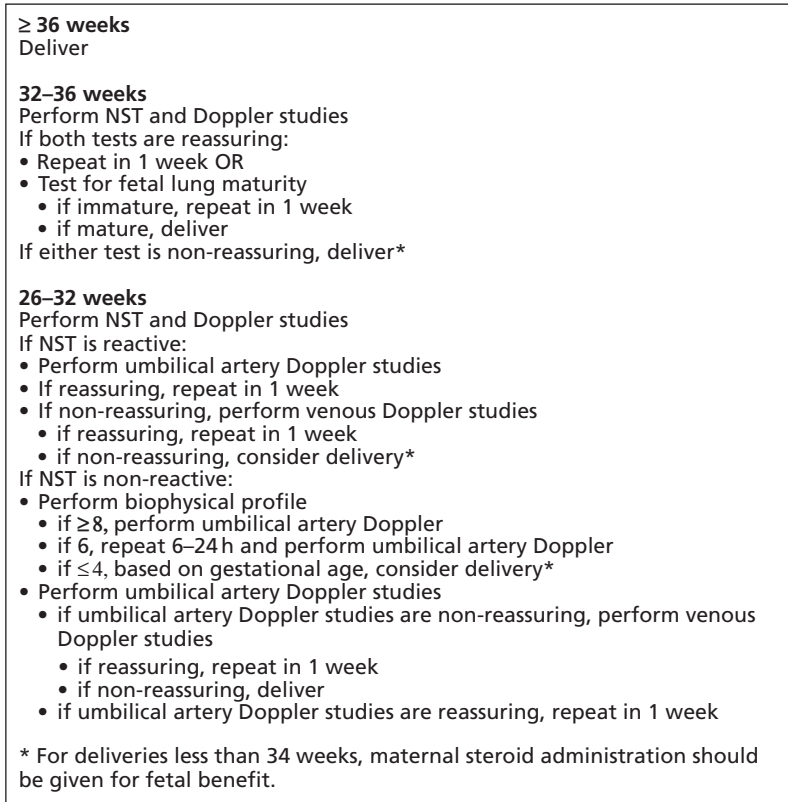


Fig. 13.6 Algorithm for the management of intrauterine growth restriction (IUGR).

based on the gestational age of the fetus. The presence of oligohydramnios warrants further additional work-up, particularly because this may be a sign of compromise in the growth-restricted fetus. Oligohydramnios may represent underperfusion of the kidneys with subsequent decrease in urine output and thus cardiovascular compromise of the fetus. Nevertheless, management of oligohydramnios should include a brief hospitalization to rule out other etiologies for oligohydramnios such as preterm premature rupture of the membranes, maternal dehydration, or pre-eclampsia. The patient should be hydrated in the hospital. Delivery should be considered if the fetus is beyond 32 weeks' gestation, after administration of betamethasone or dexamethasone for fetal benefit and after consultation with neonatology.

Rh sensitization

The management of Rh sensitization is first initiated after diagnosis of the disease, routine blood typing, and Rh and antibody screen. When the antibody screen shows the presence of an antibody that places the fetus at risk for fetal anemia, the patient should undergo serial screening with antibody titers. Once a critical threshold has been met by a specific titer of that antibody, the patient must undergo evaluation for fetal anemia. Most hospital laboratories use either a 1 : 16 or 1 : 32 cut-off and it is critical that each practitioner knows what that threshold should be for each hospital. Once the critical threshold has been reached, the patient needs to undergo either:

- 1** an amniocentesis for assessment of $\Delta OD450$ in the amniotic fluid, or
- 2** middle cerebral artery peak systolic velocity assessment using pulsed wave Doppler velocimetry.

If the latter is available, it should receive priority simply because it avoids the risk associated with an amniocentesis. If an amniocentesis is performed and $\Delta OD450$ is in the high zone 2 or zone 3 of the Liley curve, then that fetus must undergo fetal blood sampling for documentation of the anemia and transfusion. Alternatively, if the middle cerebral artery peak systolic velocity is used to assess fetal anemia, a 1.55 MoM should be used as a threshold to move towards fetal blood sampling and transfusion. Delivery of the anemic fetus receiving blood transfusion can be accomplished between 36 and 37 weeks' gestation with documentation of fetal lung maturity. If fetal blood sampling is performed at a very preterm gestation (<34 weeks), administration of betamethasone or dexamethasone should be considered.

Preterm labor

Use of medications such as indomethacin or ibuprofen for tocolysis inhibits prostaglandin synthase inhibitors, thus reducing the production of prostaglandins which may affect the ductus arteriosus. A ductus arteriosus effect is not typically seen within the first 48 h of treatment. Assessment of the

velocity within the ductus arteriosus should be performed beyond that time if the patient continues on a prostaglandin synthase inhibitor. Should constriction develop, the tocolytic agent should be discontinued.

CONCLUSIONS

Color and pulsed wave Doppler velocimetry is a useful component of ultrasound evaluation of the fetus with Rh disease, growth restriction, congenital heart disease, or fetal arrhythmias. While Doppler ultrasound has been used in other fetal conditions, no study has demonstrated any clear clinical benefit for its use outside those stated above. The use of umbilical artery Doppler velocimetry as adjunct to antepartum testing reduces mortality. The use of Doppler velocimetry to interrogate blood flow in the precordial vein of the fetus may assist the practitioner in delivering the very preterm fetus prior to end organ injury; studies evaluating this are in progress.

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Fetal echocardiography

Joshua A. Copel and Charles S. Kleinman

INTRODUCTION

Congenital heart disease occurs in approximately 8 of 1000 live births. Of these, approximately half are relatively minor ventricular septal defects or valve stenoses that are of little hemodynamic significance, and probably are undetectable prenatally. The remainder are significant lesions that may benefit from prenatal detection, parental counseling, and obstetric–pediatric planning for delivery and neonatal care.

PATHOPHYSIOLOGY

Most types of congenital heart disease are thought to be inherited in a multifactorial fashion, with both genetic and environmental contributions. The indications used for fetal echocardiography, a prenatal ultrasound technique that can detect most significant congenital heart disease, reflect that. Most patients referred for fetal echocardiography have had prior affected children, and the recurrence risk for these families is approximately 2–3%.

The pathophysiology of congenital cardiac anomalies varies with the type of anatomic abnormality that is present. The underlying mechanisms include failures of cell migration, leading to failure of a structure to form, or diminished flow, inhibiting the normal growth of a downstream structure (e.g. poor flow across the foramen ovale and mitral valve predisposing to a coarctation of the aorta).

STRUCTURAL HEART DISEASE

Diagnosis and work-up

In patients without risk factors for congenital heart disease, full fetal echocardiography, which is generally more time-consuming and expensive than general obstetric sonography, is not indicated unless cardiac anomalies are suspected. Many risk factors for congenital heart disease have been described (Table 14.1).

Table 14.1 Indications for fetal echocardiography.

Familial risk factors

History of congenital heart disease
 Previous sibling
 Paternal

Mendelian syndromes that include congenital heart disease

Noonan
 Tuberous sclerosis

Maternal risk factors

Congenital heart disease
 Cardiac teratogen exposure
 Lithium carbonate
 Alcohol
 Phenytoin
 Valproic acid
 Trimethadione
 Carbamazepine
 Isotretinoin
 Maternal metabolic disorders
 Diabetes mellitus
 Phenylketonuria

Fetal risk factors

Extracardiac anomalies
 Chromosomal
 Anatomic
 Fetal cardiac arrhythmia
 Irregular rhythm
 Tachycardia (>200b/min) in absence of chorioamnionitis
 Fixed bradycardia
 Non-immune hydrops fetalis
 Lack of reassuring four chamber view during basic obstetric scan

The four-chamber view of the heart has been suggested as an easy way of screening for congenital heart disease, although its sensitivity to significant cardiac anomalies has varied in the literature. Approximately one-third of cases of major heart disease are detected according to a review of the world's literature on screening prenatal ultrasound.¹ Our own experience suggests that it

Table 14.2 Standard fetal echocardiographic views and what to see.

Four chamber

Situs: check fetal position and stomach

Axis of heart to the left

Intact interventricular septum

Atria approximately equal sizes

Ventricles approximately equal sizes

Free movement of mitral and tricuspid valves

Foramen ovale flap (atrial septum primum) visible in left atrium

Long-axis left ventricle

Intact interventricular septum

Continuity of the ascending aorta with mitral valve posteriorly

Interventricular septum anteriorly

Short axis of great vessels

Vessel exiting the anterior (right) ventricle bifurcates, confirming it is the pulmonary artery

Aortic arch

Vessel exiting the posterior (left) ventricle arches and has three head vessels, confirming it is the aorta

Pulmonary artery–ductus arteriosus

Continuity of the ductus arteriosus with the descending aorta

has a very high positive predictive value, with at least half of patients referred for abnormal four-chamber views actually having cardiac anomalies.

Full fetal echocardiography includes obtaining all of the views in the fetus routinely obtained in postnatal echocardiography (Table 14.2). Additionally, spectral and color Doppler, and M-mode data, can be obtained as indicated. The two-dimensional examination should be sufficient to exclude significant heart disease in the vast majority of affected individuals. The more sophisticated studies are especially useful in cases of suspected structural or functional abnormalities.

MANAGEMENT

When a cardiac anomaly is found, a full, detailed fetal scan to detect any other anomalies is mandatory. Many fetal syndromes include cardiac anomalies, and accurate counseling requires complete enumeration of associated anomalies. A fetal karyotype should be sought, as chromosome anomalies are seen in a

large segment of fetuses with congenital heart disease. In our experience at Yale, 28% of fetuses with congenital heart disease and an extracardiac anomaly were aneuploid, and 15% of those with congenital heart disease and no identifiable extracardiac anomaly were also chromosomally abnormal.

Overall survival once a cardiac lesion is found depends on the nature of the cardiac problem, the presence of extracardiac anomalies, the karyotype, and the presence of fetal hydrops. Fetal hydrops in association with structural heart disease is virtually universally fatal. Aneuploid fetuses may have dismal prognoses even in the absence of heart disease, and a finding such as trisomy 18 may make repairing even a straightforward ventricular septal defect inadvisable.

Lesions that can be repaired in a biventricular heart carry a better long-term prognosis than those that result in a univentricular heart. Several groups have now reported that infants who are known to have congenital heart disease prenatally do better than those whose cardiac defects are only found after birth.²⁻⁴

FETAL ARRHYTHMIAS

Diagnosis and management

The largest group of fetal arrhythmias are intermittent and caused by atrial, junctional, or ventricular extrasystoles. They carry a small risk of coexistent structural abnormality. A greater risk exists of an unrecognized tachyarrhythmia, or the development of a tachyarrhythmia later in gestation. Atrial extrasystoles predispose the fetus to development of re-entrant atrial tachycardia, which can lead to fetal hydrops. Weekly auscultation of the fetal heart along with avoidance of caffeine or other sympathomimetics is suggested until resolution of the arrhythmia.

Fetal tachycardias represent a management challenge, because determination of the precise electrophysiologic cause of the arrhythmia is essential to any rational management strategy, but fetal electrocardiography is not yet feasible in the presence of intact membranes. The differential diagnoses of fetal tachycardias include re-entrant atrial tachycardia, atrial flutter, and ventricular tachycardia. The treatment of these disorders differs significantly, and appropriate medications for one may be contraindicated for another. The treatment of these disorders differs significantly, and appropriate medications for one may be contraindicated in another. There is marked variation in first-line treatment based on cardiologists preferences. For example, even digitalis, the old first-line treatment for re-entrant tachycardia is contraindicated if there is Wolff-Parkinson-White syndrome, which cannot be diagnosed prenatally. Thus management is best determined in conjunction with local pediatric electrophysiology experts, and should be regionalized at centers of expertise. The correct diagnosis, which should be based on combinations of M-mode, Doppler, and color Doppler-M-mode imaging, is essential to appropriate therapy.

If there is a fetal bradycardia the first step is to determine if there is a regular or an irregular atrial rate. If the atrial rate is regular and slow, that is below 100b/min, there may be sinus bradycardia, which should prompt a complete evaluation of fetal well being. The most common clinically important fetal bradycardia results from complete heart block, which will demonstrate a normal atrial rate with a slower ventricular rate whose beats do not occur in conjunction with atrial beats. This is usually caused by maternal antibodies associated with lupus erythematosus and Sjögren syndrome, termed SSA/ro and SSB/la. A smaller group of patients, without maternal antibodies, may present with congenital complete heart block in a setting of complex congenital heart disease involving the central fibrous body of the heart (e.g. left atrial isomerism, corrected transposition of the great arteries). In these patients the prognosis is directly related to the complexity of the heart disease and the association with congestive heart failure. A more benign cause of fetal bradycardia, which may be mistaken for 2:1 heart block, is blocked atrial bigeminy. In such cases the atrial rate is not regular, but rather demonstrates paired beating in which a premature atrial beat follows closely after a normal atrial beat with no ventricular response to the premature beat. This arrhythmia has no significance beyond that of isolated atrial extrasystoles.

Follow-up

The fetus with congenital heart disease should be carefully followed by ultrasound up to delivery. Structural lesions may evolve prenatally even as they do postnatally.⁵ It is particularly important to evaluate areas of potential obstruction, and the relationships of the great arteries to the ventricles. Fetuses with significant arrhythmias (including re-entrant tachycardias, atrial flutter, and complete heart block) should also be followed at a center with experience in the prenatal medical management of fetal arrhythmias, by a team that includes perinatologists, pediatric cardiologists, and adult electrophysiologists. Delivery need not be by cesarean section except in the presence of selected fetal arrhythmias that do not permit adequate fetal heart rate monitoring. For fetuses with lesions that are expected to render the neonate dependent on ductus arteriosus patency for systemic or pulmonary perfusion, prostaglandin E₁ should be available in the nursery at the time of delivery to keep the ductus open.

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Fetal biophysical profile

Michael P. Nageotte

INTRODUCTION

The fetal biophysical profile (BPP) is an important method of antepartum fetal surveillance. The BPP score is a composite of four acute or short-term variables: fetal tone, movement, breathing, and non-stress test; and one chronic or long-term variable: amniotic fluid volume.

PHYSIOLOGY

All five parameters of the BPP are regulated by the fetal central nervous system (CNS). The fetal CNS is highly sensitive to the level of oxygenation, and therefore these biophysical variables are directly influenced by the state of oxygenation of the fetus.¹

The four short-term variables respond to fetal hypoxemia in a predictable fashion. The BPP that appears earliest in the fetal life is the last to disappear with onset of fetal asphyxia. In early intrauterine development, the fetal tone center appears in the cortex, and begins to function at 7–8 weeks followed by fetal movements at 9 weeks' gestation. Fetal breathing becomes regular at 20–21 weeks, whereas fetal heart rate reactivity is controlled by the hypothalamus and medulla, and appears late in the second trimester. As an immediate response to hypoxemia, the fetus decreases its activity to conserve energy and minimize oxygen consumption. This leads to a decrease in fetal movements, which directly correlates with fetal heart rate accelerations. In the presence of progressive hypoxemia, clinical studies have confirmed that reactivity in the non-stress test (NST) and fetal breathing movements are the first biophysical variables to disappear, followed by cessation of fetal movements, and lastly a lack of fetal tone.^{2,3}

Fetal urine production is the predominant source of amniotic fluid volume and is directly dependent upon renal perfusion. In response to sustained fetal hypoxemia, there is a long-term adaptive response mediated by chemoreceptors located in the aortic arch and carotid arteries. This results in 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 non-essential organs (lung, kidney) by means of peripheral vasoconstriction. In cases of prolonged or repetitive episodes of fetal hypoxemia, there is a persistent decrease in blood flow to the lungs and kidneys resulting in a reduction in the amniotic fluid production leading to oligohydramnios. Amniotic fluid volume therefore is a reflection of chronic fetal condition. On average, it takes approximately 13 days to progress from normal to abnormal fetal amniotic fluid volume.⁴

PERFORMING AND INTERPRETING THE BIOPHYSICAL PROFILE

The NST is first performed within 20–30 min with the patient in semi-Fowler position. This is followed by the sonographic evaluation of fetal biophysical activities including fetal tone, movement, and breathing. Amniotic fluid volume is measured by holding the transducer perpendicular to the floor. The largest vertical pocket is selected and should at least be 1 cm in diameter. The composite of all four quadrants' deepest vertical pockets is termed as the amniotic fluid index (AFI). A total of 30 min is assigned for obtaining ultrasound variables. A normal variable is assigned a score of 2 and an abnormal variable a score of 0 (Table 15.1).

A composite score of 8 or 10 is considered normal and correlates with the absence of fetal acidemia. A score of 6 is equivocal, and the test should be repeated in 24 h, except in cases of oligohydramnios with intact membranes. In this particular instance, either delivery or close fetal surveillance is indicated,

Table 15.1 Fetal biophysical profile. (Modified from Manning *et al.* 1980.¹)

Biophysical variable	Normal (score = 2)	Abnormal (score = 0)
Non-stress test	Reactive: ≥ 2 accelerations of ≥ 15 b/min for >15 s in 20 min	Non-reactive: < 2 accelerations of ≥ 15 b/min for ≥ 15 s in 20 min
Fetal breathing movements	≥ 1 episode of ≥ 30 s in 30 min	Absence or < 30 s in 30 min
Gross body movements	≥ 3 discrete body/limb movements in 30 min	≤ 2 discrete body/limb movements in 30 min
Fetal tone	≥ 1 active extension/flexion of limb, trunk, or hand	Slow or absent fetal extension/flexion
Amniotic fluid volume	≥ 1 pocket of fluid ≥ 2 cm in two perpendicular planes	No pocket > 1 cm in two perpendicular planes

depending on the gestational age. BPP scores of 4, 2 or 0 indicate fetal compromise and delivery should be strongly considered.

BPP score correlates well with fetal acid–base balance. A direct relationship has been shown between the BPP score and fetal blood pH obtained either with antepartum cordocentesis⁵ or cord gases at elective cesarean section in non-laboring patients.⁶ A normal BPP score virtually rules out the possibility of fetal acidemia being present at the time of testing.

A normal BPP result is highly reassuring, with a stillbirth rate of 0.8 per 1000 within 1 week of the test.⁷ In other words, the BPP has a false-negative rate of 0.7–2.3 per 1000 tested patients. The positive predictive value of BPP for evidence of fetal compromise (non-reassuring fetal heart rate tracing in labor, acidemia, etc.) is approximately 50%, and a negative predictive value of 99.9%. A BPP score of 6 has a false-positive rate of 75% and a score of 0 virtually always identifies fetal compromise.⁸ Fetal death rates are increased 14-fold in the absence of fetal movements, and 18-fold if fetal breathing movements are absent. Vibroacoustic stimulation (VAS) has been shown to improve BPP score in more than 80% cases without increasing false-positive rate, and may reduce the likelihood of unnecessary obstetric intervention.⁹ Consequently, use of VAS is commonly utilized during BPP testing.

INDICATIONS

American College of Obstetricians and Gynecologists recommends testing in the following situations:¹⁰

- Women with high-risk factors for fetal asphyxia and stillbirth should undergo antepartum fetal surveillance:
 - *Maternal conditions:* antiphospholipid syndrome, hyperthyroidism, hemoglobinopathies, cyanotic heart disease, systemic lupus erythematosus, chronic renal disease, diabetes mellitus, hypertensive disorders
 - *Pregnancy-related conditions:* pregnancy-induced hypertension, decreased fetal movements, oligohydramnios, polyhydramnios, intrauterine growth restriction, post-term pregnancy, isoimmunization, previous fetal demise, multiple gestation
- Testing may be initiated at 32–34 weeks for most patients. However, it may begin as early as 26 weeks' gestation in pregnancies with multiple risk factors, when fetal compromise is suspected
- A reassuring test should be repeated on a weekly or a twice weekly basis
- Test should be repeated in the event of significant deterioration in the clinical status regardless of the time elapsed since the last test
- Severe oligohydramnios (no vertical pocket of more than 2 cm) requires either delivery or close maternal and fetal surveillance

BPP can either be used as a primary test for fetal well being in high-risk conditions or, more commonly, as back-up test for a non-reactive NST. In the pres-

ence of a reactive NST, BPP parameters do not aid in the assessment of the fetal status, and therefore BPP should be used as a back-up test only for patients with a non-reactive or equivocal NST.

DRAWBACKS

BPP, unless videotaped, cannot be reviewed later and may take a longer period of time to perform if the fetus is in a quiet sleep state.

MODIFIED BIOPHYSICAL PROFILE

Modified BPP is a simplified version of the BPP aimed at reducing the time needed to obtain all five parameters of a conventional BPP. It takes into consideration the two most important predictors of fetal well being: NST and amniotic fluid volume. Assessment of NST and amniotic fluid volume appears to be as reliable as the BPP in predicting long-term fetal well being.¹¹ The rate of still-birth within 1 week of a normal modified BPP is the same as the BPP (0.8 per 1000). As modified BPP significantly cuts down on the number of BPPs performed, full BPP can be reserved for non-reassuring or equivocal NSTs only.¹²

CLINICAL IMPORTANCE

BPP is a non-invasive, easily performed test of fetal well being that is highly accurate in detecting fetal hypoxemia. Fetal hypoxemia is a cause of fetal compromise, and assessment of BPP can reliably predict the presence and severity of fetal hypoxemia or acidosis. There is an inverse relationship between the last BPP score before delivery and adverse long-term outcomes: cerebral palsy, mental retardation, cortical blindness, deafness, and learning disabilities. The use of BPP may not only provide reassurance in a setting of a non-reactive NST, but may also serve as a means to decrease fetal morbidity and mortality by timely intervention.

CONCLUSIONS

Fetal BPP can be used as a primary surveillance test or as a back-up for non-reassuring NST, and is an accurate method of excluding fetal acidemia. A BPP score of 8 is considered normal, 6 equivocal, and less than 6 abnormal. Intervention is indicated in a fetus with a BPP score of 4 or less.

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PART 3

*Special
procedures*

Chorionic villus sampling

Ronald J. Wapner

INTRODUCTION

Prenatal diagnosis continues to be an important part of obstetric practice. Currently, over 15% of pregnancies are at sufficient genetic risk to warrant invasive testing. The majority of these procedures are indicated for either advanced maternal age (14% of pregnant women are 35 years or older) or for women having positive serum screening results (5%). Other indications include:

- 1 pregnancies at risk for Mendelian disorders identified through either a previous affected child or population screening
- 2 the birth of a previous child with a chromosome abnormality
- 3 a parent with a balanced chromosome rearrangement

Until approximately 1980, second trimester amniocentesis was the predominant prenatal diagnostic procedure. More recently, first trimester ultrasound-guided aspiration biopsy of the developing chorion frondosum (chorionic villus sampling [CVS]) has been developed. The retrieved chorionic villi are then either cultured or directly analyzed to identify fetal cytogenetic, biochemical, or molecular disorders. This earlier testing provides genetic information at a time in gestation when reproductive decision-making is more private and safe.

TECHNIQUES

Either a transcervical or transabdominal approach to CVS can be used. In the hands of operators skilled in both they are equally safe, with the choice for any patient based on placental location, ease of sampling, and operator or patient preference. Over 95% of patients can be sampled using either approach, but one approach is clearly preferable to the other in approximately 5% of cases.

Transcervical chorionic villus sampling

The patient is placed in the lithotomy position, a speculum inserted, and the vagina prepped with a povidine-iodine solution. The bladder should be partially

filled to allow adequate visualization of the cervix and uterus. Overfilling will displace the uterus and make sampling more difficult. A specially designed polyethylene catheter, placed over a malleable stainless steel stylet having a blunt rounded tip is used for sampling. The most frequently used catheter has a 5.7 French diameter and is 27 cm long. Prior to insertion, the distal 3–4 cm of the catheter is gently curved to facilitate passage through the cervix.

The sonographer visualizes the cervix and chorion frondosum simultaneously. The operator then inserts the catheter tip into the cervix until it reaches the internal os. Ultrasound monitoring continues, as the catheter is advanced into the chorion frondosum parallel to the chorionic membrane. Care must be taken that the catheter does not perforate the membrane but remains within the appropriate tissue plane of the frondosum. Penetration into the underlying decidua basalis will cause bleeding and also must be avoided. While continuous imaging of the catheter tip is imperative, tactile sensation is equally necessary. Little to no resistance is encountered when the tip is passed in the appropriate plane. Conversely, the underlying decidua has a gritty sensation. The catheter is inserted through a sufficient portion of the chorion frondosum to allow an adequate sample size. Once appropriately placed, the stylet is removed, a 20-mL syringe containing 5 mL of tissue culture media is attached and suction applied as the catheter is slowly withdrawn.

Transabdominal chorionic villus sampling

With the transabdominal approach used most commonly, a 20-gauge spinal needle is inserted into the chorion frondosum. Once in place, a 20-mL syringe containing 5 mL of media is attached and the tip is passed through the body of the frondosum remaining parallel to the chorionic membrane. Three to five “to and through” aspirations through as much of the frondosum as possible will usually retrieve sufficient tissue.

Some operators prefer a two-needle technique in which a thin-walled 18-gauge spinal needle is inserted through the maternal abdominal wall just into the myometrium. Once in place, the stylet is removed and replaced with a 20-gauge needle which is used for the villus aspiration. This approach has the advantage of allowing repetitive insertions of the aspiration needle without the need for multiple maternal sticks. However, with experience, the single-needle approach can aspirate sufficient tissue with one insertion in over 90% of cases.

Timing of procedure

Procedures are usually performed between 10 0/7 and 13 6/7 weeks' gestation. For reasons discussed later, they should almost never be performed prior to the 10th week of gestation. Successful and safe transabdominal procedures can be performed throughout the second and third trimester if a rapid karyotype is needed or severe oligohydramnios is present.

Pre- and postprocedure care

Procedures are preceded by genetic counseling to identify additional genetic risks and to appropriately inform the patient of the procedural and genetic risks present. A negative cervical culture for gonococcus is suggested prior to the procedure but testing for other organisms such as chlamydia and group B streptococcus is unnecessary. Because CVS routinely results in a small fetal to maternal bleed, maternal blood type and a recent antibody screen should be available. Rhesus negative women should receive postprocedure RhoGAM (Rh-immune globulin). Existing blood group sensitization is a contraindication to CVS because postprocedure elevations in antibody titers have been described.

No specific postprocedure care is required but patients should be made aware of the risk of postprocedure bleeding and spotting. Patients should report any leakage of amniotic fluid, fever, chills, or malaise occurring within 2 weeks of the procedure.

COMPLICATIONS AND RISKS OF CHORIONIC VILLUS SAMPLING

The most frequent complication of CVS is spotting or a small amount of vaginal bleeding. This is usually limited in nature and not associated with an increased risk of pregnancy loss. This occurs following approximately 7–10% of transcervical procedures and 1% or fewer of those performed transabdominally.

Other more serious complications include acute rupture of the membranes, leakage of fluid, and chorioamnionitis. Each of these complications is rare and occurs in less than 1 in 1000 procedures. Rupture of membranes can be avoided by continuous ultrasound observation of the tip of the sampling instrument. Chorioamnionitis can occur after transcervical or transabdominal sampling from either accidental passage of the transabdominal needle through the maternal bowel or inadvertent transmission of vaginal organisms into the uterus. The rarity of post-CVS chorioamnionitis makes preprocedure vaginal culture or the use of prophylactic antibiotics unnecessary.

Pregnancy loss

In experienced centers, the rate of miscarriage from the time of CVS until 28 weeks' gestation is approximately 2.5%. The majority of these are background losses and overstate the rate of procedure-induced losses. The best information available for patient counseling are prospective studies comparing CVS with second trimester amniocentesis in which patients are assigned to a procedure sufficiently early in the pregnancy to account for the discrepancy in background losses between the first and second trimester. Such studies have been performed in Canada, USA, UK, and Denmark and have demonstrated no statistically increased procedure-induced loss rate with CVS. When compared with amniocentesis performed prior to 14 weeks' gestation, post-CVS loss rates and

rates of leakage of amniotic fluid were less. A single, multicentered, European study revealed a 4.6% greater post-CVS loss rate compared with second trimester amniocentesis (95% confidence interval [CI], 1.6–7.5%). The discrepancy between this study and the others appears to be related to the inexperience of the European physicians in performing the relatively new procedure of CVS. Studies comparing transcervical with transabdominal CVS have revealed, in general, equal safety. However, occasional studies have demonstrated a slightly higher risk with transcervical CVS. In most experienced centers, patients are counseled that the procedure-induced miscarriage rates for CVS and second trimester amniocentesis are equivalent and in the range of 1 in 200 to 1 in 300.

Procedure-induced fetal malformations

There is substantial evidence to suggest that CVS performed less than 63 days post-LMP (last menstrual period) may increase the frequency of fetal limb reduction defects. Oromandibular limb hypogenesis has been uniquely described following early CVS as have other severe reduction defects. The mechanism most frequently suggested is fetal vascular hypoperfusion/reperfusion injury. When procedures are performed after 63 days, no increased risk of any type of limb or other defects has been confirmed. Therefore, to assure fetal safety, procedures should be delayed until 70 or more days post-LMP.

TISSUE ANALYSIS

The collection of adequate tissue can usually be confirmed through direct visualization of the villi within the sampling syringe. The villi appear as white, fluffy, branching tissue with a frond-like appearance which can easily be differentiated from the amorphous-appearing decidua. On occasion, direct observation is inadequate to confirm a sufficient volume of villi (usually 10 mg or more) and the use of a dissecting microscope will be necessary. If insufficient tissue is obtained on the initial pass, a second insertion can be performed without additional risk. More than two insertions is associated with an increased risk of miscarriage, but may, in rare cases, be necessary.

Chorionic villi are composed of multiple tissue components. The outer budding cells are cytotrophoblast, which surround a mesenchymal core. Within the mesenchymal core are fetal blood vessels containing fetal blood cells. Because of the spontaneous mitosis occurring in the cytotrophoblast, villi can be analyzed almost immediately as opposed to analysis of the mesenchymal core which requires tissue culture. While this “rapid prep” can be performed as quickly as 2 h, most laboratories now carry out a 24–48 h preparation. Mesenchymal core culturing is usually available between 5 and 10 days. Any results from the rapid prep should be considered preliminary because discrepancies between these and the culture have been reported. In these

situations, the culture results are considered the more reliable, but follow-up amniocentesis may be required for final resolution.

Preparation for certain biochemical or molecular diagnosis can be complicated. Because of this, the laboratory performing the analysis should be contacted prior to sampling to discuss any specific alterations of tissue handling. In general, there is sufficient DNA in a CVS sample for almost all routine DNA analyses.

Reliability of results

CVS results reflect those of the fetus in approximately 98% of cases. Discrepancies can rarely occur from contamination of the sample with maternal decidua cells. While this has occurred previously, the larger samples now retrieved by experienced operators and the greater sophistication of the laboratory personnel currently make this cause of potential error negligible. The more common cause of discrepancy is “confined placental mosaicism” (CPM) in which an abnormal cell line is found along with a euploid line despite a fetus with a normal karyotype.

CPM can only be assumed once true fetal mosaicism has been excluded. Although 1% of CVS samples are mosaic, the abnormal cell line is only confirmed in the fetus 10–40% of the time. In cases of placental mosaicism, amniocentesis is required to elucidate the extent of the abnormal cell line. While a normal amniocentesis significantly reduces the risk of fetal involvement and offers reassurance, false-negative results have occurred.

CPM can also serve as the initial clue to the presence of uniparental disomy with the potential for significant phenotypical consequences. For this reason, CPM for known imprinted chromosomes such as 15 (Prader–Willi syndrome), 7 (Russell–Silver syndrome), or 14 requires further investigation to confirm biparental inheritance.

When an abnormal cell line is identified in the placenta, the potential for an adverse pregnancy outcome is also increased. Ten to 20% of cases of CPM will have either perinatal loss, preterm birth, intrauterine growth restriction, or miscarriage. The specific chromosome involved, the tissue source (cytotrophoblast or mesenchymal core), and the percentage of abnormal cells determine the impact of the aneuploid cell line. Currently, no specific management improves the outcome.

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Genetic amniocentesis

Katharine D. Wenstrom

INDICATIONS

Antenatal diagnosis of genetic disorders is one of the major advances in perinatology. Many genetic conditions can be diagnosed by amniotic fluid studies. The following are indications for genetic amniocentesis:

- Maternal age of 35 years or older at the time of delivery with a singleton pregnancy
- Maternal age of 33 years or older at the time of delivery with a twin pregnancy
- Parent or previous child with chromosomal abnormality
- Both parents carriers for a recessive disorder diagnosable by amniotic fluid analysis
- Parent with an autosomal dominant disorder diagnosable by amniotic fluid analysis
- Mother a carrier for an X-linked recessive disorder diagnosable by amniotic fluid analysis
- Parent or previous child with a neural tube defect
- Elevated maternal serum alpha-fetoprotein
- Multiple marker screening test indicating increased risk of Down syndrome or trisomy 18
- Ultrasound examination of fetus identifying a major structural malformation or two or more minor dysmorphisms

TIMING

The ideal time for genetic amniocentesis is 14–20 weeks' gestation. At 14 weeks, the amniotic fluid volume is high enough to make the procedure easy to perform, and it continues to increase with each successive week of gestation. Performing the procedure before 18–20 weeks usually leaves enough time to complete cell cultures and evaluate laboratory tests before it is too late to consider pregnancy termination should an abnormality be detected. Technically, the procedure can be performed before 14 weeks. However, early

amniocentesis, performed between 11 and 13 $\frac{6}{7}$ weeks, has been associated with a higher pregnancy loss rate than the traditional procedure, as well as an increased incidence of positional foot deformities. Some reports have also suggested an increased incidence of neonatal respiratory distress after early amniocentesis.

TECHNIQUES TO IMPROVE SAFETY

The use of ultrasound guidance makes amniocentesis a safer procedure. It decreases the number of dry taps and thus the need for additional needle insertions, and decreases the incidence of bloody taps. Whenever possible, amniocentesis should be performed without putting the needle through the placenta. However, during early pregnancy the placenta may cover as much as two-thirds of the uterine wall, making it difficult to obtain amniotic fluid without traversing placental tissue. Using a 22-gauge needle reduces placental trauma in cases in which the placenta must be punctured in order to obtain a fluid sample. Operator experience also plays a major part in both the success and the safety of amniocentesis; as the number of procedures performed by the operator increases, the number of unsuccessful taps, repeated needle insertions, and procedure-related morbidity and pregnancy loss reduces. The pregnancy loss rate after a second trimester amniocentesis is usually quoted as approximately 1 in 200 to 1 in 300; however, data from a recent large multicenter trial of Down syndrome screening (the FASTER trial) indicate that in experienced hands, the procedure-related loss rate is closer to 1 in 1000.

AMNIOCENTESIS PROCEDURE

Before starting the procedure, make sure the following sterile items are ready for use:

- Betadine® (povidone-iodine) solution and sterile 4 × 4 gauze sponges, *or*
- A sterile package of three Betadine-soaked sponge sticks
- A fenestrated drape (optional)
- A sterile ultrasound transducer sleeve or a large sterile glove
- Sterile ultrasound gel
- A 5-mL syringe containing 1% lidocaine without epinephrine (optional)
- A 3 $\frac{1}{2}$ -inch, 22-gauge spinal needle with stylet
- One 5-mL and two 10-mL (or one 20-mL) disposable syringes
- Two sterile 15-mL plastic centrifuge tubes for fluid transport
- If this is a multiple gestation, plan to use a separate sterile needle for each sac, assemble extra syringes and transport tubes, and prepare one 10-mL syringe containing 1 mL indigo carmine diluted in 9 mL sterile saline for each sac except the last)

As a preliminary step, use ultrasound scanning to:

- Document the number of fetuses and their viability.

- Document gestational age by measuring the fetal biparietal diameter, head circumference, abdominal circumference, and femur length.
- If not already carried out, perform an anatomic survey of each fetus.
- Assess placental location and amniotic fluid volume.
- Ideally, locate a tapsite away from both fetus and placenta. If there is no such site, locate an area where fluid can be obtained by traversing the thinnest portion of placenta possible.

When the ideal tapsite has been identified, proceed as follows:

- Prep the abdomen three times with Betadine solution.
- Drape the abdomen (optional).
- Infiltrate the skin with a local anesthetic (optional). Most operators do not use a local anesthetic because it is generally ineffective (it numbs only the skin, and the uterus is the source of procedure-related pain) and its use increases the number of needle insertions.
- Put a sterile sleeve (or a sterile glove) over the ultrasound transducer so that it can be used to guide needle insertion.
- Apply sterile ultrasound gel.
- Activate the biopsy guide function programmed into most ultrasound machines; the biopsy guide indicates on the ultrasound screen the path the needle will take, and thus improves insertion accuracy. Alternatively, after locating an ideal spot for needle insertion, insert a finger under the transducer and push down on the uterus while watching the screen; this will establish where the needle will enter the uterus.
- Alert the patient that there will be a needle stick.
- Insert the needle briskly under ultrasound guidance.
- Remove the stylet.
- Observe for a drop of amniotic fluid or attach a syringe and aspirate; if no fluid appears, rotate the needle 90° and try again. Occasionally, the needle pushes the membranes ahead of it (tenting of the membranes), which should be visible by sonography—in this setting, reinsert the stylet and briskly advance the needle a short distance to achieve membrane puncture.
- When fluid appears, aspirate the first 3–4 mL into the 5-mL syringe. Because this fluid could be contaminated with maternal cells, do not use it for genetic studies; use it for measurement of amniotic fluid alpha-fetoprotein or discard it.
- Attach a larger (10 or 20 mL) syringe, and aspirate approximately 20 mL.
- If the procedure is being carried out on a multiple gestation and it is not obvious which sac has been sampled, inject 2 mL indigo carmine diluted in 8 mL sterile saline into the sac *after* the fluid specimen has been collected but *before* the needle has been removed, as a marker.
- Disengage the syringe and withdraw the needle; it is not necessary to reinsert the stylet.

- Transfer the amniotic fluid into sterile centrifuge tubes.
- Keep at room temperature and transport to the laboratory as soon as possible (within 24 h).
- Inform the laboratory of the reason for referral, pertinent family or patient history, and any specialized tests required.

DOCUMENTATION

In addition to generating an ultrasound report documenting the preprocedure ultrasonographic examination of the fetus, record the following data:

- 1 The number and location of each needle insertion
- 2 The clarity, color, and total volume of amniotic fluid removed
- 3 Whether there was blood aspiration on needle insertion, during fluid aspiration, or after withdrawal of the needle
- 4 The postprocedure fetal heart rate
- 5 The patient's blood and Rh type
- 6 Patient instructions

Following the amniocentesis, use ultrasound to show the patient the fetal heart rate and postprocedure amniotic fluid volume. If the patient is Rh-negative and unsensitized, administer 300 µg Rh-immunoglobulin (see the protocol on Rh immunization in patients who are Rh-negative).

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Third trimester amniocentesis

Nancy Chescheir

INTRODUCTION

The techniques for aspiration of amniotic fluid via abdominal needle placement in the third trimester of pregnancy do not differ substantially from the techniques used in the second trimester. However, there are nuances that are important. In addition, the risk–benefit analysis and indications for amniocentesis may differ.

INDICATIONS

While the majority of second trimester amniocentesis is performed to obtain fetal cells for chromosomal or DNA analysis, this indication makes up a lesser proportion of indications for third trimester amniocentesis. The primary reasons in the third trimester are:

- 1 Pulmonary maturity testing prior to elective delivery.
- 2 Evaluation for infection and pulmonary maturity in patients with preterm labor, premature rupture of the membranes, or growth restriction.
- 3 Bilirubin testing in amniotic fluid of isoimmunized pregnancies.
- 4 Karyotype analysis after third trimester identification of fetal structural abnormalities, amniotic fluid volume abnormalities, or growth restriction.

It is important to recognize that except for individuals in the first category of indications, the rate of fetal and neonatal morbidity and mortality is higher amongst fetuses with these problems than among infants without them. This increase in complications coupled with the paucity of data collected on patients who have undergone third trimester amniocentesis makes it difficult to determine the procedure-related risks of third trimester amniocentesis. In general, it is critical that the information gained by the amniocentesis would potentially alter clinical management to a degree that overrides the risks of the procedure.

RISKS

Discussions with the patient should include an evaluation of the following risks:

1 Failure to obtain a sample

- In a study of 562 consecutive women undergoing third trimester amniocentesis by operators of different levels, five (0.8%) were unsuccessful.¹
- Relative to earlier gestations, amniocentesis in the third trimester is more frequently performed in the setting of relatively low amniotic fluid.
- Uterine contractions, such as Braxton Hicks contractions and premature labor contractions, are common in this setting and can disturb initial needle placement, increasing the risks of failure to maintain intra-amniotic needle placement.
- Stark *et al.*² reported a 98.4% success rate in obtaining a sample among 913 women with complete data following amniocentesis performed for pulmonary maturity.

2 Rupture of the membranes. In the study of 562 consecutive amniocentesis procedures, there was one case of premature rupture of the membranes.¹**3 Infection**

- While infection is the likely etiology of many of the pregnancy losses following second trimester amniocentesis, there is little data to make that assertion in third trimester procedures. Likewise, there is little data to argue that intra-amniotic infection occurs less commonly. The majority of pregnancy losses following second trimester amniocentesis occur during the second and third week postprocedure, presumably because of the time necessary for an intra-amniotic infection to become clinically significant. Many patients who undergo third trimester amniocentesis are delivered within 3 weeks of the amniocentesis, thus pre-empting the development of clinical infection.
- Amniocentesis in the setting of maternal HIV is in general contraindicated and should be avoided unless the unquantifiable risk of vertical HIV infection is less than the information to be gained.
- Patients with other bloodborne pathogens such as hepatitis B, hepatitis C, and cytomegalovirus (CMV) should be told that it is theoretically possible to increase the risk of fetal infection via amniocentesis.

4 Fetal–maternal hemorrhage

- If possible the placenta should be avoided because of the increased risk of fetal–maternal hemorrhage with transplacental amniocentesis. If not possible, choose a relatively thin portion of the placenta for needle placement.
- Rh-negative women at risk for isoimmunization should receive Rh-immunoglobulin (RhIg) at the time of amniocentesis if the neonatal blood type will not be known within the next 24–48 h. An argument could be made that in order to avoid patients “falling through the cracks” all Rh-negative women should receive RhIg at that time. It is important that a standard procedure is followed in this regard.

5 Laboratory failure

- The presence of meconium in the amniotic fluid can impair biochemical analysis for pulmonary maturity testing and occurs with increasing frequency as term is approached.
- Intra-amniotic blood can also compromise performance of some biochemical tests.
- It is possible that the cloning efficiency of third trimester amniocytes is less than that at earlier gestations, decreasing the likelihood of being able to obtain a full karyotype. Fluorescence *in situ* hybridization (FISH) analysis should be considered along with karyotype in the third trimester in order to lessen the impact of this problem.³

6 Need for urgent delivery

- Gordon *et al.*¹ found no incidences of emergency cesarean delivery for non-reassuring heart tones within 48 h of third trimester amniocentesis among 562 women.
- Stark *et al.*² reported the results of 962 lung maturity amniocentesis. In this series, six (0.7%) required emergency delivery: three were related to non-reassuring fetal heart tones, one because of placental bleeding, one because of placental abruption and one because of uterine rupture.

PROCEDURE

After discussing the possible risks of the procedure and the relative importance of the information to be gained, the patient should affirm her consent by signing a document.

- She should be asked to empty her bladder and a brief ultrasound performed with the patient in a position that results in uterine displacement (such as sitting up or left-sided tilt) to confirm fetal head position, localize the placenta, and identify available pockets of amniotic fluid.
- The woman's abdomen should be washed, typically with an iodine- and/or alcohol-containing fluid. Wash the woman's abdomen much wider than the skin immediately overlying the likely pocket of fluid to be targeted as fetal movement can alter the image abruptly.
- All procedures should be carried out using ultrasound guidance. The transducer should be covered in sonic gel and then encased in a sterile sleeve, such as a sterile glove. Confirm the absence of a latex allergy prior to using latex products.
- Place sterile sonic gel on the maternal abdomen or on the sterile covered ultrasound transducer.
- Localize the pocket of fluid, trying first to avoid pockets near the fetal face and other relatively immobile body parts and secondarily try to avoid the placenta.

- Local anesthesia may be used to infiltrate the skin through which the needle will pass. The patient must know that the anesthesia will not affect the discomfort associated with the needle passage through her uterus.
- Using a 20- or 22-gauge sterile needle clearly long enough to reach the selected fluid pocket, insert the needle through the skin using ultrasound guidance. If the needle placement is co-planar (along the length of the transducer) with the transducer, then the needle tip should be first visible just below the skin edge. Observe the needle to the edge of the uterus and then alert the patient that she may feel some cramping. Insert the needle through the uterine wall. It can take a small wrist jab to get the needle to go through the membranes without tenting them.
- If you use ultrasound guidance transplaner (perpendicular to the transducer) you will not see the length of the needle, but rather the tip only. Do not advance the needle under either circumstance without visualizing the needle tip.
- Place the needle deeply enough into the cavity that in the event of a uterine contraction or movement of the needle when changing syringes the needle will not withdraw into the uterine wall or anterior placenta.
- Once the needle is placed in the amniotic cavity, remove the stylet from the needle and withdraw the necessary amount of fluid required for the tests to be performed.
- If a karyotype is to be performed, confirm that the appropriate syringes and tubes that are non-toxic to fibroblasts are available. If bilirubin testing is to be carried out, confirm that dark tubes are available to avoid light exposure of the fluid.
- If the fluid begins to flow and then stops, rotate the needle to reposition the bevel. If the flow does not restart, reimaging the needle tip to confirm appropriate placement of the needle.
- After completing the withdrawal of the fluid, remove the needle with one smooth move.

FOLLOW-UP

After completing a third trimester amniocentesis, fetal monitoring for 20–30 min is appropriate. Antibiotic prophylaxis is not necessary. If reassuring, the patient can be discharged from the testing unit and await the results of her testing. The patient should be alerted to the fact that it is common to feel some uterine contractions following an amniocentesis. It is also not unusual for there to be a small volume of fluid leaking shortly after the procedure, presumably because of fluid tracking out of the hole in the membranes immediately after the needle is removed.

She should report the loss of a large volume of fluid, the onset of fevers or chills, or if uterine contractions do not subside. An evaluation should be

performed then that includes knowledge of the reason for the amniocentesis in the first place.

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Fetal blood sampling

Alessandro Ghidini and Anna Locatelli

INTRODUCTION

Fetal blood sampling (FBS) refers to three techniques used to gain access to fetal blood: cordocentesis (also known as funiculocentesis or percutaneous umbilical blood sampling); intrahepatic blood sampling; and cardiocentesis. Intrahepatic blood sampling is considered a less preferable option because it carries a higher risk of procedure-related fetal loss;¹ it is thus generally reserved for cases in which cordocentesis fails or cannot be performed because of fetal position. Cardiocentesis has an even higher risk of fetal death (5%).

TECHNICAL CONSIDERATIONS

After viability, the procedure should be performed near to an operating room because an emergency cesarean delivery may be required. A sample of maternal blood should be drawn before the procedure for quality control of the fetal samples obtained. The maternal abdomen should be cleaned with an antiseptic solution and draped. Local anesthesia is optional for diagnostic procedures, while it is useful for therapeutic procedures (e.g. transfusions). Intravenous access is recommended to permit easy and rapid administration of analgesics, antibiotics, and fluids. Broad-spectrum antibiotic prophylaxis is administered 30–60 min prior to the procedure because up to 40% of procedure-related fetal losses are associated with intrauterine infection.² Antenatal corticosteroids may be given at least 24 h prior to the procedure to enhance fetal lung maturity in fetuses at less than 34 weeks' gestation. Most real-time ultrasound machines are equipped with an on-screen template of the needle tract to target the sampling site. A needle-guiding device attached to the transducer may decrease the risk of cord laceration or needle displacement.³ A “free-hand technique” is commonly employed because it provides flexibility for adjusting the needle path. A 20- to 22-gauge spinal needle is generally used. The length of the needle should take into account the thickness of the maternal panniculus, location of the target segment of cord, and the possibility that intervening events, such as uterine contractions, may increase the distance

between the skin and target. The standard length of a spinal needle is 8.9 cm, but longer needles are available (15 cm). Amniocentesis, if indicated, should be performed prior to cordocentesis to avoid blood contamination of the fluid specimen.

It is essential to identify either a fixed segment of the cord or the insertion site of the umbilical cord in the placenta (preferable), as these sites will be the target of most procedures. It is easier and safer to sample the umbilical vein than an artery; puncture of the artery has been associated with a greater incidence of bradycardia and longer postprocedural bleeding.⁴ Upon entering the umbilical cord, fetal blood is withdrawn into a syringe attached to the hub of the needle. Proper positioning of the needle can be confirmed by injection of saline solution into the cord and observation of turbulent flow along the vessel. An initial sample should be submitted to distinguish fetal from maternal cells. Contamination with maternal blood or amniotic fluid can alter the diagnostic value of the specimen. The purity of the fetal blood sample is commonly assessed using the mean corpuscular volume of red blood cells (RBCs) because fetal RBCs are larger than maternal RBCs. The Londersloot test can also detect maternal blood contamination based upon different susceptibilities of fetal and adult hemoglobin to acid elution: in one test tube with 0.1 M KOH add a few drops of maternal blood, in a similar tube add a few drops of presumed fetal blood; maternal blood will turn the fluid to brown, fetal blood to pink in 20 s. Dilution with amniotic fluid can be inferred by a similarly proportional decrease in the number of RBCs, white blood cells, and platelets in the specimen. Blood samples are placed into tubes containing EDTA or heparin and mixed well to prevent clotting. The maximal amount of blood removed should not exceed 6–7% of the fetoplacental blood volume for the gestational age, which can be calculated as 100 mL/kg estimated fetal weight.⁵

After sampling, the needle is withdrawn and the puncture site monitored for bleeding. If an intrauterine transfusion is performed after sampling, the fetal heart rate should be monitored intermittently by interrogating an umbilical artery near the sampling area using pulse or color Doppler. The fetal heart rate of a viable fetus is also monitored for 1–2 h after the procedure.

COMPLICATIONS

Maternal complications related to the procedure are unusual. Bleeding from the puncture site is the most common complication of cordocentesis, occurring in up to 50% of cases.⁴ Cord hematoma is less common and generally asymptomatic, but can be associated with a sudden fetal bradycardia. Expectant management is recommended in the presence of reassuring fetal monitoring and a non-expanding hematoma. Bradycardia is more commonly noted among growth-restricted fetuses.

Fetal losses

Losses that occur within a short time after the procedure are considered to be procedure-related. A review of the published series of low-risk cases found an overall risk of fetal loss of 1.4% before 28 weeks' gestation, and an additional 1.4% risk of perinatal death after 28 weeks.⁶ This loss rate is approximately six times higher than that of a general obstetric population near term. Another large study compared pregnancy outcome in 1020 women with no known fetal anomalies undergoing cordocentesis at 16–24 weeks' gestation with matched control subjects.⁷ The pregnancy loss rates before 28 weeks in the cordocentesis and control groups were 1.8% and 0.7%, respectively, and 1.5% and 1.1%, after 28 weeks.

The most important risk factors for procedure-related loss include operator experience and indication for the procedure; the risk of fetal loss is substantially higher in the presence of fetal pathology, such as fetal growth restriction or non-immune hydrops.

INDICATIONS

The traditional indications for FBS are diagnosis of heritable disorders; rapid karyotyping; diagnosis of fetal infection; and determination of fetal Rh(D) status, and some direct fetal therapy via the fetal umbilical vessels. New technologies can provide the same information from chorionic villus sampling or amniocentesis, procedures that can be performed at an earlier gestational age and with lower rates of fetal loss than FBS.

Cytogenetic diagnosis

Diagnostic cordocentesis for karyotype analysis is indicated when results are required within a few days, such as when the time limit for legal termination is near or when delivery is imminent. Typical examples of these situations are:

- *Fetal structural anomaly*: the prevalence of chromosome anomalies is 12% in fetuses with an isolated structural anomaly and 29% in fetuses with multiple anomalies.
- *True mosaicism abnormalities at amniocentesis*: for confirmation of fetal involvement for a trisomy 8, 9, 13, 18, 21, or sex chromosomes at amniocentesis. However, the absence of abnormal cells in fetal blood does not exclude the possibility of a mosaic cell line in fetal tissues other than blood.

Congenital infection

Fetal blood sampling has a limited role in the prenatal diagnosis of congenital infections such as toxoplasmosis, rubella, cytomegalovirus, varicella, parvovirus, and syphilis. Amniocentesis is currently the primary tool used to diagnose fetal infection and guide parental counseling because polymerase chain

reaction (PCR) and traditional microbiologic techniques allow isolation of the infectious agent in amniotic fluid, ascites, pleural fluid without need to access fetal blood. FBS may still be useful in the presence of fetal hydrops following parvovirus infection, which is usually caused by severe anemia.

Coagulopathies

The majority of inherited hematologic disorders can be diagnosed by molecular genetic testing on amniocytes or chorionic villi. FBS has a role in the prenatal diagnosis of some congenital hemostatic disorders with a risk of intrauterine or early postnatal hemorrhage. Fresh frozen plasma should be available for fetal transfusion at the time of FBS because excessive bleeding has been reported after sampling in fetuses with coagulopathies, such as severe von Willebrand disease and hemophilia. Von Willebrand disease is usually an autosomal dominant disorder. Only in homozygous cases (i.e. the offspring of two heterozygote parents) are hemorrhagic manifestations severe enough to warrant prenatal diagnosis. In such cases, the affected fetuses had extremely low levels of all components of the factor VIII complex (i.e. VWF and factor VIII Ag). Prenatal diagnoses of deficient factors V, VII, and XIII have been reported using FBS.

Platelet disorders

Quantitative platelet disorders can be caused by immunologic or genetic disorders. FBS can be useful in the prenatal diagnosis and management of immunologic thrombocytopenias, while it has largely been supplanted by DNA markers on amniocytes or chorionic cells for the diagnosis of genetic alterations in platelet count or function. Because exsanguination after cordocentesis has been reported in fetuses affected with alloimmune thrombocytopenia (ATP) and Glanzmann thrombasthenia, it is important to have concentrated platelets available for transfusion prior to needle withdrawal. These platelets are usually obtained from maternal thrombocytophereses to minimize the risks of transfusion-related infections with pooled donor platelets. A transfusion of 15–20 mL of platelet concentrate increases the fetal platelet count by $70 \times 10^9/L$ to $90 \times 10^9/L$, which is adequate to prevent cord bleeding. It is prudent to slowly transfuse the platelets while awaiting the fetal platelet count, as dislodgement of the needle before transfusion can have fatal consequences for the fetus affected.

The most common immune-mediated thrombocytopenias of importance to the obstetrician are idiopathic thrombocytopenic purpura (ITP) and ATP.

The risk of neonatal intracranial hemorrhage is 1% for infants of mothers with ITP. No association between the incidence of intracranial hemorrhage and mode of delivery has been reported. Nevertheless, some physicians recommend FBS and that a fetal platelet transfusion or atraumatic cesarean delivery be

performed to reduce the risk of neonatal intracranial bleeding if the fetal platelet count is less than $50 \times 10^9/L$.⁸

Neonatal ATP involves the human platelet antigen (HPA)1a in 75–90% of cases. Because maternal screening for the condition is not recommended, the diagnosis is considered after the birth of an affected infant. Approximately 1.6–2.5% of mothers are HPA-negative; approximately 6–12% of them can become immunized against HPA-incompatible fetal platelets. After maternal immunization has occurred, a specific antiplatelet IgG antibody crosses the placenta and produces fetal thrombocytopenia in approximately 50% of cases. The most serious consequence of ATP is intracranial hemorrhage in the offspring, which occurs in 10–30% of cases (with 25–50% of these occurring *in utero*). In families with an affected fetus or infant, the rate of recurrence is in excess of 75–90% and the thrombocytopenia in the second affected child is always as or more severe than in the previous infant. In such cases, paternal platelet specific antigens should be typed. Fathers homozygous for the specific HPA involved in the ATP will necessarily have HPA-specific positive offspring. In cases of paternal heterozygosity (which occurs in approximately 25% of white people), fetal platelet typing can be performed by PCR on amniotic fluid. Only fetuses HPA-incompatible for the relevant HPA antigen are at risk for severe thrombocytopenia from alloimmunization. Therefore, these families are candidates for prenatal evaluation of platelet type and number.

The optimal management of ATP is not established. Management options proposed are as follow.

Fetal therapy

Fetal therapy with *in utero* platelet transfusions either weekly or immediately before delivery. The protocol entails serial FBS for platelet count every 1–3 weeks, with platelet transfusions if the platelet count is below $100 \times 10^9/L$.⁹ Frequent FBS and transfusions are necessary because the lifespan of transfused platelets is only 5–7 days. Delivery is accomplished by cesarean section at fetal lung maturity documented. The invasiveness of this protocol multiplies the procedure- and transfusion-related infection risks. A review of this approach reported a fetal loss rate of 1% per transfusion and 5% per pregnancy.

Maternal therapy

Maternal therapy with a weekly infusion of high-dose (1 g/kg of maternal weight) intravenous immunoglobulin (IVIG) administered to the mother of an HPA-incompatible fetus. In one protocol, serial FBSs are required to document initially fetal thrombocytopenia (platelet count of less than $100 \times 10^9/L$), to monitor the fetal response to treatment, and finally to document the platelet count prior to labor. FBS may be performed every 4–6 weeks. Series using this protocol found a low response rate in one-third of cases, usually the most

severely affected fetuses (initial platelet count of less than $20 \times 10^9/L$).¹⁰ Salvage therapy with high-dose steroids (60mg/day prednisone) in fetuses unresponsive to IVIG can increase the platelet count in 50% of cases. Delivery by elective cesarean section is recommended unless the fetal platelet count is documented to be above $50 \times 10^9/L$. An alternative protocol calls for empiric weekly administrations of IVIG therapy to the mother of an HPA-incompatible fetus with a history of a child affected by ATP.¹¹ This approach avoids the risks of FBS, but can result in unnecessary and expensive IVIG treatments. Although such a protocol will not detect fetuses who are not responding to IVIG, the risk of intracranial hemorrhage is negligible even in such cases, provided the mother received IVIG. Cesarean delivery should be performed in the absence of documentation of an adequate fetal platelet count just prior to delivery.

Fetal growth restriction

FBS was traditionally used in such cases to identify possible causes of early-onset, severe growth restriction, such as karyotype anomalies or fetal infection. The risk of aneuploidy is higher with more severe growth disorders, earlier gestational age at diagnosis, and when growth restriction is associated with polyhydramnios, structural anomalies, or both. Availability of new diagnostic techniques on amniotic fluid (e.g. fluorescence *in situ* hybridization [FISH] analysis or PCR) has obviated much of the need for FBS. Blood gas analysis may show hypoxemia and acidemia and may possibly assist in the identification of the optimal timing for delivery. However, FBS carries a 9–14% risk of procedure-related loss among growth-restricted fetuses, thus its value for longitudinal assessment of fetal well being is unproven. Moreover, the level of acidemia that can be tolerated by the fetus, with little or no neurologic sequelae is unknown, as is the effect of gestational age on this level. Therefore, interruption of pregnancy based upon blood gas analysis appears to have a limited role below 32 weeks' gestation because the risks of preterm birth are well known, while those of acidemia are poorly understood.

Multiple gestation

Twin–twin transfusion syndrome (TTTS) is a complication of monochorionic twin pregnancies and is caused by unidirectional arteriovenous anastomosis without (or with fewer) compensatory arterioarterial anastomoses, resulting in an imbalance in net blood flow between the twins. The diagnosis of TTTS is based upon ultrasonographic criteria. FBS has little diagnostic value for this condition. It has been proposed that FBS may have a role in the management of TTTS by assessing the severity of the intertwin discrepancy in hematocrit for the timing of delivery and to allow fetal transfusion in the presence of severe anemia to prevent brain injury and/or fetal death. More data are needed before such an approach can be recommended.

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Fetal reduction

Mark I. Evans

INTRODUCTION

Powerful ovulation stimulation agents, with or without assisted reproductive techniques, such as *in vitro* fertilization (IVF), GIFT, and ZIFT, have allowed literally millions of previously infertile couples to have their own children. A disturbing and sometimes catastrophic side-effect, however, has been an ever-increasing proportion of multifetal pregnancies. Data from the Society of Assisted Reproductive Technologies (SART) suggest that 25% of IVF pregnancies result in twins, and 5% produce triplets or more. In some programs the percentages are significantly higher. Over the past two decades, a limited number of groups have developed the procedure of multifetal pregnancy reduction (MFPR) in an attempt to improve the perinatal mortality and morbidity of multifetal pregnancies. By convention, the term *multifetal pregnancy reduction* is used for procedures, mostly in the first trimester, that are performed for fetal number *per se*. *Selective termination* is used for procedures, mostly in the second trimester, for diagnosed fetal abnormalities.

Collaborative data show overwhelmingly that vast improvements have been achieved in outcomes in pregnancies, which have been reduced in most cases to twins. However, the data continue to show that perinatal morbidity and mortality are related not only to the number of remaining fetuses, but also to the starting number despite successfully performed procedures.

Counseling about expected outcomes is dependent upon exact starting and finishing numbers (Fig. 20.1). For patients starting with triplets, the counseling has become far more complex; lowest loss rates are associated with reduction to twins (Fig 20.2).

DIAGNOSIS AND WORK-UP

Evolving experience with fetal reduction procedures has demonstrated that the likelihood of spontaneous loss of individual embryos diminishes by approximately 9 weeks' gestation. Collaborative data furthermore demonstrate that loss rates following the procedure are lowest between 8 and 13 weeks, and are

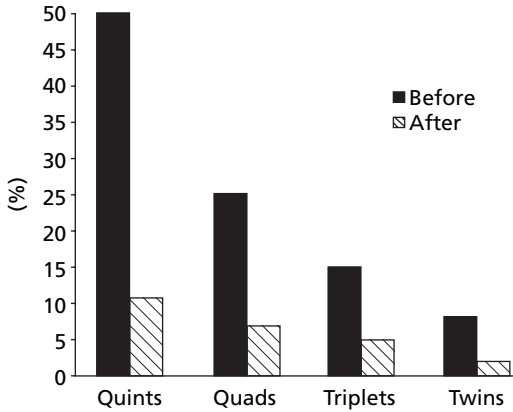


Figure 20.1 Risk reduction in multifetal pregnancies.

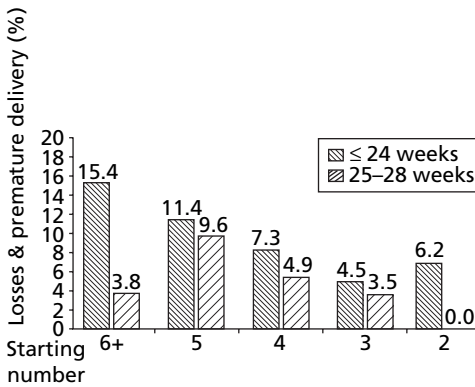


Figure 20.2 Multifetal pregnancy reduction. Loss and very premature by starting number.

somewhat higher outside that window. Careful ultrasound to correctly identify fetal number and to look for the presence of abnormalities such as nuchal membranes or significant growth retardation can best be performed at 11 weeks or more, and allows for selective judgment as to which embryos to reduce. Published data reveal a lower than expected rate of congenital malformations in children in reduced pregnancies, suggesting that to some degree, fetuses with abnormalities are more likely to be reduced. Furthermore, careful assessment for identical twins, fetuses with shared placentas, or vascular lakes, can likewise be used to reduce later complications. In an ever-increasing

proportion of cases, very experienced geneticists are performing chorionic villus sampling. Molecular tests and cytogenetic analysis performed before reduction lower the risks of aneuploidy in remaining fetuses.

MANAGEMENT

Fetal reduction is now mostly performed by transabdominal needle insertion of intrathoracic potassium chloride. The patient is prepped and draped, and a 22-gauge needle is inserted into the chosen amniotic sac. Once the needle is in the amniotic cavity, it is localized over the fetal thorax. In the author's experience, the needle can be best guided into the thorax of the embryo with a sharp thrust. Careful placement is necessary as poor localization may render the procedure ineffective or impossible to accomplish. Furthermore, leakage of excessive potassium chloride (KCl) outside the fetus may result in weakened membranes. In the first trimester, the needle should be placed above the diaphragm and clearly within the thorax. The stylet is removed, a 3-mL syringe is attached, and the plunger is pulled back to check for negative pressure and to ensure that no amniotic fluid comes up the shaft. Once this has been accomplished, a 5-mL tuberculin syringe filled with KCl is attached, and the plunger of the syringe is slowly pushed forward. If the KCl is entered too quickly, the pressure of the fluid may push the embryo off the needle. Commonly, a pleural effusion can be seen giving a pulmonary outline, which is a virtual guarantee of immediate cessation of cardiac activity. After cardiac cessation has been confirmed, the needle can be withdrawn. In most cases, a separate transabdominal needle insertion per embryo is best, as significant angling of the needle through maternal tissue is actually far more painful than a separate needle insertion.

COMPLICATIONS

The major risk of fetal reduction is loss of the pregnancy. Loss rates are correlated with starting number, averaging 5% for pregnancies starting with triplets, 7% for quadruplets, and 11% for quintuplets or more. Such loss does, however, have to be compared with the background loss rate for twin pregnancies known in early gestation, which is nearly 10%. Thus, the overall effect of MFPR is to significantly reduce the risks of the pregnancy. Pregnancies reduced to twins starting as triplets, quadruplets, and quintuplets behave as if they started as twins. These statistics are vast improvements over unreduced higher order multiples. There have been no known episodes of damage to surviving fetuses. Loss of one of the remaining two fetuses has been seen later in pregnancy in approximately 5% of cases. There have been no known episodes of coagulopathies and testing for such was abandoned long ago.

For the last two decades, most experienced operators have reduced pregnancies to twins. Our recent data, however, suggests that for patients who start with

twins a reduction to a singleton actually lowers the loss rate and should be a reasonable option to consider.

FOLLOW-UP

An ultrasound performed approximately a week after the procedure is recommended to ensure that all has gone as planned, and to get a baseline to watch growth of the remaining fetuses. Rh_o (D) immunoglobulin (RhoGAM) is used for patients as appropriate, and the pregnancy can be managed in a generally expectant way. Alpha-fetoprotein will be not be useful as values will be very high. Ultrasound becomes the principal method for diagnosis of fetal well being.

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Intrauterine transfusion

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PATHOPHYSIOLOGY OF HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN

Hemolytic disease of the fetus and newborn (HDN) is primarily due to rhesus isoimmunization. Other causes of HDN and/or anemia include infections (e.g. parvovirus, cytomegalovirus), ABO incompatibility, atypical antibodies (e.g. Kell antibodies), massive fetomaternal hemorrhage, secondary to trauma, vasa previa, or twin–twin transfusion syndrome. The detection of any of these disorders requires intensive surveillance and in a minority of cases fetal transfusion. Atypical antibody reactions (anti-c, Kell, E, C, and Fya) are cumulatively common. Kell antibodies, when present, may pose management problems as discussed later in this chapter.

Mild HDN (mild jaundice with no anemia) constitutes 45–50% of cases and most babies require no treatment. Moderate HDN (severe jaundice with moderate anemia) constitutes 25–30% of cases which if not treated may give rise to kernicterus (bilirubin encephalopathy). Severe HDN (hydrops fetalis) occurs in 20–25% of Rh-affected babies, often requiring invasive diagnostic and therapeutic procedures. These babies have severe hemolytic anemia requiring either intrauterine intravascular blood transfusion (IUIVT) and/or intrauterine intraperitoneal blood transfusion (IUIPT).

Diagnosis of HDN has traditionally required amniocentesis to determine Δ OD450 levels. However, current ultrasound Doppler techniques such as measurement of peak systolic velocity of the middle cerebral artery (MCA) of the fetus can help in identifying the fetus with moderate to severe fetal anemia. This provides a complementary and non-invasive testing technique for fetal assessment. Doppler velocimetry has reduced the need for invasive diagnostic testing and is particularly useful in fetal anemia resulting from Kell antibodies. In this condition, antibody titers do not correlate well with the severity of the disease.

Criteria for cordocentesis

- 1 Amniotic fluid $\Delta OD450$ values in zone 3 or upper zone 2 (usually considered upper 20%)
- 2 An elevated amniotic fluid $\Delta OD450$ value showing an upward trend
- 3 Sonographic features of hydrops
- 4 Elevated MCA Doppler peak systolic velocity (PSV) >1.5 MOM (multiples of the median) for gestational age

Criteria for intrauterine transfusion

- 1 Fetal hematocrit (Hct) of $\leq 25\%$ or Hct ≥ 2 standard deviations (SD) below the mean Hct for the gestational age
- 2 Anemia and sonographic signs of hydrops (pericardial effusion, ascites, scalp edema, or pleural effusion)

DIAGNOSIS OF HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN

Amniocentesis allows the ascertainment of bilirubin levels using $\Delta OD450$. This corresponds with severity of fetal hemolytic disease and anemia.

Ultrasound allows documentation of signs of hydrops such as ascites, pleural effusion, pericardial effusion, and skin or scalp edema.

Doppler flow ultrasound measures the PSV of the MCA. Anemia results in a hyperdynamic fetal circulation manifested by an increase in the blood flow velocity on Doppler insonation.

TECHNIQUES

Intrauterine intravascular transfusion procedure

Timing of intrauterine transfusion

- *Earliest time:* 18–20 weeks' gestation
- *Latest time:* 34 weeks' gestation

(NB technical ease of performing transfusion, e.g. anterior placenta location, and amniotic fluid lung maturity status are pertinent considerations in deciding latest gestational age for transfusion.)

Procedure

- 1 Admit patient to labor and delivery unit. An operating room with appropriate anesthetic and nursing staff should be readily available (within easy physical access) in case immediate operative delivery is needed. Alternatively, the procedure may be performed in the operating room.
- 2 Flush all needles and syringes with heparin to prevent clotting.
- 3 Maternal and fetal monitoring (vital signs) as deemed appropriate. Maternal intravenous access will be needed.

- 4 Prophylactic antibiotics (e.g. cefazolin 1 g intravenously) before starting the procedure.
- 5 Use ultrasound to identify a suitable area for needle insertion. Avoid the placenta if possible, because transplacental needle insertion increases fetomaternal transfusion and the risk of further sensitization.
- 6 Adequate anesthesia/analgesia as deemed appropriate. Use meperidine 25 mg intramuscularly (may administer an additional dose if necessary); promethazine 12.5 mg intramuscularly (may repeat dose once); lidocaine 1% given subcutaneously
- 7 Clean and drape the abdomen using sterile techniques. The ultrasound transducer is placed in a sterile sleeve.
- 8 Use a 20- or 22-gauge, 75–150 mm spinal needle. Insert needle into the umbilical vein (under ultrasound guidance) at the placental cord insertion. If there is no alternative, a free loop of cord may be accessed although this requires considerably greater skill. Avoid side-to-side or jerking motions that may cause shearing effect and lacerate the fetal blood vessels.
- 9 Fetal paralysis is achieved using pancuronium bromide 0.1 mg/kg intravenously or pancuronium 0.1 mg/kg intravenously.
- 10 Aspirate fetal blood for blood type, Rh type, fetal blood gases, and complete blood count (CBC). The initial or opening Hct will guide transfusion rate and volume. The Hct, mean corpuscular volume (MCV), platelet count and Betke–Kleihauer test will help to differentiate between maternal and fetal blood.
- 11 Transfuse group O, Rh-negative, cytomegalovirus-negative, washed, irradiated, packed red blood cells (cross-matched against maternal blood) into the fetus at a rate of ~ 10 mL/kg/min depending on the opening Hct. Transfusion red cells should be tightly packed to Hct of 75–90% in an effort to avoid fluid overload in the fetus. The transfusion rate is usually 3–5 mL/min and transfusion volume ranges from 30 to 100 mL packed RBC.
- 12 Periodically confirm correct intravascular placement of the needle as evidenced by the sonographic appearance of “bubbling” in the umbilical venous circulation.
- 13 Intermittently image the fetal heart during the procedure to assess the rate and contractility.
- 14 Transfusion formula:

$$\text{Volume of packed RBC required for transfusion} = \frac{\text{estimated fetal blood volume (mL)} \times \Delta\text{Hct}}{\text{Hct of packed RBC to be transfused}}$$

where $\Delta\text{Hct} = \text{desired Hct} - \text{initial or opening Hct}$. Estimated fetal blood volume is 125 mL/kg for 18–24 weeks, 100 mL/kg for 25–30 weeks, and 90 mL/kg for more than 30 weeks' gestation.

- 15 Document the final or closing Hct (a desirable endpoint being Hct of 30).
- 16 Tocolytics may be used prior to and/or after the procedure if clinically indicated.
- 17 Monitor mother with fetus in the labor and delivery unit until she is fully recovered from anesthesia and preferably up to 12 h after procedure.
- 18 Final ultrasound to confirm normal cardiac contractility and absence of significant intra-amniotic or cord hematoma before mother is discharged home.
- 19 Repeat IUIVT every 1–4 weeks (as clinically indicated) until 34 weeks' gestation. Thereafter, delivery of baby is the preferred option instead of further IUIVT.
- 20 Use MCA Doppler to monitor fetal anemia and to determine timing of next transfusion. The fetal Hct decreases approximately 1%/day.
- 21 Recommend twice weekly BPP (biophysical profile) and MCA Doppler to detect anemia.
- 22 Delivery in a tertiary institution with expert neonatal and perinatal management team is recommended.

Intracardiac transfusion of packed RBC is an option when the umbilical vein is collapsed because of fetal hypotension. The fetus is usually moribund at this stage. Access into any of the cardiac chambers, preferably the left or right ventricle, will permit blood transfusion.

The **intrahepatic** route is an alternative when the umbilical vein is not within reach. However, few perinatologists have experience with either the intracardiac or intrahepatic route of blood transfusion. These techniques are not therefore routinely recommended.

Intrauterine intraperitoneal transfusion

- 1 Preoperative procedure will be as in steps 1–4 above.
- 2 Advance an 18-gauge needle (19- or 20-gauge needle may also be used) with its Teflon sheath through the maternal abdomen into the fetal peritoneal cavity under ultrasound guidance. The needle is removed and the Teflon sheath left in place. Inject a small amount of air (2–3 mL) or saline solution and note the presence of bubbles to help confirm correct location of the tip of the needle in the peritoneal cavity.
- 3 Aspirate any ascites and discard the fluid. The goal is to aspirate ascitic fluid about twice the volume of the intended blood transfusion but no more than 150 mL.
- 4 Transfuse group O, Rh-negative, cytomegalovirus-negative, washed, irradiated, packed RBCs (cross-matched against maternal blood) into the fetus

at a rate of 5–10 mL/min. The transfusion is performed with a 30-mL syringe connected to a three-way stopcock. The volume (V) of blood to be transfused is calculated thus:

$$V \text{ (mL)} = (\text{gestational age in weeks} - 20) \times 10 \text{ mL.}$$

- 5 Absorption of blood from the peritoneal cavity takes approximately 3 days in the non-hydropic fetus and 6–7 days in the hydropic fetus.
- 6 Intraperitoneal transfusion is initiated when hydrops with significant ascites is first noted.
- 7 Prophylactic antibiotics (e.g. cefazolin 1 g intravenously) prior to or after the procedure.
- 8 Tocolytics may be used during and/or after the procedure if clinically indicated.
- 9 Monitor fetus and mother until she is fully recovered and for several hours after procedure. Observe for post procedure heart rate irregularities.
- 10 Final ultrasound before mother is discharged home.
- 11 Daily fetal kick/movement counts and BPP twice weekly.
- 12 Repeat IUIPT every 1–4 weeks (as clinically indicated) until 34 weeks' gestation. Thereafter, delivery of baby is the preferred option over repeat IUIPT. With resolution or improvement of the hydrops, intravascular transfusion may be used if further treatment is warranted.

COMPLICATIONS OF IUIVT AND IUIPT

Maternal complications

- 1 Infection (bacterial and viral) secondary to surgical procedure (IUIVT, IUIPT) or caused by transfusion of blood products
- 2 Maternal tissue trauma
- 3 Worsening RBC isoimmunization

Fetal complications

- Fetal hemorrhage
- Fetal trauma
- Fetal death : fetal loss rates of 0.5–2% per procedure.
- Exsanguination is more likely to happen when fetoscopy or large bore needle (16-gauge) is used for the procedure.
- Acute refractory fetal distress.
- Premature rupture of the membranes.
- Premature labor.
- Hyperkalemia.
- Umbilical cord hematoma or umbilical vein compression or thrombosis.
- Cardiac tamponade.
- Fetal hepatitis.

- Necrotizing enterocolitis.
- Prolonged neonatal marrow suppression with decreased Hct, white blood cell count, and platelet count.

FOLLOW-UP

Perform MCA Doppler velocimetry and BPP twice weekly with daily fetal kick/movement count. In addition, ultrasound provides an opportunity for fetal surveillance to identify any signs of developing hydrops such as increasing ascites, cardiomegaly, pericardial effusion, pleural effusion, skin or scalp edema.

Although the fetus may respond favorably to blood transfusion by being more active, the hydrops may take 1–2 weeks to resolve.

TIMING OF DELIVERY

Delivery may be carried out after 34 weeks' gestation if there is documentation of fetal lung maturity using the lecithin:sphingomyelin ratio, phosphatidyl glycerol level, lamellar body count or other standardized methods of testing fetal lung maturity. Lung maturity may be delayed in Rh-immunized fetuses possibly as a result of delay in surfactant production. Antepartum steroids (betamethasone or dexamethasone) ought to be administered to induce lung maturity.

Delivery may be indicated, even before 34 weeks' gestation, if there is lack of improvement in spite of IUIVT, and/or IUIPT or if there is persistent fetal bradycardia. Worsening hydrops such as increasing ascites and pericardial effusion, pleural effusion, and scalp edema may warrant delivery.

CONCLUSIONS

Intrauterine transfusion decreases the fetal mortality from maternal isoimmunization through prevention or reversal of hydrops fetalis, correction of fetal anemia, and prolongation of the duration of pregnancy and the achievement of pulmonary maturity. Immunoprophylaxis against Rh disease is a standard of care that has been highly successful. Unfortunately, it has not eliminated the problem of RBC sensitization in pregnancy. For this unfortunate group of patients, the development of cerebral Doppler velocimetry techniques has permitted frequent surveillance while reducing the need for invasive procedures for the detection of significant fetal anemia. Doppler velocimetry requires a careful and standardized approach. Failure to adhere to proper techniques will result in false-negative results with significant adverse consequences for the fetus.

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External cephalic version

Monica Longo and Gary D.V. Hankins

INTRODUCTION

Breech presentation at term complicates 3–4% of pregnancies. Following publication of the Term Breech Trial Collaborative Group results, the American College of Obstetricians and Gynecologists (ACOG) concluded that a planned vaginal breech delivery may no longer be appropriate. This recommendation was based on the increased neonatal mortality, and serious morbidity associated with planned vaginal versus planned cesarean delivery of the singleton term breech. When data from this trial was adjusted to reflect practice in the USA, implementation of a policy of planned cesarean birth for breech presentation would result in seven cesarean births to avoid one infant death or serious morbidity. This was felt to be a sufficient justification to alter practice and no longer perform planned vaginal breech delivery. Hence, ACOG recommended that obstetricians continue their efforts to reduce breech presentations in singleton gestations through the application of external cephalic version (ECV) whenever possible.

Most groups have reported a 60–70% success rate with ECV, resulting in a significant reduction in cesarean rate to 30–40% in women who present with a breech presentation at term. Several studies have reported the use of epidural or spinal anesthesia in women who had failed attempts at ECV without central neuraxial blockade. In this setting, success rates varied from 40% to 89%. Because these series have been small to date, have been associated with fetal complications, and the cost has exceeded that of expectant management, we recommend neuraxial blockade only when performed in a setting that will allow immediate cesarean delivery in the event of complications. Further, if ECV fails it is prudent to proceed with cesarean delivery using the neuraxial anesthesia already in place.

PATHOPHYSIOLOGY

Factors that contribute to breech presentation include gestational age, uterine relaxation associated with multiparity, multiple gestation, polyhydramnios,

oligohydramnios, uterine leiomyomas, placenta previa, fetal anomalies such as hydrocephalus, and maternal uterine anomalies. When the diagnosis of breech presentation is made, the clinician should evaluate for these associated and causal factors. Finally, it is well established that breech presentation is associated with an increased risk for cerebral palsy, regardless of the route of delivery.

DIAGNOSIS

Leopold maneuvers should be performed at each clinic visit during the third trimester to determine fetal presentation. If breech presentation is suspected, an obstetric ultrasound should be carried out to confirm presentation, estimate fetal weight, and rule out fetal or maternal abnormalities. Exclusion criteria for ECV are shown in Table 22.1.

MANAGEMENT

- 1 Schedule the ECV on labor and delivery at 37 weeks or later. Intrapartum ECV at term in early labor can be considered and neuraxial anesthesia will enhance success in this setting.
- 2 Anesthesia and immediate operative facilities must be available if an emergency cesarean section should become necessary. The patient should be nothing-by-mouth after midnight prior to the scheduled ECV.
- 3 Obtain informed consent, including permission to proceed with emergency cesarean delivery if necessary.
- 4 Perform a real-time ultrasound examination to confirm a non-vertex presentation, adequate amniotic fluid (amniotic fluid index ≥ 5 cm), the absence of any gross fetal anomalies, and to determine placental location.

Table 22.1 Exclusion criteria for performing external cephalic version (ECV).

Premature rupture of membranes
Third trimester bleeding
Oligohydramnios
Evidence of placental insufficiency, e.g. severe intrauterine growth restriction (IUGR)
Suspected chronic abruption
Pre-eclampsia
Known nuchal cord
Placenta previa
Previous uterine surgery that would contraindicate vaginal trial of labor
Fetal anomaly
Maternal uterine anomaly
Any other contraindication for vaginal delivery

- 5 Obtain a reactive non-stress test and secure intravenous access. Type and screen for two units of packed red blood cells if the prenatal antibody screen is positive or unknown (should emergency cesarean section become necessary).
- 6 Consider using a uterine relaxant, which may include terbutaline sulfate 250 µg subcutaneous or intravenous injection, or ritodrine hydrochloride intravenously at 100 µg/min for 10–15 min, or magnesium sulfate as a 4-g intravenous dose given over 20 min. The subcutaneous terbutaline regimen is the least complex and least expensive tocolytic for this purpose.
- 7 Anesthesia is not recommended for the procedure unless delivery is planned if the procedure fails utilizing the same conduction anesthesia.
- 8 Ten minutes after administration of a uterine relaxant, the ECV can be attempted with one or two operators (Figs 22.1 and 22.2).
 - *Two operators.* The first operator attempts to lift the breech out of the pelvis (the critical aspect of the procedure) while the second operator attends to the head. A forward roll is usually attempted if the fetal head crosses the maternal midline. A back flip can be used if the initial method fails or if the fetus does not cross the midline. This method requires sub-

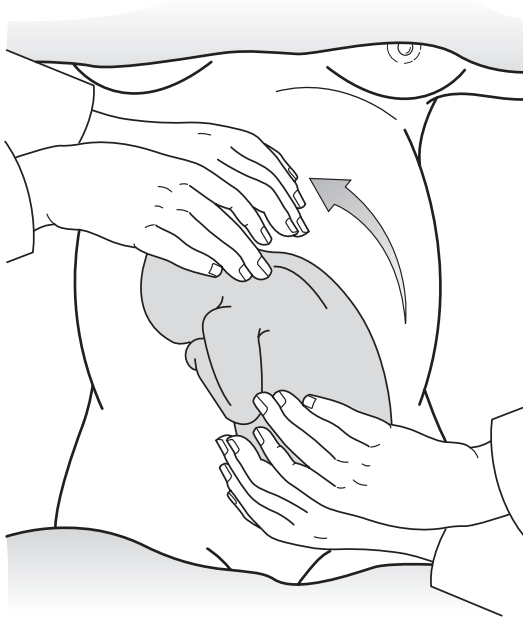


Figure 22.1 External cephalic version with two operators.

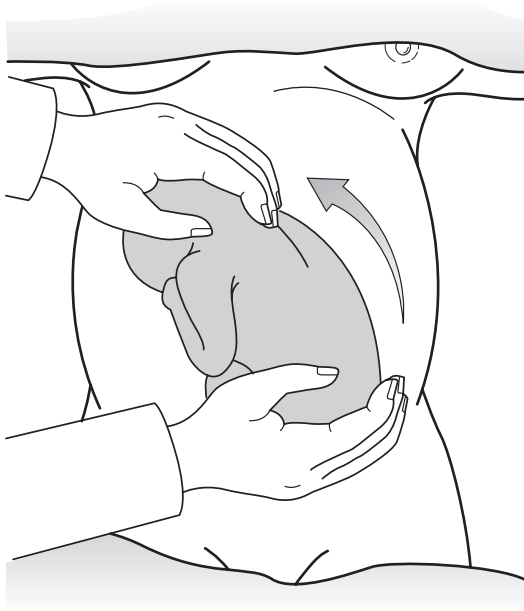


Figure 22.2 External cephalic version with a single operator.

stantial teamwork to ensure that the vectors created by each attendant facilitate, rather than cancel, the forces necessary to turn the fetus.

- *Single operator:* The procedure can be attempted in a similar manner with a single operator.
- 9** Discontinue the procedure with evidence of fetal intolerance, maternal request, or after three failed attempts.
 - 10** Obtain real-time ultrasonography to confirm version outcome. If more than one attempt is made or if the attempt is prolonged, visualize the fetal heart rate every 30–60 s. Discontinue the procedure if fetal bradycardia is observed.
 - 11** Always administer Rh immunoglobulin to Rh-negative unsensitized women following the procedure.
 - 12** Fetal heart rate monitoring should be continued postprocedure until a reactive non-stress test is obtained or for at least 30 min, whichever is longer.
 - 13** In the event of failed version, the woman should be counseled on the risks and benefits of all treatment options. Most will elect a cesarean section which can be scheduled at 39 weeks. Persistence of the breech

presentation should be confirmed with ultrasound prior to the cesarean procedure. If ECV is attempted intrapartum under conduction anesthesia, and if it fails, the woman should be counseled for timely delivery by cesarean section.

COMPLICATIONS

Complications include fetal heart rate decelerations, cord accidents, failed version, reversion to breech, ruptured uterus, and abruptio placentae. Versions performed at gestational ages less than 37 weeks present a higher risk for preterm delivery and reversion to breech.

CONCLUSIONS

Careful assessment of fetal presentation in the third trimester is imperative. Otherwise, patients may be deprived of the option of ECV to decrease the risk of cesarean section. ECV is a very valuable tool in the armamentarium of the obstetrician when managing the term breech presentation. Before the procedure, fetal well being and any contraindications should be determined. Informed consent and counseling with regard to the likelihood of success of the procedure should be carried out. Postversion assessment for fetal presentation on subsequent encounters is vital in these patients.

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Induction of labor

Anna M. McKeown and Michael P. Nageotte

INTRODUCTION

Induction of labor, the stimulation of uterine contractions for the purpose of vaginal birth, is one of the most commonly practiced procedures in obstetrics, occurring in approximately 20% of pregnancies. Labor induction is indicated when the maternal or fetal benefits from delivery outweigh the risks of prolonging the pregnancy.

Indications for induction vary in acuity and may be for elective or medical reasons. The indications for delivery include, but are not limited to, those described in the American College of Obstetricians and Gynecologists (ACOG) Technical Bulletin No. 10¹ (Table 23.1). The indication and plan for delivery should be clearly outlined with the patient and documented in the medical record. Induction of labor has its own inherent risks and these should be discussed with the patient prior to the initiation of the induction procedure.

Patient selection is an important aspect of induction success. Careful selection of appropriate patients reduces the risks of prolonged labor, chorioamnionitis, and cesarean delivery. The mode of induction is often dictated by the patient's cervical status. Cervical readiness for labor can be communicated by using the Bishop score (Table 23.2). The Bishop score, first described as the likelihood of spontaneous labor ensuing in multiparous women, is a systematic assessment of cervical status that facilitates choosing an induction agent (see below) and predicting induction success.² A Bishop score of less than 6 indicates an unfavorable cervix which may require a prelabor induction agent to "ripen" the cervix. In contrast, with a higher Bishop score, the cervix is more likely ready for labor and an agent that induces contractions may be used. The higher the Bishop score, the greater the likelihood of induction success. There are a variety of induction agents to choose from, some mechanical and others pharmacologic. The indication for induction, Bishop score, and following summaries can be employed to determine appropriate management algorithms for patients.

Table 23.1 Patient selection for induction of labor. (Adapted from American College of Obstetricians and Gynecologists 1999.¹)*Potential indications*

Pre-eclampsia, eclampsia

Pregnancy-induced hypertension

Chorioamnionitis

Suspected fetal jeopardy, evident by biochemical or biophysical indications (e.g. fetal growth restriction, isoimmunization)

Maternal medical problems (e.g. diabetes mellitus, renal disease, chronic hypertension, chronic obstructive pulmonary disease)

Fetal demise

Logistic factors (e.g. risk of rapid labor, distance from hospital)

Post-term gestation

Contraindications

Placenta or vasa previa

Abnormal fetal lie

Funic presentation/cord prolapse

Prior classical uterine incision

Active genital herpes infection

Pelvic structural deformities

Invasive cervical carcinoma

Table 23.2 Bishop score. (Adapted from Bishop 1964.²)

	0	1	2	3
Dilation (cm)	0	1–2	3–4	5–6
Effacement (%)	0–30	40–50	60–70	80
Station	–3	–2	–1 to 0	+1 to +2
Consistency	Firm	Medium	Soft	—
Position	Posterior	Mid	Anterior	—

CERVICAL RIPENING AGENTS**Mechanical****Membrane stripping**

Induction of labor by “stripping” the amniotic membranes is a common practice. Most studies have reported membrane stripping to be safe with fewer post-date inductions being required. The “stripping” of membranes performed by

manually separating the membranes from the lower uterine segment during a cervical examination results in an increase in phospholipase A_2 and prostaglandin $F_{2\alpha}$ release. The production and release of prostaglandins is known to be an important event in the onset of labor.^{3,4} In patients undergoing labor induction, the use of membrane stripping has been reported to be associated with a decreased need for oxytocin and a higher vaginal delivery rate.⁵ A randomized controlled trial of post-term pregnancies demonstrated that a significant number of patients went into labor spontaneously within 72 h after membrane stripping when compared with a cohort of women who did not have membrane stripping.⁶

Foley bulb

Mechanical dilation of the cervix with a balloon catheter was first described in 1863. Since that time, there have been modifications; however, the concept remains unchanged. The Foley balloon catheter can be used as a mechanical method of cervical ripening by applying local pressure on the cervix by filling the balloon after it is placed in the endocervical canal. This pressure facilitates cervical ripening, most likely by stimulating the release of local prostaglandins and triggering the Ferguson reflex. A recent randomized controlled trial found the intracervical Foley catheter to be comparable with misoprostol alone or in combination with a Foley catheter for preinduction cervical ripening.⁷ Placement of the catheter requires some skill, but generally can be placed without difficulty (Table 23.3).

Pharmacologic

Prostaglandin E_1

Prostaglandin E_1 (PGE_1) is a prostaglandin labeled for use by the US Food and Drug Administration (FDA) for prevention of peptic ulcer disease. More recently, PGE_1 has been used (off label) as an effective and inexpensive cervical ripening agent. Misoprostol, a synthetic PGE_1 currently comes in tablet form and can be administered intravaginally or by mouth. Misoprostol is dispensed in 100 μg tablets that can be cut in quarters for convenient use. The dose most commonly recommended for a term pregnancy induction is 25 μg every 3–6 h placed in the posterior fornix. Repeat dosing is not recommended if there are three or more contractions in 10 min. Numerous clinical trials have documented the safety of using misoprostol for cervical ripening and labor induction. Studies evaluating misoprostol uniformly demonstrated a decreased cesarean section rate, a higher incidence of vaginal delivery within 24 h of initiation, and a decreased need for oxytocin.⁸ When used in higher doses (50 μg or more), misoprostol has been reported to have a higher rate of tachysystolic uterine contractions (six or more contractions in 10 min in two consecutive 10-min periods) when compared with either placebo or PGE_2 .¹ An important

Table 23.3 Technique for intracervical balloon catheter placement.

Instruments

Sterile speculum and gloves
Adequate lighting
26 French (or 30 mL balloon catheter)
Ring forceps (2)
Sterile scissors
50 mL saline

Procedure

A 26 French catheter is placed into the endocervical canal using a sterile speculum and direct visualization or manual palpation
The tip of the catheter may be shortened using sterile scissors to facilitate placement (care to cut distal to the balloon)
Test inflating balloon prior to placement
Tip of catheter may be placed in endocervix or just beyond into lower uterine segment
Insufflate balloon with 30–50 mL saline
Withdraw balloon slightly so it resides in the endocervical canal at level of internal os
Tape catheter to leg with traction
Remove if membranes rupture or after 12 h

consideration in the use of misoprostol for labor induction is the reported increased occurrence of uterine hyperstimulation and the potential for disruption of the uterine scar in patients with a previous cesarean delivery.¹

Prostaglandin E₂

Prostaglandin E₂ (PGE₂) for cervical and vaginal application has been approved for cervical ripening and induction of labor. PGE₂ alters the cervical collagen milieu, which results in separation of tightly knit collagen bundles and an increase in the intervening ground substance. This is characterized clinically as softening and effacement of the cervix.

The FDA approved a low-dose preparation of 0.5 mg PGE₂ to be placed intracervically. Alternatively, a 1–3 mg gel can be made from 20 mg suppositories and placed in the posterior vaginal fornix. With either administration, PGE₂ enhances cervical ripening and increases the likelihood of successful induction, decreases the incidence of prolonged labor, increases uterine contractions and lowers oxytocin requirements.⁹ In the nulliparous patient with a less favorable cervix, the enhancement of contractility mimics spontaneous labor more closely than oxytocin or amniotomy.¹⁰ PGE₂ is recommended for use in the patient with a low Bishop score (6 or less), and is also effective in patients with

premature rupture of membranes.¹¹ After placement of PGE₂, the patient should remain recumbent for 30–60 min. Thereafter, the patient is monitored for 1–2 h. If uterine activity is infrequent, the patient may be kept on monitoring, transferred to an antepartum floor, or possibly discharged. If there is an increase in uterine activity, the fetal heart rate and contraction pattern should be continuously monitored. A second dose may be administered 6 h after initial dose if regular contractions are not present and the fetal heart rate is reassuring.

Prostaglandins should not be used for induction of labor in the setting of frequent fetal heart rate decelerations because of the limited ability to terminate the effects on uterine contractility quickly. If uterine hyperstimulation occurs, the administration of subcutaneous or intravenous terbutaline (0.25 mg) may result in quiescence of uterine hyperstimulation. When used appropriately, the maternal side-effects and incidence of uterine hypertonicity with prostaglandin use is low.

Labor-inducing agents

Amniotomy

Amniotomy can safely and effectively induce or augment labor. This observation of the effect of amniotomy stems from the release of prostaglandins, which stimulate uterine contractions. Endogenous oxytocin production does not seem to be involved in this process.

In the patient with a Bishop score of more than 8, artificial rupture of membranes induces labor successfully, with only rare need for oxytocin augmentation.² Amniotomy also produces beneficial effects for the augmentation of labor. Proponents of the active management of labor protocol hail amniotomy as a key component for induction success. Research verifies that there is a significant shortening of labor when amniotomy is performed in the setting of cervical dilation of 3 cm or more.¹²

Prior to performing amniotomy, care should be taken to ensure the fetal head is well applied to the cervix and group B streptococcus status confirmed. The fetal heart rate should be recorded immediately following amniotomy. Labor will usually commence shortly thereafter, and if oxytocin is being used concomitantly its dosage may need adjustment.

Oxytocin

Theobald first described the continuous infusion of oxytocin in 1948. More than a half a century of subsequent usage has confirmed its safety, but the precise regimen remains debatable. This stems from the fact that oxytocin has different responses in different patients (i.e. nulliparous versus multiparous, and elective induction versus augmentation). The 1999 ACOG Technical Bulletin¹ lists two intervals for the administration of oxytocin. One is considered

to be low dose (physiologic) with longer dosing intervals and the other high dose (pharmacologic), with intervals that are closer. In 1984, Seitchik *et al.*¹³ published research that demonstrated the pharmacokinetics of oxytocin. They showed that a 40-min period is needed to reach steady-state concentrations, but uterine response occurs rapidly, within 3–5 min.

Recommendations for the selection of a particular regimen vary (high dose versus low dose). Multiple studies have found both protocols effective in establishing adequate labor patterns, but when focusing on outcomes, the high-dose protocol has consistently demonstrated a faster induction time with fewer failed inductions. Lopez-Zeno *et al.*¹⁴ found, in a select patient population (nulliparous), that high-dose oxytocin, in the setting of an active management protocol, decreased cesarean section rate, time in labor, and maternal infectious morbidity. For a brief summary of the various protocols for oxytocin delivery, refer to Table 23.4.

Labor inductions are becoming increasingly more common. In the USA, we have witnessed a doubling of the induction rate in the past two decades. Con-

Table 23.4 Utilization of oxytocin.

Indications

For the induction or augmentation of labor

Contraindications

Those patients in whom a vaginal delivery is contraindicated

Administration

15 units of oxytocin in 250 mL IV fluid = 60 mU/mL (rate of 1 mL/h = 1 mU/min)

Induction

Start at a rate of 1 mU/min and increase by 1–2 mU/min every 40–60 min to a maximum of 20–30 mU/min

Augmentation

Multiparae (low dose)

Start at a rate of 1 mU/min and increase by 1–2 mU/min every 40–60 min to a maximum of 20–30 mU/min

Nulliparae (low versus high dose)

Can use low-dose protocol (above)

High-dose protocol:*

Start at 6 mU/min and increase by 6 mU increments every 15 min to a maximum of 36 mU/min until adequate labor reached (defined as seven uterine contractions in 15 min)

*Adapted from Lopez-Zeno *et al.* 1992.¹⁴

currently, there has been focused attention on new modalities, protocols, and understanding of the science of labor induction. Despite new advances, the Bishop score and patient selection are still the two most critical factors for determining induction management and predicting success.

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Amnioinfusion: indications and techniques

Catherine Y. Spong

INTRODUCTION

Amnioinfusion was first described by Carey in 1957. In the early 1980s, Miyazaki and colleagues demonstrated that amnioinfusion was useful in relieving variable and prolonged decelerations during labor, based on the assumption that the fluid being replaced acts as a cushion and prevents or relieves cord compression. Since that time, a number of indications have been evaluated, studying both prophylactic amnioinfusion (used to prevent a condition from occurring) and therapeutic amnioinfusion (used to treat a condition). Amnioinfusions can be performed transcervically, in the setting of ruptured membranes, with the use of a sterile catheter placed transcervically, or transabdominally under ultrasound guidance through a sterile needle, similar to an amniocentesis.

The infusion is usually given as a bolus of 250–600 mL normal saline at room temperature followed by either a re-evaluation and repeat if needed or a continuous infusion at 3 mL/min (180 mL/h). Subsequently, indications for this procedure have been expanded by other authors. Studies have shown that the use of an amnioinfusion does not affect the length of labor and the solution can be used at room temperature.

INDICATIONS

Supported by data

- Repetitive variable decelerations, prolonged decelerations.
- To improve diagnostic ability with oligohydramnios (mid-trimester transabdominal amnioinfusion).

Areas that have been studied but the studies are too heterogeneous to support use

- *Failed version.* Single trial demonstrating benefit.
- *Treatment/prophylaxis of chorioamnionitis.* The trials are too heterogeneous to draw conclusions for clinical practice.

- *Prevention of variable decelerations in the setting of oligohydramnios or preterm premature rupture of the membrane (PPROM).* The trials are too heterogeneous to draw conclusions for clinical practice.
- *Prevention of pulmonary hypoplasia in PPRM.* The trials are too heterogeneous to draw conclusions for clinical practice.
- *Prevention of complications from gastroschisis.* Case reports of 2–5 patients, no clinical trials.
- *Prevention of meconium aspiration syndrome without repetitive variable decelerations.* In trials comparing amnioinfusion with no amnioinfusion in the presence of meconium, the infants who developed repetitive variable decelerations were not allowed to have an amnioinfusion. These trials supported the finding that amnioinfusion was beneficial in this setting. However, in a trial that compared amnioinfusion with standard care, where the latter allowed amnioinfusion for the development of repetitive variable decelerations, there was no improvement with amnioinfusion alone. Furthermore, studies evaluating routine implementation of amnioinfusion for all patients with meconium aspiration syndrome have shown no improvement in meconium aspiration with routine amnioinfusion. This suggests that prophylactic amnioinfusion for the presence of meconium is not beneficial over therapeutic amnioinfusion for repetitive variable decelerations. Thus, in the setting of meconium aspiration syndrome, amnioinfusion should be initiated if repetitive variable decelerations occur.

CONTRAINDICATIONS

- Ominous fetal heart rate (FHR) patterns:
 - Repetitive late decelerations
 - Flat baseline
 - Tachycardia of 180 bpm or more in absence of maternal temperature
 - Variable decelerations with overshoot
- Cord prolapse
- Significant vaginal bleeding (previa vs abruptio)
- Uterine hyperactivity or hypertonia
- Acute prolonged deceleration in a patient with previous cesarean section

TECHNIQUE

Transvaginal

- 1 An amniotic fluid index (AFI) prior to the decision to initiate amnioinfusion may be beneficial, if the AFI is normal, it is unlikely that the amnioinfusion will be able to relieve the repetitive decelerations.
- 2 Perform vaginal examination to rule out cord prolapse; insert an intrauterine pressure catheter and apply a scalp lead (optional). The intrauterine catheter must be correctly inserted *into the amniotic cavity*, not the

extramembranous or intracervical space. The fetal heart tracing should be constantly monitored and the uterine fundus palpated to rule out uterine hyperstimulation.

- 3 Connect amnioinfusion tubing to the intrauterine catheter and start wide-open gravity drip amnioinfusion with the saline held approximately 1.25 m above the catheter tip (approximately 25–30 mL/min). In emergency cases of acute bradycardia, use a hand pump to increase the infusion rate to 70–80 mL/min and at the same time make preparations for cesarean section (Fig. 24.1).
- 4 Initially, amnioinfuse 500 mL by gravity or by pump and, if desired, another 500 mL by gravity drainage. This volume and rate of infusion do not cause fetal bradycardia, uterine hyperstimulation, or hypertonia. A continuous infusion may be started at 180 mL/min.

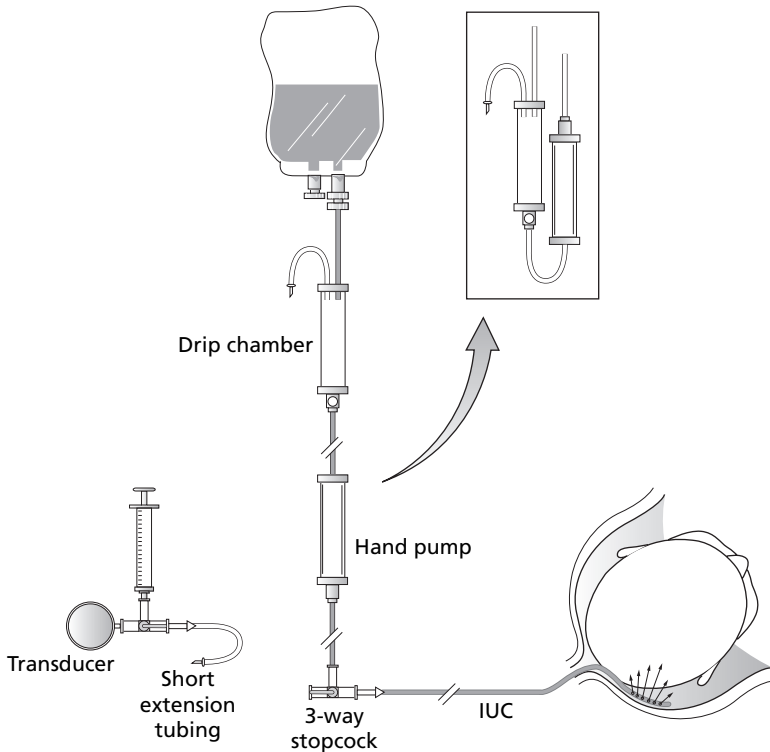


Fig. 24.1 Amnioinfusion set-up with blood pump intravenous tubing (inset). When filling the intravenous tubing, the blood pump must be held in an inverted position to get primed.

- 5 The amount of fluid leakage can be measured by pad weighing but bedside sonographic assessment is much easier. If a large, continuous fluid leakage occurs, a repeat vaginal examination should be performed to rule out intra-cervical coiling of the catheter.

Transabdominal

- 1 Preparation for an amniocentesis, use a 20-gauge needle. After documentation of placement of the needle, slow infusion of 50–200 mL normal saline at room temperature. Continuous monitoring with ultrasound of the location of the fluid to confirm placement and evaluation of fetal well being. Additional fluid may be infused if deemed necessary by ultrasound.
- 2 Re-aspiration of the infused fluid can be obtained for karyotype analysis.

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PART 4

*Maternal
disease*

Sickle cell disease

Chad K. Klauser and John C. Morrison

INTRODUCTION

Sickle cell disease represents the most common of the various hemoglobinopathies, affecting over 2.5 million people in the USA. It is a common genetic disease and frequently complicates pregnancy management. Sickle cell anemia (Hb S-S) and hemoglobin SC disease (Hb S-C), also known as sickle cell disease, represent the most frequently occurring hemoglobin abnormalities, as well as having the most significant impact on pregnancy. Sickle cell disease has a significant prevalence in the African-American population, with 1 in 12 possessing the sickle cell trait. Among this same population, the birth prevalence of sickle cell anemia (Hb S-S) is 1 in 600, while Hb S-C occurs at a rate of 1 in 1250. Hemoglobin beta-thalassemia is somewhat less frequent, with a known prevalence of 1 in 1667.

Sickle cell trait (Hb A-S) is associated with much less untoward outcomes during pregnancy, but its identification is important in offering complete genetic counseling to patients. In addition, it has been associated with twice the rate of urinary tract infections during pregnancy when compared with matched controls, and more recently has been linked to placental abnormalities resulting in stillbirth and growth restriction. Hemoglobin S-thalassemia (Hb S-Thal) usually results in only a mild anemia, although its manifestations are variable based on the percentage of Hb S present. Anemia and vaso-occlusive episodes are characteristic of sickle cell diseases, with the exception of Hb A-S. Hemoglobin S-S has been associated with increased complications such as pre-eclampsia, preterm labor, premature preterm rupture of membranes, intrauterine growth restriction, antepartum admission, spontaneous abortion, and stillbirth. Hemoglobin S-C disease has similarly been linked to intrauterine growth restriction and antepartum admission.

PATHOPHYSIOLOGY

Both Hb S-S and Hb S-C are hemoglobinopathies characterized by autosomal recessive defects in the structure and function of the hemoglobin molecule.

Sickle hemoglobin results from a gene mutation that substitutes a valine for glutamic acid at the sixth position in the hemoglobin beta-subunit. A missense mutation leading to the substitution of lysine in the sixth position results in hemoglobin C disease. These structurally abnormal molecules function normally in the presence of adequate oxygenation. However, in the presence of relative hypoxia, the substituted amino acid forms a hydrophobic bond with adjacent chains, forming tetramers that strand and buckle the cell wall. This structural change is responsible for the characteristic sickle shape. Hypoxia may be initiated by infection and/or exacerbated by extremes in temperature, acidosis, and dehydration; all of which contribute to the abnormal, elongated sickle shape of the red blood cell. These malformed red blood cells may precipitate microvascular occlusion, resulting in further hypoxia, and ultimately tissue infarction. The hyperviscosity of pregnancy contributes to the process, and significant maternal and fetal morbidity may ensue. The life of the deformed red blood cell is only 12 days, significantly shorter than a normal circulating red cell (120 days). This results in a state of chronic anemia and increased clearance of the cells by the reticuloendothelial system.

DIAGNOSIS

While universal screening of pregnant patients for hemoglobinopathies is not recommended, certain ethnic groups are known to carry a higher risk for these hemoglobinopathies and will benefit from testing. In addition to the African-American population, hemoglobin S is frequently found in patients of Caribbean or Central American descent. The frequency of hemoglobin C is increased in peoples of Mediterranean, as well as African descent. Beta-thalassemia is frequently found in populations from North Africa, Italy, Greece, or India. In addition, any patient with a family history of a hemoglobinopathy should be tested.

Previously, solubility testing was frequently used as an initial screen for hemoglobinopathies. However, the solubility test will frequently fail to identify trait carriers for hemoglobin B, C, D, E, and thalassemia, therefore this test is not recommended as an initial screen. It may be useful in situations when a rapid test result could alter immediate clinical management. Instead, hemoglobin electrophoresis should be the initial test for those from high-risk populations, or when anemia or abnormal mean corpuscular volume (MCV) values are detected on routine prenatal complete blood counts (CBCs). If a hemoglobinopathy is identified, the partner should be appropriately tested. If they are found to be affected, antenatal diagnosis may be offered in the form of DNA-based testing utilizing amniocentesis, chorionic villus sampling, or percutaneous umbilical blood sampling. These testing modalities should be offered after counseling by the obstetrician or a genetic counselor. There is significant variability in the course of sickle cell disease, with some experiencing frequent

crises, debilitating complications, and even death, while others are relatively asymptomatic. The life expectancies for sickle cell anemia have also increased, approaching 42 years for males and 48 years for females, while those with Hb S-C are significantly higher, 60 and 68 years respectively.

MANAGEMENT

Prior to 1970, a maternal mortality rate of 11% was reported, with fetal loss as high as 52%. Improved management has dramatically decreased the maternal mortality to less than 1%. Controversy exists concerning the role of transfusion during pregnancy. While its benefit may be questionable in the uncomplicated pregnancy, transfusions have been found to lower the incidence of painful crises in pregnancies effected by vaso-occlusive episodes. Exchange transfusions are usually reserved for women with complications such as acute chest syndrome, stroke, severe anemia, or pain crises increasing in severity or frequency. Transfusions may be beneficial in women with recurrent pregnancy losses or those with multiple gestations, to maintain a hemoglobin level above 9 g/dL. Regardless, patients with sickle cell disease require more frequent pre-natal evaluations, usually every 1–2 weeks. The patient should also be monitored closely for early signs of infections or the onset of a vaso-occlusive crisis.

A management protocol for sickle cell disease is as follows:

- 1 Confirm the diagnosis and recommend testing for the partner.
- 2 Genetic testing should be offered and the patient should be counseled as to the expected course of pregnancy.
- 3 Discontinue hydroxyurea ideally prior to conception. While found to be teratogenic in animals, few data exist on its use during human pregnancy.
- 4 Obtain a CBC every 2 weeks. Perform iron studies to determine if iron deficiency is a contributing factor to the anemia. The patient should take supplemental folic acid. Exogenous iron should be given if indicated by iron studies.
- 5 A urinalysis with culture and sensitivity should be performed each trimester.
- 6 Ensure the patient has received a pneumovax vaccine in the past 5 years (ideally prior to pregnancy). Influenza and hepatitis vaccinations should be documented and updated if needed as per standard protocol.
- 7 Weekly fetal assessments in the form of non-stress test (NST), contraction stress test (CST), or biophysical profile should be initiated at 34 weeks. A baseline ultrasound at 14–16 weeks should be obtained, followed by repeat sonography at 24–26 weeks, then every 3–4 weeks until delivery, specifically targeting appropriate fetal growth.
- 8 Consider exchange transfusion if Hb A is less than 20% or in the presence of frequent pain crises.
- 9 Vigilance to identify evidence of infection or onset of pain crisis.

- 10 Monitor for signs of preterm delivery or onset of pre-eclampsia.
- 11 Expect routine term delivery, with cesarean section reserved for obstetric indications. Supplemental oxygen and laboring in the left lateral position should be considered, as well as adequate hydration during prolonged labors.
- 12 Epidural anesthesia and oxytocin use is not contraindicated during labor.
- 13 Postpartum contraceptive counseling is recommended.

COMPLICATIONS

While significant fetal and maternal morbidity have dramatically decreased with current therapies, vaso-occlusive crisis occur in up to 70% of pregnant patients with Hb S-S and 30% with Hb S-C. Infection must be excluded when a patient presents with pain, and obstetric complications including preterm labor, pre-eclampsia, abruption, or pyelonephritis must be evaluated. Management is similar to non-pregnant patients, including hydration, oxygen therapy, and appropriate analgesia. Consideration for exchange transfusion or direct transfusion should be made for the patient with frequent vaso-occlusive crises during the gestation. Should infection be suspected, sources should be actively sought and empiric antibiotics used until the etiology of the infection is identified. During a pain crisis, assessments of the fetus may be effected, including a non-reactive NST or abnormal biophysical profile. Antenatal assessments should normalize as the crisis subsides. Preterm delivery and intrauterine growth restriction are more common in patients with sickle cell disease. Evaluation for both complications should be routinely undertaken. Stillbirths tend to be increased among patients with frequent and severe vaso-occlusive crises.

FOLLOW-UP

Following delivery, continued surveillance for crisis or a thrombotic event is imperative. Contraceptive options include permanent sterilization, progestin-only pills, or medroxyprogesterone (Depo-Provera®, Pharmacia, Milton Keynes, UK). Randomized controlled trials do not exist to contraindicate combination oral contraceptives, but other methods are preferable.

FUTURE DIRECTIONS

Research goals include improving diagnostic and treatment capabilities and a continuing search for a possible cure. Preimplantation genetic diagnosis has been successful in diagnosing affected embryos, allowing affected parents with the trait or disease the option to forgo embryo implantation. Free fetal DNA found in the maternal circulation is being investigated as a source for fetal genetic testing for the defect, forgoing invasive procedures such as chorionic villus sampling, amniocentesis, or percutaneous umbilical blood sampling (PUBS). Additionally, gene therapy is a continual source of investigation,

attempting to introduce genes into the hematopoietic system capable of producing Hb A molecules. Currently, bone marrow transplants are the only cure, although the complications are significant and matched donors rare. Improvements in the process of bone marrow donation and transplantation continue. These include the collection of sibling donor cord blood for stem cell transplantation, allowing marrow transplants without undergoing painful marrow harvesting. Finally, attempts of *in utero* hematopoietic stem cell transplantation are being evaluated as a potential antenatal therapy, avoiding postnatal stem cell transplantation. While thus far unsuccessful in the treatment of hemoglobinopathies, research continues to overcome existing barriers.

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Isoimmune thrombocytopenia

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INTRODUCTION

Isoimmune or idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder where antiplatelet antibodies cause destruction of platelets by the reticuloendothelial system (RES). Acute ITP is usually self-limiting and occurs predominantly in children, most often following a viral illness. The chronic form is more common in women than men and the peak incidence occurs in the third decade of life. It is estimated that ITP complicates 1–2 of every 1000 pregnancies.

PATHOPHYSIOLOGY

The autoantibodies are usually immunoglobulin G (IgG) and are directed against platelet-specific membrane glycoproteins. Antigen–antibody complexes are removed from the circulation by the RES, primarily the spleen, resulting in decreased circulating platelets. The rate of platelet destruction is greater than the rate of platelet production in the bone marrow, leading to thrombocytopenia.

Since platelet counts have been included in automated complete blood cell (CBC) reports and because this test is routine in pregnancy, an increased incidence of thrombocytopenia has been noted in pregnant patients. Many women with mild thrombocytopenia noted late in gestation are misdiagnosed as having ITP when they actually have gestational thrombocytopenia. In this mild disorder, C3 (activated complement) rather than IgG binds to platelets. Platelet counts usually remain above $70,000/\mu\text{L}$ and normalize within 2–12 weeks postpartum. These patients are generally asymptomatic without a previous history of decreased platelets except perhaps in previous pregnancies. The recurrence risk of gestational thrombocytopenia is unknown. The risk for neonatal thrombocytopenia is negligible.

While the majority of women with ITP will have a history of easy bruising, petechiae, epistaxis, and gingival bleeding, a portion of women with ITP are

asymptomatic. Maternal hemorrhage rarely occurs unless the platelet count is less than 10,000–20,000 μL . Pregnancy is not thought to increase the incidence of or to worsen ITP. However, ITP may have a profound impact on pregnancy as severe thrombocytopenia places the mother at risk for hemorrhage in both the antepartum and postpartum periods. ITP may also affect pregnancy as there is a small risk that it may be associated with neonatal thrombocytopenia which places the neonate at risk for poor outcomes such as intracranial hemorrhage and subsequent long-term adverse neurologic outcomes.

Maternal antiplatelet IgG antibody can cross the placenta, bind to fetal platelets, and enhance the destruction of fetal platelets resulting in transient neonatal thrombocytopenia. There is an approximately 10% risk that the neonate will have a platelet count of less than 50,000 μL and a less than 5% risk that the neonate will have a platelet count of less than 20,000 μL . Neonatal platelet counts of less than 50,000 μL can result in minor bleeding such as purpura, ecchymoses, and melena. Rarely, fetal thrombocytopenia associated with ITP can lead to intracranial hemorrhage irrespective of mode of delivery. Serious bleeding complications are thought to be less than 3%, and the rate of intracranial hemorrhage is thought to be less than 1%, which is greater than the risk among neonates born to women without ITP. The actual incidence of neonatal thrombocytopenia and associated hemorrhage is uncertain as no large-scale studies exist. The correlation between maternal and fetal platelet count is poor, and no non-invasive method is currently available to detect neonates at risk. It is thought that women with a history of splenectomy, a platelet count of less than 50,000 μL at some time during the pregnancy, and a previous child with neonatal thrombocytopenia are at increased risk for fetal or neonatal thrombocytopenia. Circulating antibodies also may be associated with increased fetal risk. Maternal administration of steroids and or intravenous gammaglobulin has no demonstrable therapeutic effect on the fetal platelet count.

DIAGNOSIS

ITP is a diagnosis of exclusion as there are no diagnostic tests specific for the disorder and there are no pathognomic signs or symptoms for the disorder.

Exclude other causes of decreased platelets in pregnancy such as:

- 1 Gestational hypertension
- 2 HELLP syndrome
- 3 Drug reaction
- 4 Laboratory error
- 5 Systemic lupus erythematosus
- 6 Antiphospholipid antibody

- 7 Lymphoproliferative disorder
- 8 Human immunodeficiency virus infection
- 9 Hypersplenism
- 10 Disseminated intravascular coagulation
- 11 Thrombotic thrombocytopenic purpura
- 12 Hemolytic uremic syndrome
- 13 Congenital thrombocytopenia
- 14 Gestational thrombocytopenia

Diagnostic criteria include:

- 1 Persistent thrombocytopenia (platelet count less than 100,000 μ L).
- 2 Peripheral smear may show decreased number of platelets with enlargement of those that are present.
- 3 Bone marrow aspirate (not essential for diagnosis) shows normal or increased number of megakaryocytes.
- 4 Absence of splenomegaly.
- 5 Antiplatelet antibodies may or may not be detectable.
- 6 Normal coagulation studies.

ANTEPARTUM MANAGEMENT

Pregnant women with a history of ITP require serial assessment of their platelet counts as these counts may fluctuate during pregnancy. Monthly testing is suggested for the first two trimesters. In the third trimester, patients should be tested every other week and then weekly as they approach term. Consultation with a physician who is experienced with ITP is suggested. Pregnant women with ITP and thrombocytopenia should be encouraged to restrict their activity and to avoid trauma, alcohol, aspirin, and all medications that are platelet inhibitors. They should also avoid intramuscular injections, and they should treat fevers with acetaminophen.

The goal of therapy in pregnant patients with ITP and thrombocytopenia is to decrease the risk of bleeding complications associated with severe thrombocytopenia. Platelet function is usually normal despite decreased numbers of platelets. Thus, maintaining a normal platelet count in these patients is not necessary.

The general consensus is that treatment is not required unless the platelet count is significantly less than 50,000 μ L or if the patient is symptomatic. However, counts greater than 50,000 μ L may be desired at delivery and for regional anesthesia. It is important to note that treatment is indicated for the maternal status and not for fetal indications, as these therapies have not been proven to decrease the risks of neonatal thrombocytopenia and subsequent hemorrhage. The initial treatment for ITP is prednisone 1 mg/kg orally once daily. Improvement in platelet count is usually noted within 3–7 days. The maximal response is usually noted within 2–3 weeks. The dosage should be

increased as necessary. Once the platelet count has increased to an acceptable level, the dosage can be tapered by 10–20% until the lowest dose required to maintain the platelet count at an acceptable level is determined.

If the patient remains refractory to steroids, or if the platelet count is less than 10,000 μL , or if the platelet count is less than 30,000 μL and the patient is symptomatic or predelivery, intravenous immunoglobulin (IVIG) may be warranted. A response may be noted from 6 to 72 h following administration of IVIG. If IVIG is being considered, consultation with a physician familiar with this treatment is suggested.

If there is no response to IVIG, splenectomy should be considered. Removal of the spleen removes the primary site of platelet destruction and antibody production. Splenectomy has been associated with complete remission of ITP, but has not consistently been found to be beneficial in patients who fail IVIG. While splenectomy can be performed safely in pregnancy, the procedure should be avoided as it is technically difficult and may incur fetal risks. The procedure may be warranted in pregnancy if platelet counts are less than 10,000 μL and the patient has failed both prednisone and IVIG therapy. The optimal timing for splenectomy is the second trimester. If splenectomy is deemed necessary in the third trimester, cesarean delivery followed by the procedure should be considered. In addition to the flu vaccine, pregnant women with a history of splenectomy should be vaccinated against pneumococcus, meningococcus, and *Haemophilus influenzae*.

Platelet transfusion should only be utilized as a temporizing measure for severe hemorrhage or to help prepare a patient for surgery. Donor platelets do not survive for long periods of time in women with ITP. The medications usually used to treat ITP such as colchicines, vinca alkaloids, cyclophosphamide, danazol and other potentially teratogenic agents are avoided in pregnancy as they are thought to have adverse effects on the fetus.

INTRAPARTUM MANAGEMENT

The most significant clinical dilemma relating to ITP is that the fetus may be at risk for neonatal thrombocytopenia and for severe bleeding complications. The risk is small, but unfortunately there is no test that can accurately discern if a fetus is at risk for severe thrombocytopenia. At the present time, obtaining a fetal platelet count prior to delivery is not thought to be necessary. Scalp sampling while in labor is often inaccurate and technically challenging. Meanwhile, cordocentesis involves a 1–2% risk of emergent cesarean delivery secondary to complications. Vaginal delivery is not contraindicated in these patients and cesarean delivery is not thought to protect these patients from fetal bleeding complications. Thus, routine obstetric management is appropriate for pregnant women with ITP. However, fetal scalp electrodes and delivery by vacuum should be avoided. Antiplatelet medications such as non-steroidal inflammatory drugs

(NSAIDs) should not be prescribed to these patients during the postpartum period. Breastfeeding is safe for women with a history of ITP.

Consultation concerning anesthesia is appropriate for patients with ITP. Neuraxial anesthesia (spinal or epidural) is generally safe in women with platelet counts of more than 80,000 μL provided that coagulation studies are normal. The risk of epidural hematoma with neuraxial anesthesia is exceedingly rare in patients with functional platelets and platelet counts greater than 100,000 μL . The risk does not increase significantly until the platelet count falls below 50,000–75,000 μL , and there are no reliable data on outcomes for these counts. Generally, neuraxial anesthesia is contraindicated in patients with platelet counts of less than 50,000 μL as the risk of hematoma is believed to be greater than acceptable. In patients with platelet counts less than 100,000 μL , there should be consultation between the obstetrician and anesthesiologist and a unified risk–benefit analysis should be presented to the patient, enabling the patient to make an informed decision regarding her choice of labor anesthesia or analgesia. If available, a thromboelastogram (TEG) can help determine if available platelets can form adequate clot.

It is recommended that these patients deliver in a hospital where all physicians caring for the patient, including the obstetrician, anesthesiologist, and pediatrician, are familiar with ITP and where potential maternal and neonatal complications can be adequately handled. The infant's platelet count should be monitored throughout the first few days of life as thrombocytopenia may develop in the postpartum period. Head ultrasound should be performed if the neonate was born with or develops thrombocytopenia.

CONCLUSIONS

ITP is a relatively rare disease in pregnancy, and is a diagnosis of exclusion. For the most part, maternal and fetal outcomes are favorable. Serial platelet counts are suggested. Consultation with a physician familiar with the care of these patients may be warranted. Platelet counts significantly less than 50,000 μL may require treatment. Likewise, symptomatic patients require treatment. Prednisone is the first-line therapy. IVIG may be necessary for refractory cases. Splenectomy is reserved for severe cases refractory to other treatments. While up to 10% of neonates may be diagnosed with neonatal thrombocytopenia, the risk for severe complications such as neonatal intracranial hemorrhage is thought to be less than 1%. Delivery in a center familiar with this disorder and the potential maternal and neonatal complications is advised. Vaginal delivery is not thought to place these patients at increased risk for fetal intracranial hemorrhage and cesarean delivery has not been proven to be protective. As a result, routine obstetric management is appropriate for the majority of these patients. However, fetal scalp electrodes and delivery by vacuum should be

avoided. The use of medications such as NSAIDs are not recommended so as to avoid interfering with the function of available platelets.

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Autoimmune disease

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SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

Systemic lupus erythematosus (SLE) complicates 1 in 2000 to 1 in 5000 pregnancies, with a fivefold increase in prevalence among African-American women. The disorder is associated with an increased occurrence of spontaneous abortion, intrauterine fetal demise (IUID), intrauterine growth restriction (IUGR), fetal distress, pre-eclampsia, and either spontaneous or indicated preterm deliveries (PTDs).

Pathophysiology

Several theories address the genesis of SLE (Fig. 27.1). The first holds that autoantibody-generating B lymphocytes are pathologically stimulated in a non-specific fashion (polyclonal B-cell activation). The second argues that endogenous antigens, rendered immunogenic by environmental or infectious damage, induce a specific antigen-driven response. In either case, immunologic damage may be mediated either by:

- 1 The formation of antibody–antigen (Ab–Ag) complexes, which, in turn, cause glomerulonephritides, arthritis, dermatitis, central nervous system (CNS) involvement, pericarditis, pneumonitis, and hepatitis.
- 2 Antibodies directed against cell-specific antigens that cause isolated cell or tissue damage (e.g. autoimmune thrombocytopenia [ATP], hemolytic anemia [HA], antiphospholipid antibody syndrome [APA Sy], leukopenia, vasculitis, and/or neonatal congenital heart block [CHB]).

The risk of developing a specific manifestation is linked to a patient's HLA-DR and HLA-DQ histocompatibility loci. Recently, a third theory has emerged specific to pregnancy outcome: antiphospholipid (aPL) antibodies activate complement in the placenta, generating split products that mediate placental injury and lead to fetal loss and growth restriction, and that complement activation by aPL antibodies in other vascular areas causes inflammation and thrombophilia.

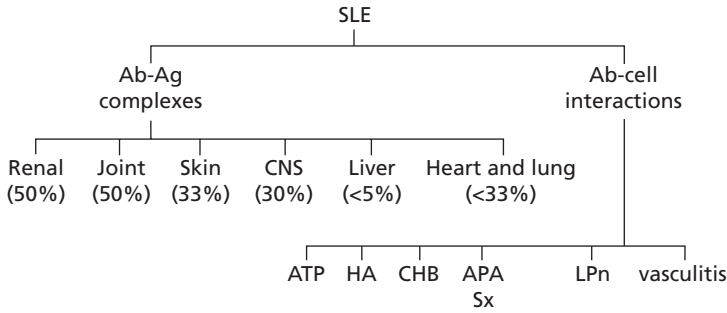


Fig. 27.1 Pathogenesis of systemic lupus erythematosus (SLE) primary immunoregulatory dysfunction.

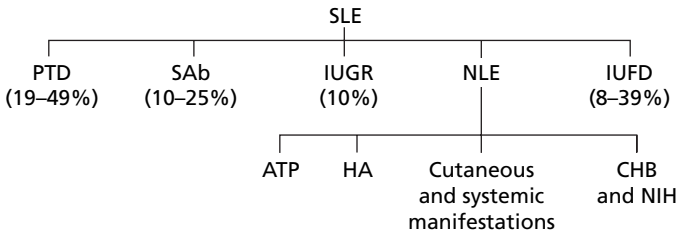


Fig. 27.2 SLE effects on fetus.

Effect of SLE on pregnancy

The prognosis for a live birth is dependent on four factors: the activity of the disease at conception and the occurrence of subsequent flares, the coexistence of lupus nephritis, development of APA Sy, and the presence of anti-SSA (Ro) antibodies (Fig. 27.2).

Lupus flares occur in 50% of patients and are more common in the first trimester. Patients with a greater than 6-month remission at conception continuing throughout pregnancy have a 90% live birth rate, while those undergoing a flare during pregnancy have a 65% live birth rate.

Clinical evidence of *glomerulonephritis* is present in 50% of SLE patients, while histologic evidence is present in 90% of patients. Subtypes include the following:

- 1 mesangial nephritis (better prognosis)
- 2 membranous nephritis (better prognosis)
- 3 focal proliferative nephritis (poor prognosis)
- 4 diffuse proliferative nephritis (poor prognosis)

Clinically evident nephrotic syndrome is associated with a 60% live birth rate. However, the development of concomitant hypertension (25%) or an elevation in the serum creatinine to greater than 1.5 mg/dL lowers the live birth rate to 50%. The presence of severe hypertension or renal failure is associated with only a 20% live birth rate.

APA Sx (25% of SLE patients) causes late first, second- and third-trimester death, IUGR, pre-eclampsia, and maternal thromboembolic phenomenon. Patients with SLE and aPL, lupus anticoagulant (LAC), or anticardiolipin antibodies (ACA) may have up to a 70% risk of recurrent pregnancy loss. The diagnosis requires laboratory evidence of either LAC or moderate to high concentrations of ACA (more than 20 GPL and MPL units) together with either a history of recurrent pregnancy loss, history of thrombosis, or autoimmune thrombocytopenia. However, the SLE-associated thrombocytopenia may also reflect antiplatelet antibodies or vasculitis.

Anti-SSA (Ro) antibodies, present in 25% of SLE patients, are associated with a HLA-DR3 histocompatibility antigen haplotype. Anti-SSA antibodies cause 95% of all CHB in fetuses with normal cardiac anatomy; however, CHB will develop in only 5% of fetuses exposed to anti-SSA antibodies, generally between 18 weeks and term. The risk of CHB increases to 33% with a previously affected sibling. These antibodies are a marker for the development of immunoglobulin G (IgG) mediated fetal cardiomyopathy, non-immune hydrops (NIH), and related stillbirths. Anti-SSA antibodies are also a marker for the development of neonatal lupus (NLE), which manifests itself as transient lupus dermatitis, systemic and hematologic abnormalities (HA and ATP), and/or CHB. Congenital SLE is far more common in female neonates (14:1 for cutaneous and systemic involvement and 2:1 for isolated CHB). The lesions generally appear within 6 weeks of birth and persist for 1 year.

Diagnosis

Patients generally present with intermittent, unexplained pyrexia, malaise, arthralgias, myositis, serositis, thrombocytopenia, nephritis, and/or CNS abnormalities. A positive antinuclear antibody (ANA) is found in 98% of patients (and 10–20% of uncomplicated pregnant patients). The diagnosis is established when four or more of the following American Rheumatism Association criteria are present:

- 1 Butterfly rash
- 2 Discoid lupus
- 3 Photophobia
- 4 Oral ulcers
- 5 Arthritis
- 6 Serositis

Table 27.1 Systemic lupus erythematosus (SLE) associated laboratory findings. (From Mill 1994.)

Antibody	HLA	Clinical feature
Anti-ds DNA	DR2	Nephritis
	DQB1	Vasculitis
Anti-SM	DR2	Nephritis
	DQw6	CNS disease
Anti-RNP	DR4	Arthritis
	DQw8	Myositis and Raynaud's
Anti-SSA (Ro)	DR3	CHB
	DQw2.1	Sjögren's syndrome
Anti-SSB (La)		Negatively associated with renal disease in SSA (+) patients
Anti-centromere		CREST syndrome
Anti-U1-RNP		Mixed connective tissue disease
LAC and ACA		Antiphospholipid antibody syndrome

CREST, calcinosis, Raynaud's phenomenon, esophageal involvement sclerodactyly telangiectasia; RNP, ribonucleoprotein.

- 7 Renal disease manifested by proteinuria greater than 500 mg/day, 3+ urine protein, and/or cellular casts on urinalysis
- 8 Neurologic abnormalities often caused by cerebral vasculitis or APA-mediated thrombosis (e.g. seizures, cerebrovascular accidents, and psychosis)
- 9 Hematologic abnormalities, including HA, leukopenia less than 4000 cells/ μ L, lymphopenia less than 1500/ μ L, and thrombocytopenia less than 100,000/ μ L
- 10 Abnormal laboratory tests, including:
 - positive ANA in the absence of drug therapy
 - (+) LE prep
 - (+) anti-SM antibodies
 - false-positive RPR (rapid plasma reagin test) (Table 27.1)

Initial visit

It is recommended that the following be obtained at the first prenatal visit.

- 1 Complete blood count (CBC) with differential and platelet count
- 2 24-h urine collection for creatinine clearance and total protein with serum creatinine

- 3 Hepatic transaminases (ALT, AST)
- 4 LAC/ACA
- 5 Indices of disease activity: ANA and antideoxyribonucleic acid (DNA) titers, and complement factors 3 and 4
- 6 Anti-SSA (Ro) antibody screen, an indicator of risk for neonatal SLE and CHB

Specific management problems

Antiphospholipid antibody syndrome (APA Sx)

The presence of LAC or moderate to high-level ACA in a pregnant patient with SLE (30% of cases) and a characteristic clinical picture should be an indication for treatment with low-dose aspirin (80 mg/day p.o.) and prophylactic heparin (unfractionated heparin 5000–10,000 IU b.i.d. subcutaneously or low molecular-weight heparin such as enoxaparin 30–60 mg/day), particularly if the patient has a history of thromboembolic phenomenon or prior fetal loss. When this regimen fails in APA Sx patients, consideration should be given to adding intravenous gamma globulin infusion (IVIG). Because of an increased risk of preterm premature rupture of membranes (PPROM), heparin, not prednisone, is recommended as first-line therapy.

Patients with anti-SSA (Ro) antibodies

Patients with SLE at risk for neonatal lupus or CHB on the basis of anti-SSA (Ro) antibodies should have fetal echocardiography performed by an experienced physician at monthly intervals starting at 18 weeks' gestation. Should the fetus demonstrate evidence of incomplete heart block or early cardiomyopathy, consideration should be given to dexamethasone therapy (4 mg/day p.o.) or plasmapheresis with IVIG therapy, or both. The former therapy should be discontinued in the presence of oligohydramnios. Pediatricians should be alerted to the risk of neonatal SLE. Infants of mothers receiving dexamethasone therapy should be observed for evidence of hypothalamic–pituitary–adrenal axis suppression.

Lupus nephritis

Patients with nephritis are at increased risk of pregnancy-induced hypertension (PIH), pre-eclampsia, and deterioration of renal function, as well as stillbirth, IUGR, and preterm delivery. While at least one-third of SLE patients with proteinuria present before pregnancy will display increases in urinary protein loss, reversible renal dysfunction occurs in only 13% and hypertension either develops or worsens in approximately 25%. The differentiation of a lupus flare from pre-eclampsia (Table 27.2) poses a clinical conundrum in SLE patients. Declining levels of C3, C4, and CH50 may occur in both disorders but tend to be more severe with lupus flares. Additional discriminators are listed in Table

Table 27.2 Differentiating a lupus flare from pre-eclampsia.

Lupus flare	Superimposed pregnancy-induced hypertension
Any gestational age	Third trimester
Diffuse SLE symptoms	Pre-eclampsia symptoms (e.g. headache)
Increased anti-DNA titer	Stable anti-DNA titer
Stable platelets (if no ATP or APA)	Thrombocytopenia
Normal AST, ALT	Elevations in AST, ALT
Normal fibronectin	Increased fibronectin
Exacerbation postpartum	Resolution postpartum

27.2. It is yet to be established whether low-dose aspirin (80 mg/day p.o.) therapy reduces the risk of superimposed pre-eclampsia in SLE patients without LAC or ACA.

Generalized SLE flare

The occurrence of a lupus flare should be treated with prednisone 60 mg/day orally for 3 weeks, with gradual tapering of the dose to 10 mg/day. Patients with evidence of membranous or diffuse glomerulonephritis should be treated with even higher doses of prednisone up to 200 mg/day and/or plasmapheresis (with gammaglobulin or fresh frozen plasma) or azathioprine. Given the osteopenic effects of glucocorticoids, patients treated with prednisone should receive calcium supplementation. In addition, they should undergo repeated glucose screens. Stress steroids must be given at delivery in all SLE patients treated with steroids during the pregnancy or for more than 1 month in the past year. Penicillamine should probably be avoided in pregnant patients because of the risk of adverse fetal sequelae. Hydroxychloroquine use is mildly controversial in pregnancy because of very rare ocular complications in the newborn, but may be preferred for women likely to experience complications from steroids, such as those with diabetes.

There are some promising experimental attempts to modulate the immune system in non-pregnant SLE patients, such as anti-B cell antibodies, IVIG, dehydroepiandrosterone (DHEA), bromocriptine, zileuton, cyclosporine, anti-CD40, LJP 394, anti-C5 complement monoclonal antibody, anti-IL-10, and immunoadsorption via perfusion of patients' blood through a column of immobilized C1q. All of these therapies are considered experimental.

Antepartum management

- 1 First-trimester ultrasound scan to establish estimated date of confinement.
- 2 Level II ultrasound and echocardiography at 18 weeks; echocardiography should be repeated monthly in patients with SSA antibodies.
- 3 Monthly ultrasounds to assess fetal growth from 18 weeks. Ultrasound assessments should be more frequent if IUGR is suspected or documented sonographically. Doppler flow studies may be useful in determining the optimal timing of delivery.
- 4 Office visits as often as every 2 weeks may be warranted beginning at 28 weeks.
- 5 Non-stress tests and/or biophysical profiles, weekly beginning at 36 weeks in uncomplicated cases or at 28 weeks and beyond given the presence of IUGR, APA Sx, SLE flare, worsening renal function, or hypertension.
- 6 24-h urine for protein and creatinine clearance every 1–2 months.
- 7 Fetuses with CHB should be assessed antepartum and intrapartum with biophysical profiles or via non-stress testing using Doppler interrogation of their atrial rate.

Timing of delivery

Uncomplicated SLE in patients with SLE in the absence of SSA antibodies, APA Sx, worsening nephritis and/or hypertension, IUGR, oligohydramnios, or superimposed pre-eclampsia, delivery can be delayed until 40 weeks provided that the twice weekly fetal testing initiated at 36 weeks is reassuring.

Deteriorating maternal or fetal health

Beyond 34 weeks' gestation

Patients beyond 34 weeks with worsening renal, liver, or CNS function; hypertension; IUGR with oligohydramnios, absent or reversal of diastolic Doppler flow, or cessation of fetal growth; or non-reassuring fetal testing should be promptly delivered. Attempts at a vaginal delivery are indicated in the absence of acute fetal distress. Intravenous magnesium sulfate prophylaxis should be used in the presence of superimposed pre-eclampsia.

28–34 weeks' gestation

Patients between 28 and 34 weeks with worsening renal or liver function, development of or exacerbation of hypertension, CNS symptoms, or uteroplacental vascular compromise should be immediately hospitalized and given appropriate medical therapy (e.g. prednisone, antihypertensives), a course of betamethasone until 34 weeks to enhance fetal lung maturity, and daily fetal heart rate testing or biophysical profiles. Delivery is indicated for deteriorating maternal blood pressures, the development of severe pre-eclampsia, or the occurrence of fetal distress. The cessation of fetal growth for more than 14 days

may be an indication for delivery after 28 weeks in the presence of severe oligohydramnios, or persistent reverse diastolic Doppler flow, or both. Again, attempts at a vaginal delivery are indicated in the absence of acute fetal distress. Intravenous magnesium sulfate prophylaxis should be used as indicated in the presence of hypertension.

24–28 weeks' gestation

Patients between 24 and 28 weeks with deteriorating maternal or fetal health should be immediately hospitalized, treated with prednisone and antihypertensives if indicated, given betamethasone to enhance fetal lung maturity, and subjected to daily fetal testing. Delivery is indicated for deteriorating maternal renal, cardiac, liver, or CNS function unresponsive to therapy, and the development of severe pre-eclampsia at bed rest, or fetal distress. Again, attempts at a vaginal delivery are indicated in the absence of acute fetal distress. Intravenous magnesium sulfate prophylaxis can be used as needed.

Less than 24 weeks' gestation

Patients at less than 24 weeks' gestation with a rapidly deteriorating maternal or fetal condition that is refractory to bed rest and medical therapy should be given the option of pregnancy termination because the prognosis is poor in these cases. However, patients should be cautioned that their maternal condition may not improve after termination.

Postpartum care

Because some believe that exacerbation after delivery may be more likely, patients need careful monitoring during the puerperium. Patients should be counseled to report any symptoms promptly. Estrogen-containing contraception should be avoided as it may contribute to the risk of thrombosis. Any prior history of thrombosis in pregnancy or on oral contraceptives would merit anticoagulation therapy for up to 12 weeks postpartum.

Serious sequelae

In general, pregnancy does not affect the natural history of SLE. However, a relapse of SLE nephritis during pregnancy can be associated with an up to 10% prevalence of irreversible renal deterioration. SLE is associated with a 1% maternal mortality, with infection (secondary to leukopenia, granulocyte dysfunction, hypocomplementemia, and functional asplenia) and renal failure the most common causes.

RHEUMATOID ARTHRITIS

Introduction

Rheumatoid arthritis (RA) is the most common autoimmune disease in women of childbearing age, with a prevalence of 1 in 2000 pregnancies. Its peak incidence is 35–40 years of age.

Pathophysiology

Rheumatoid arthritis is associated with a HLA-D4 haplotype. The disorder is marked specific CD4⁺ T-cell induction of immune response, with subsequent release of cytokines and recruitment of lymphocytes and monocytes into the synovia of small joints (e.g. wrist and hand). An anti-IgM or IgG rheumatoid factor (RF) complex deposition is also noted in 90% of patients. The resultant joint pain and effusions are mediated by local prostanoid generation, and proteolytic degradation of the cartilage via neutrophil and synovial collagenases. Specific findings include the following:

- 1 *Rheumatoid nodules*: 1–4 cm subcutaneous lumps over the elbows, various pressure points, lungs, and heart valves
- 2 *Pleuritic and pericardial effusions*: with low glucose
- 3 *Felty's syndrome*: splenomegaly and granulocytopenia
- 4 *Rheumatoid vasculitis*

Effect of pregnancy on rheumatoid arthritis

Seventy-four percent improve, with a 90% postpartum exacerbation rate. The patients with remissions have significantly greater disparity in maternal–fetal HLA-DRB1 and DQA and B antigens than those with pregnancies characterized by active disease. This suggests that the maternal immune response to paternal HLA antigens may have a role in pregnancy-induced remission of RA. It is likely that peptides derived from HLA class II molecules of the fetus might compete with or displace maternal self-peptides according to the hypothesis that a defect in the presentation or recognition of self-peptides is crucial to the genesis of RA.

Effect of rheumatoid arthritis on pregnancy

There appears to be no increased rate of spontaneous abortion, perinatal mortality, or IUGR in the presence of RA uncomplicated by APA Sx or anti-SSA antibodies.

Management

Initial treatment in pregnancy should include local steroid injections into the joint. If the response to local measures proves inadequate, begin prednisone, 5 mg every morning and 2.5 mg every evening. The utility and safety of other drugs are listed below.

- 1 *Acetaminophen*: analgesic of choice
- 2 *Non-steroidal anti-inflammatories*: avoid after 20 weeks
- 3 *Intramuscular gold salts*: may cross the placenta, creating a theoretical risk, unconfirmed clinically; may be useful in postpartum period to reduce exacerbations

- 4 *Chloroquine*: useful, but possibly rare ocular side-effects in the fetus
- 5 *D-Penicillamine*: relatively contraindicated
- 6 *Methotrexate*: should be avoided
- 7 *Azathioprine*: use if refractory to steroids
- 8 *Cyclophosphamide*: avoid

New drugs for rheumatoid arthritis

The immunomodulatory drug leflunomide has shown great promise, but is suspected to be teratogenic (Pregnancy Category X). It has an extremely long half-life, taking up to 2 years to reach undetectable levels. As a result, it should be avoided by those women of childbearing age. Tumor necrosis factor antagonists such as etanercept, adalimumab, and infliximab show great promise and may prove to be safe in pregnancy, and are Pregnancy Category B, but there are insufficient data at present to advocate their use in pregnant women. The interleukin-1 antagonist anakinra has similar promise as the latter drugs, as well as similar limitations.

SCLERODERMA

Introduction

Scleroderma is a rare autoimmune disease that affects the skin, esophagus, kidneys, and lungs. Its course is unaffected by pregnancy. It does not appear to cause a higher incidence of spontaneous abortion, but is associated with a modestly higher risk of stillbirth and preterm delivery.

Pathophysiology

Scleroderma is characterized by concentric proliferation of the intima and fibrosis of the adventitia of small arteries and arterioles. Clinical manifestations include the following:

- 1 Raynaud's phenomenon
- 2 Sclerodactyly
- 3 Telangiectasia
- 4 Cardiomyopathy, myocardial infarctions, and cardiac conduction abnormalities
- 5 Calcinosis
- 6 Dysphagia
- 7 Renal failure

Effect of pregnancy on scleroderma

While there are reports of maternal mortality associated with scleroderma, the use of aggressive antihypertensive therapy or dialysis, or both, renders such untoward outcomes rare. However, the prognosis is worsened by the presence of pulmonary and malignant systemic hypertension.

Effect of scleroderma on pregnancy

Earlier reports suggested that scleroderma was associated with high rates of pre-eclampsia (35%), preterm deliveries (30%), and stillbirths (30%). However, such adverse outcomes appear lessened with the advent of improved fetal surveillance and neonatal intensive care.

Management

Mothers should be followed for evidence of deteriorating renal function and worsening hypertension. The presence of coexisting LAC, ACA, and anti-SSA antibodies should be assessed and, if detected, managed as described for SLE patients. Fetal surveillance should follow the paradigm outlined for SLE. The hallmarks of scleroderma management in pregnancy include the following:

- 1 Serial assessment of 24-h urine collection for creatinine clearance and total protein
- 2 Serum creatinine in each trimester
- 3 Physiotherapy for hand contractures
- 4 Antihypertensive therapy (calcium-channel blockers)
- 5 Prednisone for concomitant myositis
- 6 Antacids and metoclopramide to prevent severe reflux esophagitis
- 7 Dialysis with renal failure
- 8 Institution of fetal surveillance as described for patients with SLE, including early dating ultrasound, serial scans for growth, and non-stress tests and/or biophysical profiles weekly beginning at 36 weeks in uncomplicated cases or 24 weeks and beyond given the presence of IUGR, worsening renal function, or hypertension

Complications

The development of malignant hypertension with or without renal failure represents the most important risk factor for maternal and perinatal mortality. Renal failure mandates dialysis while the treatment of malignant hypertension includes the following:

- 1 Central line/Swan-Ganz catheter (if no coagulopathy): assess cardiac output, pulmonary capillary wedge pressure, pulmonary artery pressure, and systemic vascular resistance
- 2 Electrocardiography/cardiac monitor
- 3 Pulse oximeter/arterial line
- 4 Continuous blood pressure monitoring
- 5 Oxygen therapy
- 6 Continuous fetal monitoring if undelivered and beyond 24 weeks' gestation
- 7 Hydralazine 5–10 mg every 20 min or labetalol load with 50 mg IVSS (intravenous soluset), then 60–240 mg/h; switch to oral agents when stable (e.g. labetalol 200–300 mg every 6 h)

- 8 Foley catheter and strict hourly intake and output of urine
- 9 Laboratory studies:
 - CBC with platelets and prothrombin time/partial thromboplastin time/fibrinogen
 - AST/ALT, creatinine, urate, and electrolytes
 - Type and cross

RARER AUTOIMMUNE DISORDERS

Juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis is also associated with a HLA-DR3 haplotype. It has a variable clinical presentation, including the following:

- 1 Still's disease (fever, leukocytosis, pleurisy, rash, hepatosplenomegaly): 10%
- 2 Rheumatoid-like symmetric polyarthritis: 50%
- 3 Asymptomatic arthritis of large joints: 40%

The condition is generally (70–90%) self-limited and not associated with RF IgM or IgG. In 10% of patients there will be sequelae including micrognathia and fusion of the neck, hips, and knees. Pelvic contractures can lead to fetopelvic disproportion, and X-ray or computerized tomography (CT) scan pelvimetry is indicated before pregnancy or in the third trimester.

Ankylosing spondylitis and seronegative arthropathy

These disorders are associated with a HLA-B27 haplotype. They present with insidious backache and stiffness that are worse in morning than evening. Ankylosing spondylitis (AS) and seronegative arthropathy (SNA) present as a spectrum of disorders with overlapping features (Fig. 27.3). In general, the course of AS/SNA is not affected by pregnancy, and vice versa.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) manifests as necrotizing angiitis of small and medium muscular arteries associated with fever, myalgias, arthralgias, hypertension, abdominal pain, mononeuropathy, myocardial infarction, hematuria, and hepatitis.

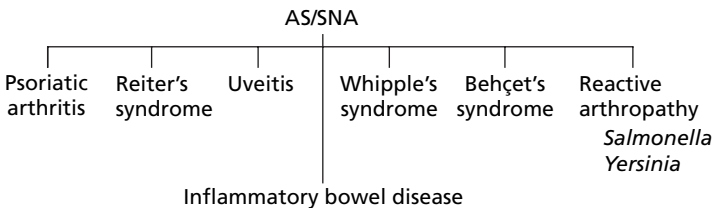


Fig. 27.3 Ankylosing spondylitis—seronegative arthropathy.

The diagnosis can be made on the basis of the following:

- 1 Clinical presentation
- 2 Anemia
- 3 Eosinophilia
- 4 Greatly increased sedimentation rate
- 5 Positive RF and ANA
- 6 Positive hepatitis B surface antigen and antibody
- 7 Polyclonal elevations in IgG and IgM

Pregnancy in patients with PAN can be associated with hypertension and renal failure, leading to a 64% maternal mortality if the disease is active at conception. However, there is no reason to terminate pregnancy because the disease tends to worsen postpartum. In general, patients should be advised to delay conception until remission. Treatment includes steroids.

Polymyositis-dermatomyositis

Polymyositis-dermatomyositis is associated with symmetric proximal muscle weakness and a dusky erythematous eruption over the face, neck, and arms with a violaceous rash over the eyelids. The diagnosis is based on the following:

- 1 Increased creatine phosphokinase
- 2 Elevated ALT/AST
- 3 Abnormal electromyographic findings, including the triad of polyphase shortening of small motor unit potentials, fibrillation, and high-frequency repetitive discharges
- 4 Biopsy: primary degeneration of muscle fibers with basophilia, necrosis, and inflammation

While pregnancy does not seem to affect the progression of the disorder, polymyositis-dermatomyositis appears to be associated with an increased perinatal loss rate. Therapies include steroids, physical therapy, and analgesia. Aggressive fetal surveillance with serial ultrasounds to assess growth as well as fetal heart rate testing and biophysical profiles initiated at 28–32 weeks appears warranted.

Sjögren's syndrome

Sjögren's syndrome is a rare autoimmune disorder often associated with prior human T-lymphotrophic virus I (HTLV-I) infection that results from lymphocytic infiltration of the lacrimal and salivary glands causing keratoconjunctivitis sicca. It is frequently associated with the presence of anti-SSA antibodies and the HLA-DQw2.1 haplotype. Fetuses may be at increased risk of CHB. Pregnancy outcomes are unaffected by Sjögren's syndrome if unaccompanied by coexistent SLE, APA Sx, CHB, fetal cardiomyopathy, or neonatal lupus.

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Cardiac disease

Katharine D. Wenstrom

INTRODUCTION

Cardiac disease is among the leading causes of maternal mortality during pregnancy. A thorough evaluation of the woman with pre-existing heart disease is ideally initiated before pregnancy, so that she can be counseled regarding the risks of pregnancy based on her specific cardiac lesion. Counseling should include a discussion of her cardiac anomaly and baseline functional status, the possibility of optimizing her cardiac status by medical or surgical means, any additional risk factors, and her risk of having a child with the same or different cardiac lesion. Perhaps most difficult, the woman's physical ability to care for a child and her life expectancy should also be addressed. During pregnancy, consultation with appropriate subspecialists as part of a team approach to antepartum and postpartum care is likely to improve both maternal and fetal outcome. Table 28.1 categorizes the risk of maternal death associated with the most common cardiac lesions.

PATHOPHYSIOLOGY

In a normal pregnancy, the cardiovascular system undergoes significant physiologic changes which may not be tolerated by the gravida with heart disease. Increases in plasma volume, oxygen demand, and cardiac output may stress an already compromised cardiovascular system. By mid-gestation, there is a 50% increase in both blood volume and cardiac output and a 20% decrease in systemic vascular resistance (Fig. 28.1). By the end of the second trimester, the heart rate has increased by 20% and blood pressure has reached its nadir. Maternal position further affects these parameters (Fig. 28.2); cardiac output decreases by 20% when the woman is supine and by 16% in dorsal lithotomy position. Cardiac output increases by another 30% during labor, and further increases occur during contractions, during the Valsalva maneuver, and with pain. At delivery, central blood volume may drop as the result of blood loss. Immediately afterward, however, uterine contraction results in an autotransfusion from the uterine circulation, and relief of vena caval compression. With

Table 28.1 Pregnancy-associated maternal mortality in cardiac disease.

Mortality 25–50%

Coarctation of aorta (with valvular involvement)
 Marfan syndrome (with aortic involvement)
 Pulmonary hypertension

Mortality 5–15%

Aortic stenosis
 Mitral stenosis, New York Heart Association (NYHA) classes III and IV
 Mitral stenosis with atrial fibrillation
 Coarctation of aorta (without valvular involvement)
 Uncorrected tetralogy of Fallot
 Marfan syndrome with normal aorta
 Artificial valve (mechanical)
 Previous myocardial infarction

Mortality less than 1%

Atrial septal defect
 Ventricular septal defect
 Pulmonic or tricuspid disease
 Patent ductus arteriosus
 Artificial valve (bioprosthetic)
 Mitral stenosis, NYHA classes I and II
 Corrected tetralogy of Fallot

loss of the placental circulation, the peripheral resistance increases, and at the same time extravascular fluid is mobilized. All these peripartum changes lead to a high output state that may persist for up to 4 weeks. The hemodynamic effects of these pregnancy-induced changes on specific cardiac lesions, along with recommendations for management, are shown in Table 28.2.

DIAGNOSIS AND WORK-UP

Heart disease should be suspected in any pregnant woman who develops dyspnea, chest pain, palpitations, arrhythmias or cyanosis, or who experiences a sudden limitation of activity. Particular attention should be given to the woman who has a history of exercise intolerance, a heart murmur predating pregnancy, or a history of rheumatic fever.

Cardiac disease should be diagnosed and fully characterized as early in the pregnancy as possible, so that the level of maternal and fetal risk can be determined and a therapeutic plan developed. The evaluation should begin with a

Table 28.2 Management of specific cardiac lesions in pregnancy.

Cardiac lesion	Hemodynamic defect	Effect on pregnancy	Management
Mitral/aortic stenosis	↓ LV filling, ↑ PVR; eventual pulmonary HTN	Fixed CO; tachy- or bradycardia will ↓ LV filling and ↓ CO Left atrial dilation leading to pulmonary congestion Arrhythmias Thrombus formation	Maintain preload, but avoid ↑ central blood volume Avoid ↓ SVR Avoid tachycardia and bradycardia Beta-blocker for persistent HR >90–100b/min
Mitral valve insufficiency	Component of regurgitation LV hypertrophy Eventual LV failure Eventual pulmonary HTN	Complications occur late in life; generally asymptomatic during pregnancy The ↓ SVR of pregnancy improves forward flow ↑ SVR during labor increases regurgitation	Treat symptomatic prolapse with beta-blocker Avoid ↑ SVR Avoid myocardial depressants Treat arrhythmias
Aortic insufficiency	LV volume overload, left heart failure, pulmonary congestion	The ↓ SVR and ↑ HR of pregnancy reduce regurgitant flow During labor, ↑ intravascular volume, ↑ SVR, and stress of labor can lead to LV dysfunction	Avoid ↑ SVR Avoid bradycardia Avoid myocardial depressants

Prosthetic valve	Component of regurgitation	Risk of embolization Valvular dysfunction Endocarditis	Full-dose anticoagulation for mechanical valve
Left-to-right shunt (septal defects)	↑ Pulmonary flow, eventual pulmonary HTN and LV failure	Small lesions: asymptomatic Large VSD associated with aortic insufficiency CHF Arrhythmia Pulmonary HTN	Avoid ↑ SVR Avoid ↑ HR If pulmonary HTN, treat as right-to-left shunt; avoid ↓ SVR
Right-to-left shunt (tetralogy of Fallot, Eisenmenger syndrome)	Blood shunted away from lungs, cyanosis	↓ SVR worsens shunt ↑ PVR during labor worsens shunt Increased hypoxia, cyanosis	Avoid hypotension Maintain preload; avoid ↓ SVR Avoid decreases in blood volume Avoid myocardial depressants Give oxygen Air filters on IV lines
Cardiomyopathy	LV dysfunction Global chamber dilation	Increased cardiac demand may lead to decompensation	↓ Afterload Careful volume administration and diuresis Inotropic support to maximize cardiac output

CHF, congestive heart failure; CO, cardiac output; HR, heart rate; HTN, hypertension; LV, left ventricle; PVR, pulmonary vascular resistance; RV, right ventricle; SVR, systemic vascular resistance; VSD, ventricular septal defect; ↓, decrease; ↑, increase.

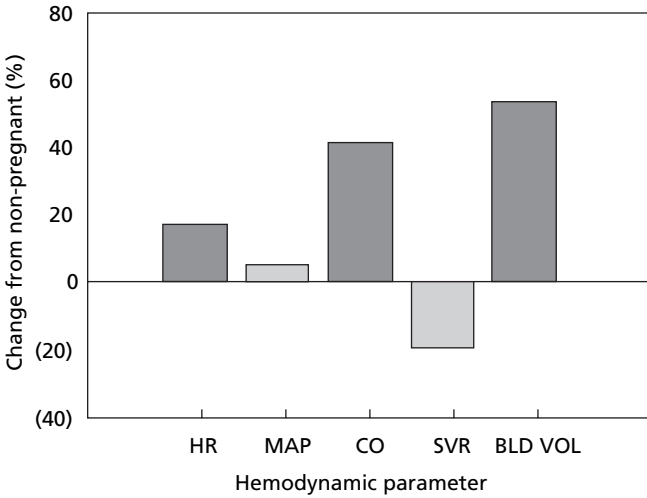


Fig. 28.1 Cardiovascular adaptation to pregnancy. BLD VOL, blood volume; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance.

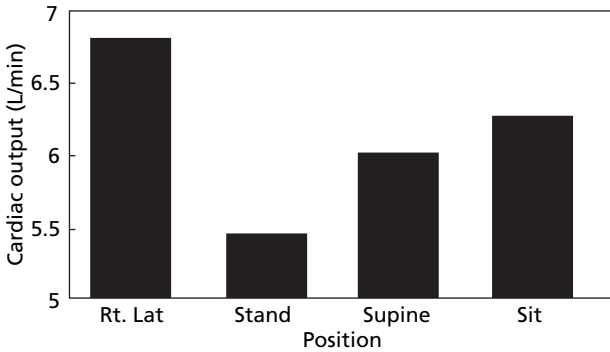


Fig. 28.2 Cardiac output changes with maternal position.

thorough history and physical examination, which allows classification of the woman's disease on a functional basis (Table 28.3). A 12-lead electrocardiogram and a transthoracic echocardiogram should be performed, and women with cyanosis should undergo percutaneous oximetry and/or arterial blood gas analysis. Any associated factors that could increase risk, such as a history of heart failure, a prosthetic valve, or a history of thromboembolism should be noted. Women determined to be at increased risk should be managed by a team

Table 28.3 Functional status in cardiac disease (New York Heart Association classification).

Class I	Asymptomatic with greater than normal activity
Class II	Symptomatic* with greater than normal activity (e.g. stair climbing)
Class III	Symptomatic with normal activity (e.g. walking)
Class IV	Symptomatic at rest

* Dyspnea, chest pain, orthopnea.

that includes a maternal–fetal medicine specialist, a cardiologist, an anesthesiologist, and a pediatrician.

MANAGEMENT

General principles for care of the gravida with cardiac disease

Key principles in the antepartum management of heart disease center on minimizing cardiac work while optimizing perfusion of the tissues including the uteroplacental bed. Any factors that could increase cardiac work, such as anxiety, anemia, infection, arrhythmia, or non-physiologic edema, should be identified and eliminated or minimized as soon as possible. Any pregnancy-induced complications such as hypertension, infection, anemia, or thromboembolism should be treated promptly. Women with cardiac disease should avoid strenuous activity during pregnancy; those whose underlying cardiac lesion involves ventricular dysfunction, who are cyanotic, or are functional class III or IV may need to limit their physical activity significantly and have specified daily rest periods. The woman's functional status should be closely monitored as pregnancy progresses. Any diminution in cardiac function or worsening of maternal functional class should prompt consideration of hospitalization. Oxygen, diuretics, and inotropes such as digitalis can be used as necessary to optimize cardiac function. Fetal assessment of growth should be monitored closely and a fetal echocardiogram performed between 18 and 22 weeks' gestational age. Depending on the maternal functional class and fetal status, weekly or biweekly evaluation of fetal well being should be considered, beginning in the third trimester.

Vaginal delivery is preferred for the patient with cardiac disease. The blood loss associated with cesarean delivery is at least twice that associated with vaginal delivery, and the hemodynamic fluctuations are significantly greater. In addition, cesarean delivery increases the risk of infection, thromboembolism, and other postoperative complications. Thus, cesarean delivery should be reserved for standard obstetric indications. Ideally, heparin should be discontinued 12 h before labor begins, but can be reversed with protamine sulfate

as necessary. Heart rate, stroke volume, cardiac output, and mean arterial pressure increase further during labor and in the immediate postpartum period, and should be monitored closely. Fluid intake and output and pulse oximetry readings should also be carefully reviewed. Lateral positioning and adequate pain control can reduce maternal tachycardia and increase cardiac output (Fig. 28.2). Patients with New York Heart Association class III or IV disease should be considered as candidates for intrapartum invasive hemodynamic monitoring. Operative assistance with the second stage of labor is recommended to decrease maternal cardiac work.

Conduction anesthesia is the preferred method of providing intrapartum pain control for the woman with cardiac disease. However, it is important to avoid hypotension when establishing regional anesthesia. Careful administration of intravenous crystalloid before placement of the catheter and slow administration of the anesthetic agent help to prevent this complication. Ephedrine is usually the agent of choice for the treatment of hypotension associated with regional anesthesia, because it does not constrict the placental vessels. However, because ephedrine increases the maternal heart rate, phenylephrine may be more appropriate for patients in whom tachycardia and increased myocardial work must be avoided (e.g. those with mitral and aortic stenosis, left-to-right shunt). A single-dose spinal technique is relatively contraindicated in patients with significant cardiac disease because hypotension frequently occurs during establishment of the spinal block. A narcotic epidural is an excellent alternative method and may be particularly effective for patients in whom systemic hypotension must be avoided (e.g. those with pulmonary hypertension).

Whether or not to provide antibiotic prophylaxis against bacterial endocarditis to women with congenital heart disease during labor and delivery is controversial. The American Heart Association and the American College of Cardiology recommend that intrapartum antibiotics be given only when bacteremia is suspected or there is an active infection. Women who are at high risk of developing infectious endocarditis (e.g. those with prosthetic valves, surgically created shunts or conduits, and those associated with a previous episode of endocarditis) can also be given prophylactic antibiotics, but women at low risk who deliver by elective cesarean or have a vaginal delivery without infection do not require prophylaxis. Other experts argue that the risk of bacteremia during labor and delivery is high, because even an episiotomy or insertion of a bladder catheter can result in transient bacteremia. Thus, any woman with congenital heart disease can be given antibiotic prophylaxis in labor. Some clinicians use the moderate-risk regimen for women who are not in the high-risk group (Table 28.4).

The immediate postpartum period is especially critical for the patient with cardiovascular disease. Blood loss must be minimized and blood pressure main-

Table 28.4 Antibiotic regimens for women with heart disease.

Standard regimen	Ampicillin, 2 g IV or IM, plus gentamicin, 1.5 mg/kg i.v. (to a maximum of 120 mg) 30 min before delivery, followed by 1 g ampicillin i.v. or i.m. or 1 g amoxicillin p.o. 6 h later; antibiotics should not be given for more than 6–8 h total
Penicillin-allergic standard regimen	Substitute vancomycin, 1 g i.v. over 1–2 h for ampicillin
Regimen for women at moderate risk	Ampicillin, 2 g i.v. or i.m., 30 min before delivery

tained, but congestive failure from fluid overload must also be avoided. For women requiring anticoagulation, heparin may be restarted 6–12 h after a vaginal delivery or 12–24 h after a cesarean delivery, along with coumarin. Heparin is then continued until the coumarin is therapeutic.

FOLLOW-UP

Approximately 4–6 weeks after delivery, the cardiovascular changes of pregnancy will have resolved and the patient should be re-evaluated by a cardiologist. The infant's pediatrician can decide whether or not to perform a cardiac evaluation of the neonate, depending on the results of the targeted fetal ultrasound examination and echocardiogram, and the newborn examination. Based on the outcome of the pregnancy and the results of the cardiac re-evaluation, the patient can be counseled regarding the risks of subsequent pregnancy, and appropriate contraception can be provided if indicated.

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Peripartum cardiomyopathy

F. Gary Cunningham

INTRODUCTION

A common time for development of heart failure in women is during labor or within 24–48 h after delivery. The term *peripartum cardiomyopathy* is used to describe women with peripartum heart failure with no readily apparent etiology. Epidemiologic studies of unexplained dilated cardiomyopathy indicate a predilection for older black women and especially those with gestational hypertension or twins. In many cases of peripartum heart failure initially attributed to idiopathic cardiomyopathy, a cause of heart failure can be determined with careful study. Common causes include chronic hypertension and obesity, which frequently coexist. Unrecognized mitral stenosis, congenital heart disease, HIV infection, or infective endocarditis may cause insidious-onset heart failure. Even after these are excluded, up to half of women with unexplained failure have evidence for viral myocarditis on endomyocardial biopsy, which is not routinely performed. Thus, the average incidence of idiopathic cardiomyopathy of approximately 1 in 5000 births likely includes many women with myocarditis. Whatever the cause, its importance is emphasized because it results in up to 8% of pregnancy-related deaths.

PATHOPHYSIOLOGY

There is usually biventricular dilation with poor contractility. This results in a low ejection fraction and high ventricular end-systolic volume and atrial end-diastolic volume.

Regardless of the underlying condition that causes cardiac dysfunction, women with peripartum heart failure often have other obstetric complications that either contribute to or precipitate heart failure. These include gestational hypertension, anemia, and infection. Pre-eclampsia worsens ventricular failure because of increased afterload. Anemia magnifies compromised ventricular function because of increased cardiac output. Similarly, infection and the sepsis syndrome increase cardiac output and oxygen utilization (see Chapter 77).

DIAGNOSIS

Women with cardiomyopathy present with signs and symptoms of congestive heart failure. Fatigue, dyspnea, orthopnea, cough, palpitations, and chest and abdominal pain are common symptoms. Physical findings are those of congestive heart failure and include elevated jugular venous pressure, rales, S₃ gallop, murmurs of mitral or tricuspid regurgitation, and peripheral edema. The blood pressure is usually normal, despite reduced pulse pressure from low cardiac output. Some women are hypertensive from vasoconstriction. The hallmark X-ray findings are impressive cardiomegaly with varying amounts of pulmonary infiltrates and pleural effusions. The electrocardiogram is usually non-diagnostic and sinus tachycardia and arrhythmias are common. Echocardiographic and Doppler flow studies with color-flow imaging confirm increased internal end-diastolic dimensions, diminished ventricular wall motion, and depressed ejection fractions.

MANAGEMENT

Therapy is given for heart failure. Furosemide and other diuretics are administered acutely and sodium intake is limited while avoiding hypokalemia. Afterload reduction is begun, but angiotensin-converting enzyme inhibitors are usually withheld until after delivery; instead, hydralazine may be used. Digitalis can be used for its inotropic effect but it must be given cautiously because approximately half of these women have complex ventricular arrhythmias. Because there is a high incidence of associated pulmonary embolism, anticoagulation with heparin is recommended by many if there is severe dilation or dysfunction.

PROGNOSIS

The distinction between peripartum heart failure from explicable causes and idiopathic cardiomyopathy is important because prognosis for the latter is much worse. Reversal of left ventricular hypertrophy by control of hypertension and weight reduction is crucial in women with underlying hypertension. Persistence of cardiomyopathy and development of ventricular arrhythmias frequently herald a worse outcome. Indeed, up to half of women with idiopathic cardiomyopathy are likely to die within 1 year. Unrelenting cardiomegaly and heart failure can only be treated definitively by heart transplantation. For women with recovered cardiac function, testing for cardiac reserve is carried out before another pregnancy is undertaken.

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Thromboembolism

Alan Peaceman

INTRODUCTION

Thromboembolism remains a leading cause of obstetric morbidity and mortality, and in the USA is the leading cause of maternal death following a live birth. It is estimated that the risk of venous thrombosis is approximately five times higher during pregnancy than in the non-pregnant state because of the hypercoagulable nature of pregnancy. Despite its risk, thromboembolism during pregnancy is a poorly studied area and significant controversy remains over the management of women at risk for this disorder.

PATHOPHYSIOLOGY

Normal pregnancy is associated with an increase in the level or activity of many of the clotting factors. These increases provide a defense against hemorrhage after delivery, but they also contribute to altering the balance of procoagulant and anticoagulant factors in the circulation toward clot formation during pregnancy. Under normal circumstances, the increased levels of clotting factors do not result in thrombus formation, but some clinical situations such as trauma or vascular injury may predispose toward lower extremity clotting. Once formed, portions of the clot can embolize to the pulmonary tree, with symptoms ranging from mild hypoxia to cardiovascular collapse. Other risk factors for thrombosis during pregnancy include venous stasis, inactivity, obesity, prior thrombosis, antiphospholipid syndrome, and thrombophilias such as Factor V Leiden.

DIAGNOSIS

The diagnosis of deep venous thrombosis (DVT) is often difficult to make clinically, especially in pregnancy. Patients presenting with asymmetric lower extremity swelling, associated with pain and erythema should be evaluated. Traditionally, venography has been the gold standard for making the diagnosis, even in pregnancy, but is being performed less frequently now because of its invasive nature and its use of radiation. Several non-invasive diagnostic tests

have been shown to be useful in the non-pregnant state; however, their accuracy is less well studied in pregnancy. None the less, many practitioners have now moved to either impedance plethysmography or compression ultrasound for pregnant women as the primary tool for evaluation of clinical symptoms in the lower extremities (Fig. 30.1). If a high index of suspicion remains after negative testing, however, venography may still be useful. The fetal radiation exposure with limited venography is very small (less than 0.05 rad).

The presenting signs and symptoms suggestive of pulmonary embolism include shortness of breath, chest pain, tachypnea, tachycardia, and decreased oxygen saturation by pulse oxymeter. The initial evaluation should include an arterial blood gas to evaluate for the presence of hypoxia and increased A-a gradient, both suggestive of an embolic event (Fig. 30.2). In non-pregnant patients, ventilation-perfusion (V/Q) scanning is often the initial diagnostic procedure, and in pregnancy is associated with minimal radiation exposure to the fetus (less than 0.1 rad). However, more than half of V/Q scans performed

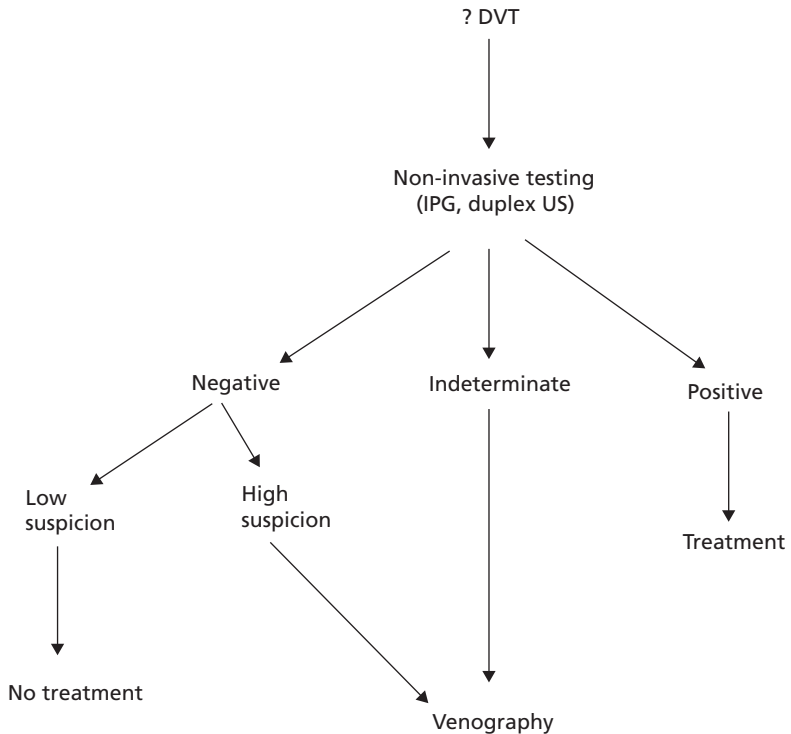


Fig. 30.1 Diagnostic protocol for suspected deep venous thrombosis (DVT). IPG, impedance plethysmography; US, ultrasound.

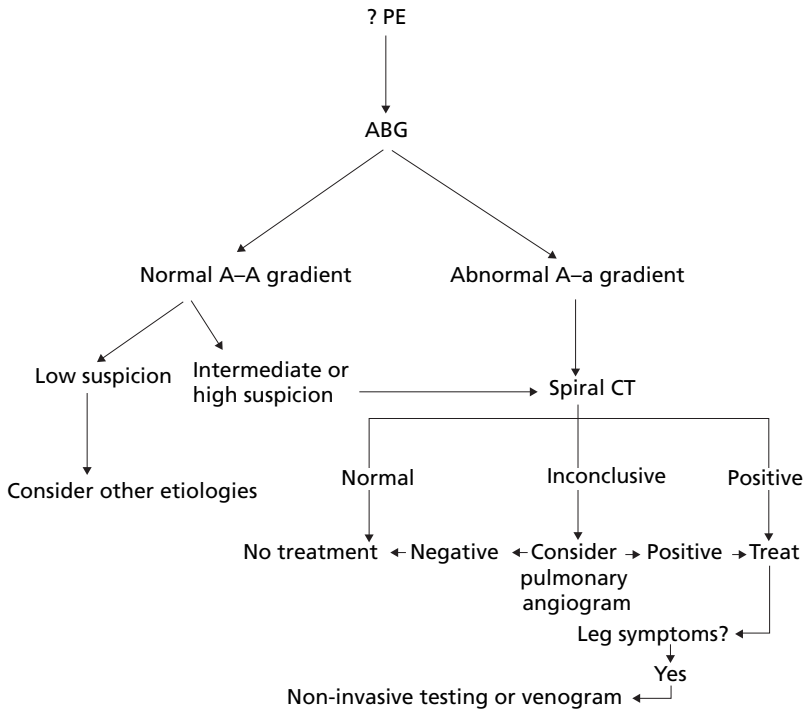


Fig. 30.2 Diagnostic protocol for suspected pulmonary embolism (PE). ABG, arterial blood gas; CT, computed tomography.

in pregnancy are non-diagnostic and require further imaging. Pulmonary angiography is the gold standard for diagnosing pulmonary embolism, but is invasive and associated with a risk of significant complications. Spiral CT scanning has proven to be useful in this evaluation, and may be more accurate than V/Q scanning. Further, it may be of use in identifying other thoracic conditions that may be responsible for the patient’s symptoms. Its use in pregnancy has not been evaluated, but is likely to be of similar accuracy as in the non-pregnant state. For these reasons, spiral computed tomography (CT) scanning is becoming a primary mode of evaluation of symptomatic pregnant patients. Because of the implications of the diagnosis of embolism on treatments during pregnancy as well as long-term recommendations, plus the risks associated with false-negative results, pulmonary angiography can still be useful in some situations where the results of testing are unsure. If a diagnosis of pulmonary embolism is made, a search for lower extremity thrombosis may be helpful in identifying the precipitating cause and directing therapy.

TREATMENT OF ACUTE THROMBOEMBOLISM

Because of the lack of clinical trials, all recommendations regarding treatment for or prevention of thromboembolism during pregnancy are based on expert opinion. None the less, consensus does exist on some of the approaches to treatment. Acute DVT or pulmonary embolism should be treated with intravenous heparin and it is important to achieve therapeutic dosage very early to prevent extension of clot (Table 30.1). After 5–10 days of intravenous therapy, either subcutaneous heparin or enoxaparin (or other forms of low molecular weight heparin), injections every 12 h are used for the remainder of the pregnancy to prevent recurrence. It is thought that the use of heparin injections requires monitoring to maintain the activated partial thromboplastin time (APTT) at least 1.5 times control throughout the dosing interval. However, with the more rapid metabolism of heparin during pregnancy, it is usually difficult to achieve prolongation of the APTT throughout the dosing interval without an excessive peak level, even when administered three times daily. For this reason, better options for prolonged therapeutic dosing include heparin by subcutaneous pump, or subcutaneous enoxaparin. Monitoring of enoxaparin when given outside of pregnancy is thought to be unnecessary for most patients, but its

Table 30.1 Management of thromboembolism.

Condition	Heparin	Enoxaparin
DVT or PE during current pregnancy	IV heparin (APTT 2–3 times control) for 5–10 days, followed by injections every 8–12 h to prolong mid-interval APTT 1.5 times control for remainder of the pregnancy; warfarin can be used postpartum	IV heparin (APTT 2–3 times control) for 5–10 days, followed by enoxaparin 1 mg/kg (up to 100 mg maximum) every 12 h; monitoring unnecessary
Patient who requires long-term therapeutic anticoagulation	Heparin every 8–12 h to prolong mid-interval APTT 1.5 times control	1 mg/kg (up to 100 mg maximum) every 12 h; monitoring unnecessary
Previous DVT or PE before current pregnancy (prophylactic treatment)	5000 units every 12 h first trimester 7500 units every 12 h second trimester 10,000 units every 12 h third trimester; monitoring unnecessary	40 mg every 12 h; monitoring unnecessary

APTT, activated partial thromboplastin time; DVT, deep venous thrombosis; PE, pulmonary embolism.

pharmacokinetics in pregnancy are incompletely studied. If monitoring is to be performed, anti-Factor Xa levels are followed. Both heparin and low molecular weight heparins do not cross the placenta, but warfarin does because of its smaller size. Warfarin is contraindicated in pregnancy because of its fetopathic effects in the first trimester (stippled epiphyses and nasal and limb hypoplasia) and the risk of fetal bleeding complications in the second and third trimesters. However, warfarin does not enter breast milk in sufficient quantities to anticoagulate the newborn, and is safe to use in the breastfeeding mother. For the patient needing full anticoagulation who prefers to take warfarin rather than frequent injections during the postpartum period, the prothrombin time (PT) is followed.

PREVENTION OF THROMBOEMBOLISM

The use of anticoagulation to prevent thromboembolism is more controversial. Traditionally, chemoprophylaxis has been recommended to pregnant patients with a history of thrombosis with the idea that pregnancy significantly increases the risk of recurrence. Anticoagulant doses lower than needed to prolong the APTT have been used (Table 30.1), unless the patient is thought to be at such increased risk that full anticoagulation is necessary. Because it is now recognized that a significant portion of these thrombotic events occur as early as the first trimester, it is prudent to start treatment soon after the pregnancy is recognized, and continue it until 6 weeks postpartum.

A recent study suggested that prophylactic anticoagulation may not be necessary in some patients with a history of venous thromboembolism. In this study of women with a single previous episode of thrombosis associated with a temporary risk factor (e.g. oral contraceptives, surgery, trauma), and no recognized thrombophilia, no recurrences were seen without treatment during pregnancy. However, the number of patients in this study was relatively small. Larger studies in the future may further support the idea that prophylactic treatment with anticoagulants is unnecessary for this type of patient.

Risks to the mother of heparin therapy include a rare thrombocytopenia and the possibility of heparin-induced osteoporosis. These risks are thought to be lower with the use of low molecular weight heparin. Heparin-induced thrombocytopenia occurs within the first week of treatment, so checking the platelet count 5–10 days after beginning therapy will provide reassurance. Up to one-third of women may demonstrate subclinical bone loss and the reversibility of this process is not assured. Significant maternal hemorrhage is a possibility in patients who are overanticoagulated.

SPECIAL CONSIDERATIONS

Patients with artificial heart valves are at a high risk for thromboembolism, stroke and valve failure, and therefore must be therapeutically anticoagulated

throughout pregnancy. Patients with a documented clot and also a family history of thromboembolic events should be evaluated for antithrombin III, protein C, or protein S deficiency because these traits are autosomal dominant with variable penetrance. Full-dose anticoagulation should be used when these conditions are identified. It is more difficult to diagnose protein S deficiency in pregnancy because levels normally decrease beginning in the first trimester; prophylaxis may be appropriate if protein S deficiency is suspected. Patients with a prior thromboembolic event who have been diagnosed with antiphospholipid antibody syndrome should be given heparin prophylaxis at a minimum, with consideration of full anticoagulation for those thought to be at significant risk. Screening for Factor V Leiden and prothrombin mutation should not be performed in patients without a history of prior thrombosis, as patients with these mutations without prior events do not need treatment.

There is concern regarding the use of epidural anesthesia during labor and delivery in patients treated with anticoagulants. Some anesthesiologists suggest avoiding regional anesthesia for 24 h from the last injection of low molecular weight heparin, especially if full-dose treatment is used. Because of its more rapid disappearance, a shorter waiting time is used for patients on heparin. For this reason, switching from low molecular weight to standard heparin at 36 weeks' gestation may increase the number of patients eligible for regional anesthesia.

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Renal disease

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INTRODUCTION

With improvements in reproductive success in women with underlying renal disease, obstetricians may be faced with this patient population more frequently. The management of pregnant women with this complication presents a challenge to obstetricians, perinatologists, nephrologists, anesthesiologists, and neonatologists. Thus, management should include a multidisciplinary approach. As the degree of renal impairment increases, there is a concomitant increase in both maternal and fetal complications. Maternal adverse effects include pre-eclampsia, eclampsia, and placental abruption, while fetal complications include fetal prematurity, low birth weight, and neonatal death.

It is important to have a basic understanding of normal physiology in healthy pregnant women when considering renal disorders in pregnancy. Within 1 month of conception, glomerular filtration rate (GFR) is increased by approximately 50% while renal plasma flow (RPF) is increased 50–80%. These changes result in normal reduction in serum levels of creatinine and urea nitrogen to mean values of 50 $\mu\text{mol/L}$ (0.6 mg/dL) and 3 mmol/L (9 mg/dL), respectively. Thus, creatinine values of 80 $\mu\text{mol/L}$ (0.9 mg/dL) and urea nitrogen values of 6 mmol/L (14 mg/dL) may represent underlying renal disease in pregnancy. In the third trimester, GFR may decrease by 20% with little effect on serum creatinine. Prepregnancy levels are achieved within 3 months postpartum.

The guidelines for managing women with chronic renal disease are based primarily on retrospective studies of more than 1000 pregnant patients whose kidney disease was diagnosed by renal biopsy. Most of the women surveyed had been normotensive, with only minimal renal dysfunction. The following concepts have emerged. Fertility and the ability to sustain an uncomplicated pregnancy generally relate to the degree of functional impairment and the presence or absence of hypertension rather than to the nature of the underlying disorder (Table 31.1). Patients are arbitrarily considered in three categories:

Table 31.1 Severity of renal disease and prospects for pregnancy. Estimates are based on 1862 women and 2799 pregnancies (1973–1992) and do not include collagen diseases.

Prospects	Category*		
	Mild (%)	Moderate (%)	Severe (%)
Pregnancy complications	25	47	86
Successful obstetric outcome	96 (85)	90 (59)	25 (71)
Long-term sequelae	<3 (9)	47 (8)	53 (92)

* Numbers in parentheses refer to prospects when complication(s) develop before 28 weeks' gestation.

- 1 *Preserved or only mildly impaired renal function*: serum creatinine ≤ 1.4 mg/dL (≤ 124 $\mu\text{mol/L}$) and no hypertension
- 2 *Moderate renal insufficiency*: serum creatinine 1.5–3.0 mg/dL or 133–275 $\mu\text{mol/L}$ (some use 2.5 mg/dL or 221 $\mu\text{mol/L}$ as the cut-off)
- 3 *Severe renal insufficiency*: serum creatinine ≥ 3 mg/dL or 275 $\mu\text{mol/L}$

Women in the first category usually have successful obstetric outcomes and pregnancy does not appear to adversely affect their underlying disease. About half of the patients with mild renal impairment experience worsening proteinuria, which can progress to severe range along with nephrotic edema. Perinatal outcome is compromised by the presence of uncontrolled hypertension and nephrotic proteinuria in early pregnancy. Perinatal mortality in this group is now less than 3%, while evidence of irreversible renal functional loss in the mother is even lower. However, this generalization may not hold true for certain kidney diseases (Table 31.2). For instance, patients with scleroderma and periarteritis nodosa, disorders often associated with hypertension, do poorly. Conception in some of these women with severe disease may be contraindicated. Women with lupus nephritis do not do as well as patients with primary glomerulopathies, especially if the disease has flared within 6 months of conception. Controversy regarding adverse pregnancy effect and the effect on the natural history of the disease process exists with other diseases such as immunoglobulin A (IgA) nephritis, focal glomerular sclerosis, membranoproliferative nephritis, and reflux nephropathy. Although it is generally agreed that as functional impairment progresses, along with hypertension, maternal and fetal risks significantly increase.

Information on women with moderate or severe dysfunction who conceive is more limited. Fetal outcome is still good in the former group, where 80–90% of the pregnancies succeed after exclusion of spontaneous abortions. Maternal

Table 31.2 Specific kidney diseases and pregnancy.

Renal disease	Effects and outcome
Chronic glomerulonephritis	Usually no adverse effect in the absence of hypertension. One view is that glomerulonephritis is adversely affected by the coagulation changes of pregnancy. Urinary tract infections may occur more frequently
IgA nephropathy	Risks of uncontrolled and/or sudden escalating hypertension and worsening of renal function
Pyelonephritis	Bacteriuria in pregnancy can lead to exacerbation. Multiple organ system derangements may ensue, including adult respiratory distress syndrome
Reflux nephropathy	Risks of sudden escalating hypertension and worsening of renal function
Urolithiasis	Infections can be more frequent, but ureteral dilation and stasis do not seem to affect natural history Limited data on lithotripsy; thus, best avoided
Polycystic disease	Functional impairment and hypertension usually minimal in childbearing years
Diabetic nephropathy	Usually no adverse effect on the renal lesion, but there is increased frequency of infection, edema, and/or pre-eclampsia
Systemic lupus erythematosus (SLE)	Controversial; prognosis most favorable if disease in remission >6 months before conception. Steroid dosage should be increased postpartum
Periarteritis nodosa	Fetal prognosis is dismal and maternal death often occurs
Scleroderma (SS)	If onset during pregnancy, rapid overall deterioration can occur. Reactivation of quiescent scleroderma may occur postpartum
Previous urinary tract surgery	Might be associated with other malformations of the urogenital tract. Urinary tract infection common during pregnancy. Renal function may undergo reversible decrease. No significant obstructive problem but cesarean delivery often needed for abnormal presentation and/or to avoid disruption of the continence mechanism if artificial sphincter present
After nephrectomy, solitary kidney and pelvic kidney	Might be associated with other malformations of urogenital tract. Pregnancy well tolerated. Dystocia rarely occurs with pelvic kidney
Wegener's granulomatosis	Limited information. Proteinuria (\pm hypertension) is common from early in pregnancy. Cytotoxic drugs should be avoided
Renal artery stenosis	May present as chronic hypertension or as recurrent isolated pre-eclampsia. If diagnosed then transluminal angioplasty can be undertaken in pregnancy if appropriate

disease progression is of greater concern because approximately one-third of women with moderate renal insufficiency may have an irreversible decline in GFR. One-third of women with moderate renal dysfunction experience worsening hypertension, while 10% may progress to end-stage renal disease. The risk of acceleration was highest (33% vs 2%) among those with an initial serum plasma creatinine >3 mg/L (177 μ mol/L). Maternal problems appear greater with severe dysfunction even before dialysis is required. The diagnosis of “superimposed pre-eclampsia” is difficult to make because hypertension and proteinuria may be manifestations of the underlying renal disorder; however, superimposed pre-eclampsia may be diagnosed in up to 80% of cases. Thus, it is primarily the maternal risk in women with moderate insufficiency, and the added likelihood of a poor fetal outcome when dysfunction is severe, that leads the clinician to the counseling of women regarding the advisability of pregnancy.

PREPREGNANCY COUNSELING

Serum creatinine elevation above 1.5 mg/dL (132 μ mol/L) and hypertension are important predisposing risk factors for permanent exacerbation of underlying renal disease, and pregnant women should be so counseled. Fertility is diminished as renal impairment progresses. Normal pregnancy is unusual when preconception serum creatinine is >3 μ mol/L (GFR <25 mL/min). The reported frequency of conception among dialysis patients is 0.3–1.5% per year. Fetal wastage is markedly increased; however, recent improvements in management of these patients has led to better rates of live births (approximately 50% of cases). With well-controlled blood pressure and minimal dysfunction, gestational outcome is similar to that of normotensive gravidas with renal disease. Ideally, diastolic blood pressure before conception should be 90 mmHg or lower.

MANAGEMENT GUIDELINES FOR PREGNANCY

Management is best undertaken at a tertiary care center under the coordinated care of a maternal–fetal medicine specialist and a nephrologist. The initial laboratory tests should include specialized tests, which help in the early detection of renal functional loss as well as superimposed pre-eclampsia. Thus, besides the usual prenatal screening tests, the following renal parameters should be determined.

- 1 Serum creatinine, its timed clearance and 24-h protein excretion: monitors for change in function
- 2 Serum urea nitrogen, albumin, and cholesterol concentrations: important in regard to nephrotic complications
- 3 Electrolytes, to control for osmolar, potassium, and acid–base homeostasis; urine analysis; and more frequent screening for bacterial culture

4 Uric acid levels, aspartate and alanine aminotransferases, lactic dehydrogenase, prothrombin time, activated partial thromboplastin time, and platelet count (superimposed pre-eclampsia screening tests) should also be determined

The number and frequency of prenatal visits should be dictated by the severity of disease and the presence of other complications such as hypertension and fetal growth restriction. In general and in most cases, women can be followed every 2 weeks until 30–32 weeks' gestation and weekly thereafter. Renal parameters should be tested every 4–6 weeks unless more frequent evaluations become necessary.

Fetal surveillance, such as biophysical profile testing, is best started at approximately 30–32 weeks' gestation, especially in nephrotic patients with hypoalbuminemia. Ultrasound testing for both gestational dating and for monitoring fetal growth is also an integral part of surveillance.

In general, diuretics should be avoided. This is especially important in nephrotic gravidas, as these women are already oligemic and further intravascular volume depletion may impair uteroplacental perfusion. Furthermore, because blood pressure normally declines during pregnancy, saluretic therapy could conceivably precipitate circulatory collapse or thromboembolic episodes. However, this recommendation is relative, because we have observed occasional patients whose kidneys were retaining salt so avidly that diuretics had to be cautiously used. This is especially true for women with diabetic nephropathy, in whom excessive salt retention may lead to volume-dependent hypertension during pregnancy. Some authorities recommend the use of prophylactic anticoagulation (i.e. mini-heparin) in nephrotic gravidas, but there are few, if any, data to prove the efficacy of such treatment.

High-protein diets were advocated in the past for women with nephrotic proteinuria, especially during pregnancy, when anabolic requirements increase, although many nephrologists currently recommend a protein-restricted diet for most patients with renal disease. Should protein be restricted in gravidas with renal dysfunction? We caution against this view, and recommend that such regimens be avoided in pregnancy until more is known regarding fetal outcome and especially brain development, first from studies in animal models and then in carefully conducted clinical trials.

COURSE OF PREGNANCY AND CLINICAL DECISIONS

Glomerular filtration rate and blood pressure are the two parameters that influence the course of the pregnancy. Evidence of renal functional deterioration or the appearance (or rapid worsening) of hypertension is best evaluated in the hospital, and failure to reverse these events is grounds for expediting delivery. Because serum creatinine determinations may be quite variable in some laboratories, decisions should not be made until the direction and rate of change

are very clear from repeat tests. It is important to remember that a decrement in creatinine clearance of 15–20% may occur normally near term, that increased proteinuria in the absence of hypertension need not cause alarm, and that such changes do not suggest a need for hospitalization.

Gravidas with pre-existing renal disease or essential hypertension are more susceptible than control populations to superimposed pre-eclampsia, which frequently occurs in midpregnancy or early in the third trimester. Superimposed pre-eclampsia, however, may be difficult to differentiate from aggravation of the underlying disease, especially in women with glomerular disease who are prone to hypertension and proteinuria. In any event, when these situations occur the patient should be hospitalized and treated as if she has superimposed pre-eclampsia, a prudent policy considering the potentially explosive and dangerous nature of this disorder.

While there is debate on whether mild hypertension (90–100 mmHg diastolic pressure, Korotkoff V) should be treated in pregnant women without underlying renal disorders, treatment is recommended for such levels of blood pressure when known renal disease is present. The goal diastolic pressure is 80 mmHg. Detection of intrauterine growth restriction (IUGR) or fetal compromise, or both, is an important consideration that will influence the timing of delivery.

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Obesity

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INTRODUCTION

It is estimated that more than 60% of adults in the USA are overweight or obese. The prevalence of obesity has increased dramatically over the past three decades. Although in the past various weight cut-offs were used to define obesity in pregnancy, currently most studies rely on the body mass index (BMI). The weight of a woman in kilograms is divided by her height in meters squared in order to calculate the BMI. The advantage of the BMI over using an individual's weight alone is to distinguish the tall woman who is not fat from the short woman who is. A BMI ≥ 29 defines obesity. This BMI is achieved by a weight of 145 pounds (lb; 66 kg) for a woman 5 feet (1.5 m) tall, and a weight of 187 lb (85 kg) for a woman 5 feet 8 inches (1.7 m) tall. Morbid or extreme obesity is often defined as a BMI ≥ 40 .

ARE THERE INCREASED RISKS?

There are increased risks of pregnancy associated with obesity. Studies of the effects of obesity on pregnancy outcomes are retrospective comparisons. Some are from individual institutions where small numbers preclude identifying an association between obesity and very infrequent occurrences; others are from large databases raising questions as to the validity of entered data. Nevertheless, the results of most studies are uniform concerning many risks and complications. The relative risks that the obese pregnant woman faces compared with her non-obese counterpart depend on how controlled the studies are for confounding variables (e.g. advanced age, low socioeconomic class).

Studies are uniform, or nearly so, regarding the following complications:

- Diabetes mellitus (mostly gestational, but also insulin dependent)
- Hypertension (both chronic and pre-eclampsia)
- Labor induction
- Dystocia in labor
- Cesarean delivery (and decreased likelihood of vaginal birth after cesarean (VBAC) success)

- Fetal macrosomia
- Shoulder dystocia
- Wound complications
- Possibly increased risk of fetal neural tube defects (studies vary)

MANAGEMENT

Obesity increases the difficulty of providing obstetric care. It is well recognized that surgery is more difficult in the obese woman, but other aspects of care are too. Clinically estimating fetal weight or presentation, anesthesia, venous access, and ultrasound examinations are more difficult.

In the presence of obesity, routine care should be modified as follows.

- 1** Dietary advice/weight gain recommendation. Suggest that the patient eat well-balanced meals to appetite. Although current guidelines suggest that the obese gravida should gain 7 kg (15 lb), do not worry if she gains little or no weight during pregnancy. In striking contrast to the situation in a small or average-sized woman, in whom weight gain during pregnancy is a predominant predictor of birth weight, birth weight in obese women is little influenced by gestational weight gain. The abundant caloric reserves and increased blood volume and cardiac output in a very large woman at the onset of pregnancy usually ensure adequate fetal nourishment. The relationship between caloric intake in pregnancy and total pregnancy weight gain is only modest. There is probably little relationship between the advice provided and the weight gain achieved during pregnancy in this situation. Prescribe vitamin and mineral supplements; interdict smoking.
- 2** Establish a reliable expected date of delivery (EDD). Many of these women do not ovulate regularly. Pelvic examination to determine size in early pregnancy and fundal height measurements in later pregnancy are compromised by obesity. Therefore, an ultrasound examination early in pregnancy is indicated (a first trimester crown–rump length is ideal in this situation). Utilize follow-up ultrasound examinations later in pregnancy in an attempt to rule out malformations (diabetes) and intrauterine growth restriction (hypertension). An estimated fetal weight by ultrasound in late pregnancy might influence the choice of route of delivery, especially in a woman with diabetes.
- 3** Rule out glucose intolerance early in the second trimester, as well as at 26–28 weeks' gestation. If there is any question on a 1-h screen, order a 3-h glucose tolerance test.
- 4** Utilize a blood pressure cuff of appropriate size. The cuff bladder should cover 80% of the arm circumference. Too small a cuff means too high a reading.
- 5** Employ third trimester fetal well being testing and induction of labor as indicated (diabetes, hypertension, postdatism).

- 6 In labor, remember the protraction disorders in the active phase of the first stage or a prolonged second stage may indicate cephalopelvic disproportion. Macrosomia increases the risks of maternal and fetal trauma. Be cautious about operative vaginal delivery.
- 7 If cesarean delivery is required, the author's preference is to open the abdomen through a vertical incision. The inferior limit of the incision should be perpendicular to the top of the pubic symphysis. If a large panniculus is present, most or even all of the skin incision may be above the umbilicus. Mechanical or pharmacologic measures to decrease the risk of thromboembolism should be considered. Administer prophylactic antibiotics after cord clamping. The author's preference for abdominal wall closure is to utilize a continuous mass closure technique. The literature is unclear as to whether suturing the subcutaneous tissues or utilizing a subcutaneous drain is helpful. The author's preference is to close the fat and not utilize a drain.

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Gestational diabetes

Donald R. Coustan

INTRODUCTION

Gestational diabetes occurs in approximately 3% of pregnancies. It is defined as diabetes that is diagnosed or first appears during pregnancy. If diabetes or prediabetes persists after delivery, the patient can be reclassified.

Risk

Perinatal mortality is approximately doubled among pregnancies complicated by undiagnosed gestational diabetes, but may be reduced to a more normal range by identification and close monitoring of such pregnancies. Neonatal morbidity is increased in the untreated gestational diabetic population. Because glucose rapidly crosses the placenta, even mild degrees of maternal hyperglycemia are reflected by fetal hyperglycemia. The fetal pancreas responds by increasing its production and release of insulin. Fetal hyperinsulinism stimulates fetal growth, causing macrosomia (approximately half of newborns of untreated gestational diabetic patients are above the 75th percentile in weight); it is also responsible for neonatal hypoglycemia, and probably for the increased incidence of neonatal respiratory distress syndrome. Macrosomic infants are more likely to require cesarean delivery or difficult vaginal delivery.

DIAGNOSIS

Screen

There may be a group of gravidas at low enough risk that serum screening is not necessary. This low-risk group is composed of women with the following characteristics: age less than 25 years; normal weight prior to pregnancy; member of a racial or ethnic group with a low prevalence of diabetes; no known diabetes in a first-degree relative; no history of abnormal glucose tolerance; and no history of poor obstetric outcome. Many clinicians find that there are few enough such patients that universal screening is most efficient. Screening is carried out by means of a 50-g oral glucose load (the patient need not be

fasting). Draw blood for plasma glucose testing 1 h later. A value of 130 mg/dL (glucose oxidase or hexokinase method) or greater dictates a 3-h oral glucose tolerance test.

Glucose tolerance test

- 1 Instruct the patient to eat three candy bars or six slices of bread per day, in addition to her usual diet, for 2 days before the test in order to be sure her insulin response is not blunted by carbohydrate depletion.
- 2 Following an overnight fast, draw blood for a fasting plasma glucose determination.
- 3 Have the patient ingest 100 g glucose (one bottle of commercially available dextrose). It is most palatable when iced.
- 4 Determine plasma glucose levels at 1, 2, and 3 h. Patient should sit quietly during this time, neither eating nor smoking.
- 5 If any two of the following (plasma or serum) values are met or exceeded, the diagnosis of gestational diabetes is made: fasting, 95 mg/dL; 1 h, 180 mg/dL; 2 h, 155 mg/dL; 3 h, 140 mg/dL.

MANAGEMENT

Diet

Patients with gestational diabetes should receive medical nutritional counseling, generally by a registered dietician or diabetes nurse educator.

Glucose monitoring

Although occasionally patients treated with diet have such normal glycemia that they can be followed with a weekly "set" of circulating glucose determinations, most patients will be instructed on daily glucose self-monitoring (fasting, 1–2 h after breakfast, lunch and dinner). Goals for glycemic control are generally the same as for patients with pre-existing diabetes. If fasting values exceed 100 mg/dL, 1-h postprandial values exceed 130–140 mg/dL, and/or 2-h postprandial values exceed 120 mg/dL, at least 20% of the time, therapy with human insulin should be instituted or adjusted.

The use of glyburide in patients needing therapy has been shown, in one study, to be associated with similar pregnancy outcomes to insulin. Because glyburide does not cross the placenta, this may be a reasonable alternative. Other oral antidiabetic agents, some of which cross the placenta, have not been evaluated with appropriately controlled trials in pregnancy, and so are not useful at the present time.

Fetal monitoring

Start weekly antepartum monitoring (non-stress or contraction stress tests) at 36 weeks' gestation. This is controversial and some authors suggest that

antepartum testing is not necessary **prior to term** in uncomplicated gestational diabetic pregnancies **in which fetal movement determinations are reassuring.**

Timing of delivery

Early delivery is not necessary if glucose levels and fetal heart monitoring are normal. If the cervix is ripe at or near term, induction is reasonable if early dating has established that the pregnancy is 39 weeks or more.

Late delivery

If the patient goes to or beyond 40 weeks and the cervix is unripe, start more frequent antepartum testing as for a patient with pre-existing diabetes. Cervical ripening agents may be helpful in avoiding post-term pregnancy, particularly when other risk factors are present.

Cesarean delivery

Gestational diabetes is not an indication for primary cesarean section. However, because shoulder dystocia is more likely with macrosomic infants of diabetic mothers, cesarean delivery without labor can be considered when estimated fetal weight exceeds 4.5 kg. Between estimated fetal weights of 4 and 4.5 kg, individualization is useful in decision-making, taking note of factors such as previous labor patterns, pelvic architecture, the normalcy of the current labor, and patient preference. Predisposing factors to shoulder dystocia in diabetic pregnancy include mid-pelvic instrumental delivery after a prolonged second stage, and such operations are best avoided.

Postpartum follow-up

All women with gestational diabetes should be tested, at about the time of their 6-week check-up, for permanent diabetes. A 75-g, 2-h oral glucose tolerance test is the standard test used. If it is normal, annual retesting is appropriate. Diabetes is diagnosed if the fasting plasma glucose exceeds 125 mg/dL or the 2-h plasma glucose level exceeds 200 mg/dL. Prediabetes is diagnosed if the fasting plasma glucose is between 100 and 126 mg/dL, or the 2-h value is between 140 and 200 mg/dL.

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Diabetes mellitus

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INTRODUCTION

Diabetes mellitus, one of the most common medical complications of gestation, is encountered in approximately 3–5% of all pregnancies. Gestational diabetes mellitus (GDM), or carbohydrate intolerance detected for the first time during gestation, represents approximately 90% of all cases, while pregestational diabetes mellitus, which includes both type 1 and type 2 diabetes mellitus, accounts for the remaining 10%.

PATHOPHYSIOLOGY

The increased perinatal morbidity and mortality associated with the pregnancy complicated by diabetes mellitus can be attributed directly to maternal hyperglycemia. Glucose crosses the placenta by facilitated diffusion. Therefore, hyperglycemia in the maternal compartment will produce fetal hyperglycemia. During the first trimester, maternal hyperglycemia, as well as other derangements in maternal metabolism, may lead to abnormal fetal organogenesis. Major fetal malformations, now the leading cause of perinatal mortality in pregnancies complicated by type 1 and type 2 diabetes mellitus, may occur in 10% or more of poorly controlled patients. Later in pregnancy, fetal hyperglycemia leads to fetal hyperinsulinemia, which has been associated with excessive fetal growth or macrosomia, as well as delayed fetal pulmonary maturation and a higher incidence of respiratory distress syndrome. The increased intrauterine fetal death rate observed in pregnancies complicated by diabetes mellitus can also be attributed to fetal hyperglycemia that results in lactic acidosis. The likelihood that any of these complications will occur is directly related to maternal glucose control, as reflected by mean glucose levels or concentrations of glycosylated hemoglobin, and the presence or absence of diabetic vasculopathy.

PREGESTATIONAL DIABETES MELLITUS

Risk assessment

Maternal and perinatal risks are increased in the presence of:

- 1 Vasculopathy, such as retinopathy, nephropathy, and hypertension
- 2 Poor glucose control
- 3 Prognostically poor signs of pregnancy, including ketoacidosis, pyelonephritis, pregnancy-induced hypertension, and poor clinic attendance or neglect

Prepregnancy care

Objectives

- 1 Determine presence of maternal vasculopathy by an ophthalmologic evaluation, electrocardiogram, and 24-h urine collection for creatinine clearance and protein excretion.
- 2 Improve maternal glucose control to reduce the risk of fetal malformations and miscarriage; assess hypoglycemic awareness.
- 3 Provide contraceptive counseling.
- 4 Educate the patient and her partner about the management plan for diabetes in pregnancy.
- 5 Determine rubella immune status and check thyroid function studies.
- 6 Begin folic acid prophylaxis to reduce risk of fetal neural tube defects.

Detection and evaluation of malformations

- 1 Identification of the population at greatest risk. Maternal glycosylated hemoglobin levels in the first trimester.
- 2 Maternal serum alpha-fetoprotein levels at 16 weeks.
- 3 Ultrasound at 13–14 weeks to detect anencephaly.
- 4 Comprehensive ultrasound at 18–20 weeks with careful study of cardiac structure, including great vessels.

Antepartum care: regulation of maternal glycemia

Target capillary glucose levels in pregnancy

Mean level	100 mg/dL
Before breakfast	<95 mg/dL
Before lunch, supper, bedtime snack	<100 mg/dL
One hour after meals	<140 mg/dL
Two hours after meals	<120 mg/dL
2 a.m. to 6 a.m.	>60 mg/dL

- 1 Capillary glucose monitoring with fasting, prelunch, predinner, and bedtime levels daily, as well as 1-h or 2-h postprandial values; glycosylated hemoglobin levels in each trimester, target $\leq 6\%$

2 Insulin therapy

- *Multiple insulin injections:* prandial insulin (regular or insulin lispro) with meals, snacks; basal insulin (neutral protamine Hagedorn [NPH]), before breakfast (two-thirds of total NPH dose) and at bedtime (one-third of total NPH dose)
- *Continuous subcutaneous insulin infusion* (insulin pump): regular or insulin lispro; continuous basal rate and boluses, in highly compliant patients

3 Dietary recommendations

- *Plan:* three meals, three snacks
- *Diet:* 30–35 kcal/kg normal body weight, 2000–2400 kcal/day
- *Composition:* carbohydrate 40–50% complex, high fiber; protein 20%; fat 30–40% (<10% saturated). Weight gain: 22–25 lb (10–11 kg)

4 General guidelines for insulin use and carbohydrate intake

- 1 unit of rapid-acting insulin lowers blood glucose 30 mg/dL
- 10 g of carbohydrate increases blood glucose 30 mg/dL
- 1 unit of rapid-acting insulin will cover intake of 10 g carbohydrate

Fetal evaluation**Assessment of fetal well being to prevent intrauterine fetal death****1 Biophysical**

- Maternal assessment of fetal activity at 28 weeks
- Non-stress test (NST), weekly at 28–30 weeks; twice weekly at 32 weeks and beyond; may alternate with biophysical profile (BPP)
- BPP or contraction stress test if NST non-reactive

2 Evaluation of fetal growth with ultrasonography if macrosomia or intrauterine growth restriction suspected.**3 Amniocentesis to assess fetal pulmonary maturation for elective delivery before 39 weeks.****Delivery****Timing**

- 1** Patients at low risk for fetal death (excellent glucose control, no vasculopathy, normal fetal growth, reassuring antepartum fetal testing, no prior stillbirth): allow spontaneous labor up to 40 weeks.
- 2** Patients at high risk for fetal death (poor control, vasculopathy, macrosomia, hydramnios, prior stillbirth): consider elective delivery at 38–39 weeks if amniotic fluid testing is mature.

Method

To reduce birth trauma, consider elective cesarean delivery if estimated fetal weight is ≥ 4500 g.

Table 34.1 Glucose control during first stage of labor in women with pregestational diabetes mellitus.

	Insulin (IU/h)	Glucose (g/h)
Latent phase	1	5
Active phase	None	10

Intrapartum glycemic control

- 1 Check capillary glucose hourly at the bedside; maintain below 110 mg/dL
- 2 Glucose control during labor (first stage) (Table 34.1)

Contraception for the patient with type 1 or type 2 diabetes mellitus

- 1 *Combination oral contraceptives*
 - Low-dose pills appear safe in patients without vasculopathy
 - Contraindicated in presence of smoking or hypertension
- 2 *Progestin-only pills*: acceptable for patients with vasculopathy
- 3 *Mechanical or barrier methods*: less effective than oral contraceptives but no effect on glucose control or vasculopathy
- 4 *Intrauterine device*: acceptable for multiparous patients
- 5 *Sterilization*: when family has been completed, especially for patients with serious vasculopathy

GESTATIONAL DIABETES**Definition (Fourth International Workshop-Conference, 1998)**

Gestational diabetes is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The definition applies irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have predated the pregnancy.

- 1 *Class A₁*: diet controlled; fasting glucose less than 95 mg/dL, 2-h postprandial glucose less than 120 mg/dL
- 2 *Class A₂*: diet and insulin or glyburide; elevated fasting and/or postprandial glucose

Consequences: why bother to screen?

- 1 *Maternal*: subsequent diabetes mellitus, shortened life expectancy
- 2 *Fetal and neonatal*
 - Macrosomia and trauma; neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia
 - Increased mortality associated with fasting hyperglycemia

Screening and diagnosis

Detection

All pregnant women should be screened for glucose intolerance since selective screening based on clinical attributes or past obstetric history has been shown to be inadequate. Screening should be by glucose measurement in plasma. The Fourth International Workshop-Conference, 1998, concluded as follows:

- 1 50 g glucose load with glucose determination 1 h later. Administered between 24 and 28 weeks' gestation, without regard to time of day or time of last meal, to all pregnant women who have not been identified as having glucose intolerance before 24 weeks. Venous plasma glucose measured 1 h later. Value ≥ 140 mg/dL indicates the need for a full diagnostic glucose tolerance test (GTT). Note: With a cut-off value of 140 mg/dL, sensitivity is 90%, and 15% of patients require a GTT. With a cut-off of 130 mg/dL, sensitivity is nearly 100%, but 25% of patients require a GTT.
- 2 A plasma glucose measurement ≥ 200 mg/dL outside the context of a formal glucose challenge test, or a truly fasting plasma glucose ≥ 126 mg/dL, suggests the diabetic state and warrants further investigation.
- 3 The recommendation for universal testing at 24–28 weeks' gestation should not preclude earlier testing in high-risk patients.

Diagnosis

- 1 100 g oral glucose load, administered in the morning after overnight fast for at least 8 h but not more than 14 h, and following at least 3 days of unrestricted diet (≥ 150 g carbohydrate) and usual physical activity. Venous plasma glucose is measured fasting and at 1, 2, and 3 h. Subject should remain seated and not smoke throughout the test. Two or more of the following venous plasma concentrations must be met or exceeded for a positive diagnosis (Table 34.2).
- 2 Repeat GTT at 32–34 weeks in patients with one abnormal value.

Antepartum management

- 1 Program of care: visits every 1–2 weeks until 36 weeks' gestation, then weekly.
- 2 Dietary recommendations in pregnancy

- *Plan*: three meals, bedtime snack
- *Diet*: 2000–2200 kcal/day

Normal weight: 30 kcal/kg ideal prepregnancy body weight

Lean: 35 kcal/kg ideal prepregnancy body weight

Obese: 25 kcal/kg ideal prepregnancy body weight

- *Composition*

Carbohydrate: 40–50% complex, high fiber

Protein: 20%

Table 34.2 Venous plasma concentrations diagnostic of gestational diabetes.

	O'Sullivan*†	NDDG‡	Carpenter & Coustan*§
Fasting (mg/dL)	90	105	95
1 h (mg/dL)	165	190	180
2 h (mg/dL)	145	165	155
3 h (mg/dL)	125	145	140

NDDG, National Diabetes Data Group.

* See Suggested reading.

† Whole blood; Somogyi–Nelson method.

‡ Plasma or serum; glucokinase or hexokinase method. Most widely used.

§ Plasma or serum; glucokinase or hexokinase method. Probably more accurate representation of O'Sullivan than NDDG values. Recommended by American Diabetes Association.

Fat: 30–40% (<10% saturated)

- *Weight gain*: 20 lb (9 kg); 16 lb (7.25 kg) for very obese

Note: Check morning urine for ketones if using caloric restriction in obese patients (1600–1800 kcal/day). Increase caloric intake if fasting ketonuria noted.

3 Encourage regular exercise, 20–30 min brisk walking, 3–4 times/week.

4 Surveillance of maternal diabetes

- Self-monitoring of capillary blood glucose to check fasting and 1-h or 2-h postprandial glucose levels daily to assess efficacy of diet.
- If fasting plasma value is >95 mg/dL and/or 1-h value is >140 mg/dL and/or 2-h value is >120 mg/dL, insulin therapy is required.
- Starting insulin dose calculated based on patient's weight; 0.8 IU/kg actual body weight per day in first trimester, 1.0 IU/kg in second trimester, 1.2 IU/kg in third trimester. Give two-thirds of total dose in fasting state: two-thirds as NPH, one-third as regular or insulin lispro; one-third of total dose as one-half regular or insulin lispro at dinner, one-half as NPH at bedtime.
- Oral hypoglycemic drug glyburide can be used as alternative to insulin; start at 2.5 mg at breakfast and 2.5 mg at dinner. Usual dose 5 mg twice daily.

Delivery

1 For patients on diet only (Class A₁), allow to go to term.

2 If undelivered at 40 weeks, begin fetal assessment with twice-weekly NSTs. Patients who have had a previous stillbirth or have hypertension should be followed with twice-weekly NSTs at 32 weeks.

Table 34.3 Venous plasma glucose levels at 6 weeks postpartum in women with gestational diabetes.

	Normal	Impaired glucose tolerance	Diabetes mellitus
Fasting (mg/dL)	<100	100–125	≥126
2 h (mg/dL)	<140	140–199	≥200

- Clinical estimation of fetal size and ultrasonographic indices should be used to detect macrosomia. To reduce birth trauma, evaluate for cesarean section if estimated fetal weight is ≥ 4500 g.
- Patients with GDM who require insulin or glyburide as well as diet to maintain normal glucose levels (Class A₂) should be followed with a program of antepartum fetal surveillance identical to that used for women with pregestational diabetes.
- Infant to be observed in special care nursery for hypoglycemia, hypocalcemia, or hyperbilirubinemia.

Postpartum care

- Evaluation for persistent carbohydrate intolerance
 - Patient can continue self-monitoring blood glucose to evaluate glucose profile.
 - At 6 weeks' postpartum, oral GTT with 75 g glucose load, administered under conditions described for 100 g oral test. Venous plasma glucose is measured fasting and at 2 h (Table 34.3).
 - If normal, evaluate at minimum of 3-year intervals with fasting glucose; encourage exercise, and if obese weight loss.
- Effects of oral contraceptives. Deterioration of carbohydrate intolerance not reported with low-dose pills.
- Recurrence risk of GDM is approximately 60%.

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Hypothyroidism

Brian Casey

INTRODUCTION

Pregnancy is uncommon in women with clinical hypothyroidism because of its association with ovulatory and menstrual disturbances. It complicates 1–3 in 1000 pregnancies. Women with clinical hypothyroidism are at an increased risk for pregnancy wastage and complications such as pre-eclampsia, placental abruption, low birth weight, and stillbirth. Treatment of women with clinical hypothyroidism has been associated with improved pregnancy outcomes. Subclinical hypothyroidism affects 2–3% of pregnant women and has recently been associated with impaired neurologic development in offspring. Screening and treatment of pregnant women with subclinical hypothyroidism has not been demonstrated to be beneficial and remains an area of controversy.

PATHOPHYSIOLOGY

Deficient thyroid hormone production from intrinsic thyroid disease has been called primary or thyroprivic hypothyroidism. The most common cause of primary hypothyroidism in pregnancy is chronic autoimmune thyroiditis (Hashimoto thyroiditis). It is a painless inflammation with progressive enlargement of the thyroid gland that is characterized by diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy and eosinophilic change. Other important causes of primary hypothyroidism include endemic iodine deficiency and a history of either ablative radioiodine therapy or thyroidectomy. Secondary hypothyroidism is pituitary in origin. For example, Sheehan syndrome from a history of obstetric hemorrhage is characterized by pituitary ischemia and necrosis with subsequent deficiencies in some or all pituitary responsive hormones. Other etiologies of secondary hypothyroidism include lymphocytic hypophysitis and a history of a hypophysectomy. Tertiary or hypothalamic hypothyroidism is very rare.

DIAGNOSIS

Clinical hypothyroidism is often characterized by vague, non-specific signs

or symptoms that are insidious in onset. Initial symptoms include fatigue, constipation, cold intolerance, and muscle cramps. These may progress to insomnia, weight gain, carpal tunnel syndrome, hair loss, voice changes, and intellectual slowness. The presence of an enlarged thyroid gland is dependent on the etiology of hypothyroidism. Women in areas of endemic iodine deficiency or those with Hashimoto thyroiditis are much more likely to have a goiter. Other signs of hypothyroidism include periorbital edema, dry skin, and prolonged relaxation phase of deep tendon reflexes. The diagnosis of clinical hypothyroidism during pregnancy is particularly difficult because many of the signs or symptoms listed above may be attributed to the pregnancy itself. For example, pregnancy is accompanied by moderate enlargement of the thyroid caused by benign hyperplasia of glandular tissue and increased vascularity. Subclinical hypothyroidism is contemporarily defined as a serum thyroid stimulating hormone (TSH) concentration above the statistically defined upper limit of normal with a serum free thyroxine (FT_4) concentration within its reference range in an otherwise asymptomatic woman.

The mainstay for the diagnosis of thyroid disease is measurement of serum TSH. The diagnosis of hypothyroidism is generally established by an elevated serum TSH and a low serum FT_4 . If the FT_4 concentration is low in the presence of a normal or depressed TSH, then pituitary or hypothalamic hypothyroidism should be suspected. The reference range of normal serum TSH concentration is 0.45–4.5 mIU/L. The normal range for FT_4 by immunoassay is 0.7–1.8 ng/dL. In pregnancy, human chorionic gonadotropin (hCG) peaks at approximately 10 weeks' gestation and has some thyroid stimulating activity because of structural homology with TSH. This results in a fall in serum TSH during the first trimester that is associated with a modest increase in FT_4 . These physiologic changes may confound the serologic diagnosis of hypothyroidism during pregnancy and underline the need for gestational age-specific TSH and FT_4 thresholds. It may be helpful to confirm the presence of either antimicrosomal or antithyroglobulin antibodies in cases where autoimmune thyroiditis is suspected. Specifically, the presence of antithyroid antibodies may identify a population of women at a particular risk for pregnancy complications or progression to symptomatic disease.

TREATMENT

The goal of treatment in pregnant women with overt hypothyroidism is clinical and biochemical euthyroidism. Levothyroxine sodium is the treatment of choice for routine management of hypothyroidism. Starting dosage is usually in the range 1.0–2.0 μ g/kg. Serum thyrotropin is then measured at 4–6 week intervals and thyroxine is adjusted by 25–50 μ g increments. Women with hypothyroidism at conception should have a serum TSH evaluated at their first visit. Approximately one-third will require an increase in thyroid replacement

during pregnancy. Therefore, during pregnancy, it is recommended that serum TSH be measured at least each trimester. Notably, several drugs may interfere with levothyroxine absorption (e.g. cholestyramine, ferrous sulfate, aluminum hydroxide antacids) or affect its metabolism (e.g. phenytoin, carbamazepine, rifampin).

Treatment of women with subclinical hypothyroidism is controversial. Studies suggesting increased fetal wastage or subsequent neurodevelopmental complications in the offspring of women with mild hypothyroidism have prompted several national organizations to recommend treatment of subclinical hypothyroidism to restore the TSH to the reference range. Importantly however, there are no published intervention trials assessing the safety or efficacy of screening and treatment to improve neuropsychologic performance in offspring of women with subclinical hypothyroidism. Currently, routine screening and treatment of subclinical hypothyroidism during pregnancy is not recommended by the American College of Obstetricians and Gynecologists.

COMPLICATIONS

Historically, clinical hypothyroidism complicating pregnancy has been linked to an increase in complications such as congenital anomalies, perinatal mortality, and neurologic dysfunction in offspring. Neurologic sequelae of maternal and fetal hypothyroidism, particularly resulting from endemic iodine deficiency, are the associated neurodevelopmental problems of classic cretinism. Spontaneous abortion has been shown to be increased in women with hypothyroidism at conception, particularly in those women with antithyroid antibodies. Pregnancy complications such as gestational hypertension, placental abruption, and preterm birth have also been associated with clinical hypothyroidism. An increase in stillbirth, which may be related to pre-eclampsia and placental abruption, has been demonstrated in mothers with clinical hypothyroidism. Earlier reports of an increase in congenital malformations in infants of hypothyroid women have not been confirmed in contemporary studies.

Pregnancy complications associated with subclinical hypothyroidism are less evident. Subclinical hypothyroidism, variously defined, has been implicated in complications such as spontaneous abortion, gestational hypertension, preterm birth, and stillbirth. However, studies in women with subclinical hypothyroidism as contemporaneously defined are needed to confirm these associations. Importantly, the results of research published in 1999 suggesting that offspring of women with subclinical hypothyroidism are more likely to have psychomotor deficiencies at 2 years of age and lower IQ scores at 7–9 years of age highlights the importance of ongoing research in this area.

FOLLOW-UP

After pregnancy in women with clinical hypothyroidism, levothyroxine therapy

should be returned to the prepregnancy dosage and TSH concentrations should be checked at 6–8 weeks postpartum. Periodic monitoring of hypothyroidism with an annual serum TSH concentration is advised because of the impact of changing weight and age on thyroid function. Women with subclinical hypothyroidism, particularly those with thyroid autoantibodies, are at an increased risk for developing clinical disease within 5 years. While treatment of these women remains controversial, yearly evaluation for the development of clinical disease is recommended.

CONCLUSIONS

Ideally, women considering pregnancy should be euthyroid prior to conception. Pregnant women with clinical hypothyroidism should have intermittent evaluation of thyroid function throughout pregnancy. Thyroxine therapy may need to be increased during pregnancy, especially in the first trimester. Pregnancy and neurologic outcomes of offspring of women with well-controlled hypothyroidism are expected to be similar to women without thyroid disease. However, the merits for screening for and treatment of pregnant women with subclinical hypothyroidism are not clear. Further studies are necessary before embarking on a public health policy of routine, universal screening for subclinical hypothyroidism.

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Hyperthyroidism

George D. Wendel, Jr

INTRODUCTION

Thyrotoxicosis is the clinical syndrome resulting from circulation of excess thyroid hormones from any etiology. Hyperthyroidism is excessive thyroid hormone production because of thyroid gland overactivity. Graves disease is an autoimmune thyroid disease, and thyroid storm is the acute exacerbation of hyperthyroidism in women with untreated or poorly controlled disease.

Hyperthyroidism may be diagnosed for the first time during pregnancy, or hyperthyroid women may conceive while receiving antithyroid medication. Women also may be in remission from antithyroid therapy, have a history of ablative therapy, or a previous infant with thyroid dysfunction. Preconception control of thyroid disease is encouraged, similar to the approach with diabetes mellitus. Good control of pre-existing disease and early recognition and treatment of new disease are important to reduce maternal and perinatal morbidity.

ETIOLOGY

The prevalence of hyperthyroidism is approximately 0.2%, and most cases result from Graves disease (85–95%). Nodular goiter and Hashimoto thyroiditis are occasionally responsible for the syndrome. Iatrogenic hyperthyroidism may occur, but is also uncommon.

Early in pregnancy, gestational trophoblastic disease (GTD) must be ruled out, because it may produce symptoms and laboratory tests consistent with thyrotoxicosis. Patients with severe hyperemesis gravidarum also may present with transient hyperthyroidism resulting from inappropriate secretion or action of human chorionic gonadotropin (hCG). This transient hyperthyroidism of hyperemesis gravidarum may be the most common cause of biochemical hyperthyroidism in the first trimester of pregnancy. Women are rarely clinically hyperthyroid and generally do not require therapy. The tests results return to normal spontaneously in both conditions after surgical treatment of GTD and correction of dehydration, respectively. Routine measurements of

thyroid function test are not indicated in either setting unless signs of hyperthyroidism are present.

CLINICAL PRESENTATION

The natural course of Graves hyperthyroidism is often characterized by exacerbation of symptoms in the first trimester and postpartum, with an amelioration of symptoms in the second half of gestation. Most antenatal, newly diagnosed hyperthyroidism is characterized by symptoms that predate conception. In pregnancy, the symptoms are frequently mild, and may mimic common hypermetabolic complaints of normal pregnancy. Irritability, nervousness, palpitations, heat intolerance, goiter, and weight loss or inability to gain weight in spite of good appetite are common initial complaints.

Persistent mild tachycardia and lack of weight gain are the signs most commonly present. Eye signs, such as lid lag, chemosis, and exophthalmos, are seen not infrequently. On examination the patient may look hyperactive with a tremor. Most women with Graves disease will have a diffusely enlarged goiter with a gland 2–6 times normal size. A hyperdynamic precordium is common, and congestive heart failure may also occur because of the cardiomyopathy of long-standing hyperthyroidism.

DIAGNOSIS

Diagnosis of hyperthyroidism is confirmed by the presence of an elevation in the free thyroxine (FT_4) concentration or in the free thyroxine index (FT_{4i}). Serum thyroid-stimulating hormone (TSH) concentration is suppressed. It is important to point out that serum TSH may be suppressed in the first trimester of normal pregnancy. Serum free triiodothyronine (FT_3) is useful in evaluating women with hyperthyroidism with suppressed TSH and normal FT_4 and its elevation may indicate T_3 thyrotoxicosis.

There are various TSH receptor antibodies that are markers for the diagnosis of Graves disease. These include thyroid-stimulating immunoglobulin (TSI), thyroid-stimulating hormone-binding inhibitory immunoglobulin (TBII). There are antithyroid peroxidase and antimicrosomal antibodies that are markers of thyroid autoimmune disease. The obstetric clinical utility of these antibodies is unclear, but some experts feel they can be used in the patient at risk of having an infant with fetal or neonatal hyperthyroidism.

MANAGEMENT AND TREATMENT

Antithyroid thioamide drugs are the treatment of choice in the management of hyperthyroidism in pregnancy. The goals of treatment are to keep the patient euthyroid on the minimum amount of antithyroid medication and to maintain the thyroid tests in the upper limits of normal.

When the diagnosis is made for the first time during pregnancy, methima-

zole (Tapazole®, King Pharmaceuticals Inc., Bristol, TN), 10–20 mg twice daily, or propylthiouracil (PTU), 100–150 mg three times daily, according to the severity of the symptoms, is given. In severe cases, up to 600 mg/day PTU or 60 mg/day methimazole can be used. Although there are pharmacokinetic differences between the two agents, there are no data that one is superior to the other. In patients with severe hypermetabolic symptoms, propranolol (10–40 mg every 6–8 h) or atenolol (25–50 mg/day) can be added for a few weeks in order to control the symptoms.

Most patients respond with an improvement in symptoms and thyroid testing within 2–6 weeks. Patients are seen every 2–3 weeks, at which times FT₄ tests are ordered. Most patients will experience a decrease in FT₄ in 2–4 weeks with chemical euthyroidism by 8 weeks. As soon as the FT₄ improves, the dosage of antithyroid drug may be reduced carefully in selected patients, although many women may require increased thioamide dosage to maintain a euthyroid state as pregnancy progresses. The goal is to keep the FT₄ in the upper limits of normal. The TSH often remains suppressed beyond the time of the normalization of other thyroid hormone tests, and its increase to normal range is not a major goal of management in pregnancy.

For patients who become pregnant while receiving antithyroid drug therapy, a similar approach should be followed, keeping in mind that the minimum amount of medication that keeps the patient euthyroid is to be used.

Side-effects of antithyroid medication occur in 3–5% of patients and consist of pruritus and skin rash. Occasionally, fever, arthralgias, or lymphadenopathy may be seen. The most severe side-effect of antithyroid drugs is agranulocytosis; however, this is uncommon. Patients should discontinue the drug in cases of sore throat, fever, or gingivitis. A complete blood count (CBC) should be performed at once. If granulocytes are definitely decreased, the drug should be discontinued. For mild side-effects, antihistamines can be used for a short period of time, and the antithyroid drug can be switched to an alternative compound.

Subtotal thyroidectomy should be reserved for selected cases, including patients with allergic reactions to both antithyroid drugs, the occasional patient who is resistant to the drugs, and patients who are unwilling to take antithyroid medication. ¹³¹I is contraindicated during pregnancy, because it can cause fetal hypothyroidism when given after 10 weeks' gestation.

Thyroid storm is an uncommon acute emergency characterized by a hypermetabolic state that may be precipitated by infection, surgery or labor in untreated or poorly controlled hyperthyroidism. Women exhibit fever, tachycardia, hypertension, altered mental status, nausea and vomiting, diarrhea, arrhythmias, and congestive heart failure. Therapy is initiated rapidly with an oral loading dose of 1 g PTU followed by 200 mg every 6 h. One hour later five drops of a saturated solution of potassium and sodium iodide (SSKI) orally every 8 h are started. Most clinicians also add 2 mg dexamethasone i.v. every

6h for four doses, and propranolol may be useful to reduce the adrenergic effects of thyroid storm. Supportive therapy includes oxygen, fluid resuscitation, antipyretics, antihypertensive agents, and critical care monitoring as indicated. Antithyroid drugs should be continued as the source of the stress that triggered the thyroid storm is also treated. Fetal monitoring is important, but aggressive treatment of maternal thyrotoxic crisis should be the primary priority to restore fetal well being.

COMPLICATIONS

Properly treated, hyperthyroid mothers develop few complications during pregnancy. In those mothers under poor control, the risk of maternal complications is increased for pregnancy-induced hypertension, preterm delivery, congestive heart failure, and thyroid storm. Neonatal complications include prematurity, intrauterine growth restriction, small for gestational age size, and neonatal death. These maternal and neonatal complications can be prevented with proper control of hyperthyroidism.

Although maternal antithyroid therapy can theoretically induce fetal hypothyroidism, there is little correlation between commonly used maternal dosage and fetal thyroid status. Neonatal hyperthyroidism occurs in approximately 2% of infants born to hyperthyroid mothers. This is caused by the placental passage of maternal TSI, which stimulates the fetal thyroid. Because there is some *in utero* balance provided by the transplacental passage of maternal antithyroid medication, symptoms occur after delivery when the beneficial effect of the antithyroid medication is gone. As maternal antibody is cleared less rapidly, infants should be followed closely for several weeks after delivery. Additionally, the mother should be aware of the early symptoms of thyroid decompensation in the newborn. A high titer of TSI antibody (more than 500% of normal) in the mother at the end of pregnancy predicts the development of neonatal hyperthyroidism.

Fetal hyperthyroidism is a very rare event that occurs in fetuses whose mothers have been treated with ablative therapy for hyperthyroidism before pregnancy. This is presumably caused by persistent high TSI antibody levels in spite of maternal euthyroidism. Fetal tachycardia, fetal goiter, and intrauterine growth restriction are suggestive of this complication. TSI should be measured in women with a history of Graves disease treated with ¹³¹I and in women with a previously affected infant; its utility in other women with Graves disease is unclear. Cordocentesis may be useful in the setting of a prior affected infant, prior maternal ablative therapy with a high TSI titer, or a fetus with ultrasonographic signs of fetal hyperthyroidism. Fetal thyroid function tests may then guide therapy to increase or decrease maternal antithyroid therapy.

POSTPARTUM PERIOD

Women with Graves disease should be followed at regular intervals following delivery, because recurrence or aggravation of symptoms is not uncommon in the first few months postpartum. Most asymptomatic women should have a TSH and FT₄ performed approximately 6 weeks postpartum.

Breastfeeding is not contraindicated in mothers taking up to 200 g/day PTU or 10 mg/day methimazole. It may be prudent to give divided doses after feeding, when possible.

Transient postpartum thyroid dysfunction may occur in women with chronic or Hashimoto thyroiditis. Mild hypermetabolic symptoms are recognized between 6 and 12 weeks postpartum with a slight enlargement of a previous goiter. This is followed in most cases by a period of hypothyroidism, with spontaneous recovery occurring in 4–8 months. This clinical entity requires no treatment in the majority of cases and may repeat itself in subsequent pregnancies.

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Acute and chronic hepatitis

Marshall W. Carpenter

INTRODUCTION

Both hepatitis B virus (HBV) and C virus (HCV) are transmitted by parenteral and sexual contact. Prevalence of HBV and HCV acute or chronic active infection in the USA is approximately 1.5 and 4 million, respectively. The annual number of new HBV infections in the USA exceeds 300,000. Approximately 40% of hepatitis cases in the USA are caused by the B virus. Acute hepatitis B affects 1 in 500 pregnancies and chronic carriage of hepatitis is found in more than 1 in 200 pregnancies. Since effective blood screening for HCV in 1990, the number of new HCV infections has fallen to 36,000 each year. HCV infection has a peak prevalence during childbearing years, with maternal carriage rates estimated at 0.5–3%. Among indigent urban patients in the USA with evidence of sexually transmitted diseases, the rate of antihepatitis C antibody has been found to be 7%. Neonatal transmission of either infection occurs primarily at childbirth.

PATHOPHYSIOLOGY

Hepatitis B, a small DNA virus, is composed of three antigens of interest: the surface antigen (HBsAg) found in serum; the core antigen (HBcAg) found only in hepatocytes; and the e antigen (HBeAg) also found in serum and indicative of a high rate of viral replication. HCV infection is caused by a single-stranded RNA virus and is characterized by a high replication rate (10^9 – 10^{12} RNA copies per day) and a short half-life of 2–3 h.

After acute maternal HBV infection in the first trimester, 10% of neonates are found to be infected. Rates as high as 90% transmission are found after third-trimester maternal infection. Among chronic carriers, hepatitis B transmission may occur in 10–20% of births. Overall, however, 85–90% of neonatal infections are acquired at the time of delivery. Without neonatal immunization, patients positive for both HBsAg and HBeAg have high probability of vertical transmission approaching 90%. T cells appear to be tolerant of HBV nucleocapsid moieties. This immune tolerance may

explain the high probability of chronic infection following perinatal exposure.

Neonatal infection with HCV is found in approximately 6% of cases of gravidas with positive HCV serology. The limited published observations of vertical transmission among women with measured viral loads suggest that among those with less than 10^6 viral copies/mL a vertical transmission rate of 4% can be anticipated, whereas among women with higher loads transmission rates of up to 25% may occur.

Estimates of anti-HCV-positive gravidas are as high as 120,000. Consequently, as many as 7200 neonates may be infected annually in the USA, accounting for as much as 20% of the HCV infection incidence. Because universal maternal screening is not generally performed, 40–50% of these infections are covert.

DIAGNOSIS

Early HBV infection is associated with the presence of HBsAg and IgM anticore antibody (HBcAb). The presence of HBeAg indicates active viral replication and high infectivity. Occasionally, IgM HBcAb is the only serologic evidence of acute HBV infection. Chronic HBV infection is characterized by persisting HBsAg and IgG HBcAb, which typically appears 6 months after initial exposure.

HCV infection is diagnosed by a positive hepatitis C antibody. Its expression can be delayed by as long as 4 months after exposure. Hepatitis RNA viral load can be measured by polymerase chain reaction, reflecting viral replication and infectivity. The utility of universal screening is a function of prevalence among reproductive age women in a given environment. Screening for HBV infection is further justified by the prophylactic utility of hepatitis B immunoglobulin (HBIG) treatment of neonates of seropositive mothers. At present there is no consensus that HCV screening is justified during pregnancy. Although such screening in high-risk groups (e.g. drug users, multiple or suspect sexual partners, elevated liver enzymes) would provide significant maternal benefit, maternal case identification has not, as yet, been shown to reduce rates of vertical transmission.

TREATMENT

Evaluation of pregnant patients presenting with acute liver dysfunction should exclude diagnoses that compete with that of HBV and HCV infection. These include hepatitis A, mononucleosis, and cytomegalovirus infections, exposure to environmental toxins and drugs, obstructive or infectious biliary disease, and autoimmune diseases. In the second half of pregnancy, pre-eclampsia, cholestasis of pregnancy, and acute fatty liver are important exclusions. Patients with acute hepatitis infection may require nutritional, fluid, and electrolyte support. Coagulopathy secondary to hepatic synthetic failure may

require correction. Less severely affected women may be managed with frequent follow-up at home. Household members and others having intimate contact with the patient should be tested and if HBsAg-negative, receive passive and active immunization.

Interferon- α has been shown to improve the natural history of both HBV and HCV Chronic infection. The development of pegylated forms of this drug (by attachment of a 12-kD polymer, monomethoxypolyethylene glycol) reduces clearance to one-tenth that of the unbound drug. This has made therapy more accessible by requiring weekly-only regimens without change in biologic activity. However, drug treatment is associated with significant symptoms of malaise and complications of myelosuppression, autoantibody formation, and possible cardiotoxicity. Given available data, its use during pregnancy is contraindicated because of possible abortifacient effects and association with myelination abnormalities and cerebral palsy when employed in the treatment of infants. A regimen of pegylated interferon α -2b has been shown to produce a dose-dependent 0.5–2.0 log decline in viral RNA levels in 24 h. In women with high viral loads, such a short-term treatment effect may avoid perinatal infection without neurotoxic effects. However, no clinical data are presently available to guide therapy.

Hepatitis C infection is also treated with ribavirin, a purine analog that inhibits viral mRNA synthesis. However, after chronic exposure, ribavirin causes extravascular hemolytic anemia and marrow suppression and has both gonadotoxic and oncogenic effects, contraindicating its use during pregnancy.

COMPLICATIONS

HBV infection-related mortality is 1%, with chronic infection demonstrable in 10–15% of patients who maintain HBsAg-positive sera. Of those, 15–30% remain infectious with HBeAg-positive sera. Although uncommon, both glomerulonephritis with the nephrotic syndrome and polyarteritis nodosa may develop as manifestations of immune complex disease secondary to HBV infection.

HCV infection persists in approximately 50% of patients. Of those, 20% demonstrate serologic and histologic chronic active hepatitis. After 10–20 years, 20–40% of those with chronic hepatitis infection develop hepatic cirrhosis. Patients with cirrhosis have an annual incidence of hepatocellular carcinoma of 1.5–2.5%.

FOLLOW-UP

Most women who have contracted either HBV or HCV infection in infancy will have mothers with established diagnoses of chronic infection. Nevertheless, a

large proportion of infected patients will only be diagnosed during pregnancy. In this circumstance, evaluation of patients with evidence of hepatocellular dysfunction or portal hypertension may require sonographic, radiologic, and magnetic resonance imaging (MRI) evaluation. Consequently, complete care of gravidas with HBV and HCV infection will include establishing medical care collaboration with an internist or gastroenterologist. This will address issues of immediate evaluation, timely decision-making during unforeseen complications of pregnancy, and appropriate surveillance and treatment after pregnancy.

Contraception counseling and maintenance is important to the welfare of the patient and her family. Both interferon α -2b and ribavirin are embryotoxic and may impair later fetal development. However, the choice of contraceptive is important. Epidemiologic studies have found an association of oral contraceptive (OCP) use and increased risk of hepatocellular carcinoma. Whether the risk of developing this cancer is higher in patients with chronic HBV and HCV infection who use OCPs is unclear. OCPs should be avoided if there is evidence of ongoing hepatocellular injury.

Infants born to mothers who are anti-HCV antibody-positive but HCV RNA-negative should be screened for the presence of anti-HCV and alanine aminotransferase elevation at 18–24 months. Infants born to HCV-viremic mothers should have these tests performed at 3-month intervals after birth. HCV RNA-negative infants with abnormal alanine aminotransferase should be tested again for viremia at 6–12 months, and for anti-HCV antibodies at 18 months. Infants with negative HCV RNA and normal enzyme levels should be tested for anti-HCV and alanine aminotransferase at 18–24 months and, if normal, considered free of infection. Most writers accept that persisting anti-HCV antibodies after 12–18 months indicates past infection and that detection of viremia in these children with or without elevated hepatic enzymes is indicative of active disease.

PREVENTION

General

Risk of hepatitis B infection after exposure can be reduced by 75% by treatment with HBIG within 14 days after sexual or parenteral exposure, with the 0.6 mL/kg dose repeated in 1 month. This passive immunization is acceptable during pregnancy.

Blood products

Blood products are routinely screened for hepatitis B and C colonization, among other pathogens. Routine screening for HBsAg has significantly decreased the incidence of post-transfusion HBV to 0.002% in the USA. Since 1990, the US

blood supply has been screened for HCV infection. First-generation tests reduced risk of per-unit HCV infection to 0.03% and second-generation anti-HCV assays has reduced the frequency 0.001%.

Workplace

Healthcare workers contracting HBV infection following exposure by needle prick has been estimated to be as high as 20%. All healthcare workers at risk for exposure to percutaneous injury or splash exposure to biologic fluids should have active immunization. Beyond the consistent use of universal precautions against infectious disease, there is no proven efficacy of any prophylaxis to prevent HCV infection.

Maternal/perinatal infection

Couples discordant for HIV infection have been found to successfully avoid male to female infection by using intracytoplasmic sperm injection assisted reproduction. The utility of these techniques in HCV-viremic men and uninfected female partners is unclear.

All gravidas should be screened for HBV infection by an HBsAg test. Children and sexual partners of seropositive women should also be screened. The Centers for Disease Control recommend universal active immunization of all infants. Offspring of seropositive women should also receive both passive and active immunization within 12 h of birth. Hepatitis B transmission may occur in 10–20% of births but can be prevented by passive and active immunization of the neonate within 12 h of birth. Enzyme immunoassay tests can detect infection within 4 weeks of exposure.

Postulated risk factors for vertical transmission of HCV infection have included parenteral drug abuse, co-infection with HIV, immunosuppression, and vaginal delivery. Most studies examining these co-morbid effects have not accounted for the effect of viral load on the risk of perinatal transmission. One report suggests that the relative risk of vertical HCV transmission among HIV-infected mothers falls when the same comparison is made only among HCV-infected women with HCV viremia. Because reported data have been inconsistent and studies flawed, no maternal intervention can be shown to reliably reduce vertical transmission. However, the association of perinatal infection risk with maternal viral load suggests that neonates should be carefully bathed immediately after birth to reduce exposure of cord and mucus membranes to infected maternal fluids.

Breastfeeding

Breastfeeding is not contraindicated in HBsAg-positive mothers if their offspring have been immunized. Breastfeeding in HCV-infected patients is

controversial. No reliable data have documented increased risk of neonatal infection associated with maternal nursing.

CONCLUSIONS

Hepatitis B and C accounts for the majority of viral hepatic infections occurring during pregnancy. Among viremic subjects, all body fluids may contain intact viruses, although the predominant route of infection is through exposure to serum. Fetal HBV infection may occur during pregnancy during a primary maternal infection. Risk of transmission of HBV increases with gestational age. Most HBV and HCV transmission to the perinate occurs during parturition. Infants have a high susceptibility to HBV infection but this may be avoided by active and passive immunization within 12 h of birth. There are no proven means to avoid perinatal HCV infection to the perinate, although careful irrigation of cord and mucous membranes may reduce exposure. Women who are viremic with either virus should undergo immunotherapy and will require reliable contraception, especially when exposed to these agents. Infants born to viremic HCV-infected mothers require frequent follow-up for serologic and hepatic function testing during the first 2 years of life.

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Asthma

Michael Schatz

INTRODUCTION

Asthma currently affects up to 8% of pregnant women, making it probably the most common potentially serious medical problem to complicate pregnancy. Although data have been conflicting, the largest and most recent studies have suggested that maternal asthma increases the risk of perinatal mortality, pre-eclampsia, preterm birth, and low birth weight infants. More severe asthma is associated with increased risks, while better controlled asthma is associated with decreased risks.

PATHOPHYSIOLOGY

Asthma is an inflammatory disease of the airways that is associated with reversible airway obstruction and airway hyper-reactivity to a variety of stimuli. Although the cause of asthma is unknown, a number of clinical triggering factors can be identified, including viral infections, allergens, exercise, sinusitis, reflux, weather changes, and stress.

Airway obstruction in asthma can be produced by varying degrees of mucosal edema, bronchoconstriction, mucus plugging, and airway remodeling. In acute asthma, these changes can lead to ventilation–perfusion imbalance and hypoxia. Although early acute asthma is typically associated with hyperventilation and hypocapnea, progressive acute asthma can cause respiratory failure with associated carbon dioxide retention and acidosis.

DIAGNOSIS

Many patients with asthma during pregnancy will already have a physician diagnosis of asthma. A new diagnosis of asthma is usually suspected on the basis of typical symptoms—wheezing, chest tightness, cough, and associated shortness of breath—which tend to be episodic or at least fluctuating in intensity and are typically worse at night. Identification of the characteristic triggers described above further supports the diagnosis. Wheezing may be present on

auscultation of the lungs, but the absence of wheezing on auscultation does not exclude the diagnosis. The diagnosis is ideally confirmed by spirometry, which shows a reduced FEV_1 with an increase in FEV_1 of 12% or more after an inhaled short-acting bronchodilator.

It is sometimes difficult to demonstrate reversible airway obstruction in patients with mild or intermittent asthma. Although methacholine challenge testing may be considered in non-pregnant patients with normal pulmonary function to confirm asthma, such testing is not recommended during pregnancy. Thus, therapeutic trials of asthma therapy should generally be used during pregnancy in patients with possible but unconfirmed asthma. Improvement with asthma therapy supports the diagnosis, which can then be confirmed postpartum with additional testing if necessary.

The most common differential diagnosis is dyspnea of pregnancy, which may occur in early pregnancy in approximately 70% of women. This dyspnea is differentiated from asthma by its lack of association with cough, wheezing, or airway obstruction.

Another aspect of asthma diagnosis is an assessment of severity. Although more complicated severity schemes have been proposed, the most important determination is whether the patient has intermittent versus persistent asthma. This distinction has both prognostic and therapeutic significance during pregnancy. Patients with *intermittent asthma* have short episodes less than three times per week, nocturnal symptoms less than three times per month, and normal pulmonary function between episodes. Patients with more frequent symptoms or who require daily asthma medications should be considered to have *persistent asthma*.

Asthma severity often changes during pregnancy, although it can either get better or worse. Patients with more severe asthma prior to pregnancy are more likely to worsen further during pregnancy. Because gestational asthma course in an individual woman is unpredictable, women with asthma must be followed particularly closely during pregnancy so that any change in course can be matched with an appropriate change in therapy.

MANAGEMENT

General

Identifying and avoiding asthma triggers can lead to improved maternal well being with less need for medications. In previously untested patients, *in vitro* (RAST, ELISA) tests should be performed to identify relevant allergens, such as mite, animal dander, mold and cockroach, for which specific environmental control instructions can be given. Smokers must be encouraged to discontinue smoking, and all patients should try to avoid exposure to environmental tobacco smoke and other potential irritants as much as possible. Effective allergen immunotherapy can be continued during pregnancy, but benefit-risk

considerations do not generally favor beginning immunotherapy during pregnancy.

Asthma medicines are classified into two types: relievers and long-term controllers. Relievers provide quick relief of bronchospasm and include short-acting beta-agonists (albuterol is preferred during pregnancy, 2–4 puffs every 3–4 h as needed) and the anticholinergic bronchodilator ipratropium (generally used as second-line therapy for acute asthma; see below). Long-term control medications are described in Tables 38.1 and 38.2.

Chronic asthma

Patients with intermittent asthma do not need controller therapy. In patients with persistent asthma, controller therapy should be initiated and progressed in steps (Table 38.3) until adequate control is achieved. Adequate control generally means symptoms or rescue therapy requirement less than three times per week, nocturnal symptoms less than three times per month, no activity limitation because of asthma, and, ideally, normal pulmonary function tests. Inhaled corticosteroids are the mainstay of controller therapy during pregnancy. Because it has the most published reassuring human gestational safety data, budesonide is considered the inhaled corticosteroid of choice for asthma during pregnancy. It is important to note that no data indicate that the other inhaled corticosteroid preparations are unsafe. Therefore, inhaled corticosteroids other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy, especially if it is thought that changing formulations may jeopardize asthma control. Based on longer duration of availability in the USA, salmeterol is considered the long-acting beta-agonist of choice during pregnancy. As described in Table 38.1, the following drugs are considered by the National Asthma Education and Prevention Program (NAEPP) to be alternative, but not preferred, treatments for persistent asthma during pregnancy:

- *Cromolyn*: decreased efficacy compared with inhaled corticosteroids
- *Theophylline*: increased side-effects compared with alternatives
- *Leukotriene receptor antagonists*: limited availability of published human gestational data for these drugs

Although oral corticosteroids have been associated with possible increased risks during pregnancy (oral clefts, prematurity, lower birth weight), if needed during pregnancy they should be used because these risks are less than the potential risks of severe uncontrolled asthma (maternal or fetal mortality).

Acute asthma

A major goal of chronic asthma management is the prevention of acute asthmatic episodes. When acute asthma does not respond to home therapy,

Table 38.1 Long-term control medications for asthma during pregnancy. (Modified from NAEPP Expert Panel Report 2004.)

Medication	Mechanism of action	Dosage form	Adult dose	Use during pregnancy
Inhaled corticosteroids	Topical anti-inflammatory	see Table 38.2		First line controller therapy
Systemic corticosteroids	Systemic anti-inflammatory			
Methylprednisolone		2, 4, 8, 16, 32 mg tablets	Short course "burst" to achieve control: 40–60 mg/day as single or divided doses for 3–10 days	Burst therapy for severe acute symptoms
Prednisolone		5 mg tablets, 5 mg/mL, 15 mg/mL		Maintenance therapy for severe asthma uncontrolled by other means
Prednisone		1, 2.5, 5, 10, 20, 50 mg tablet 5 mg/mL, 5 mg/5 mL	maintenance: 7.5–60 mg/day in a single dose in AM or q.o.d., taper to lowest effective dose	
Long-acting beta-agonists				
Salmeterol	beta-agonist mediated smooth muscle relaxation that lasts 12 h	DPI 50 µg/blister DPI 12 µg/single-use capsule	1 blister q 12 h 1 capsule q 12 h	Add on therapy in patients not controlled by low–medium dose inhaled corticosteroids
Formoterol				
Cromolyn	Non-steroidal topical anti-inflammatory	MDI 1 mg/puff Nebulizer 20 mg/ampule	2–4 puffs t.i.d.–q.i.d. 1 ampule t.i.d.–q.i.d.	Alternative therapy for mild persistent asthma
Leukotriene receptor antagonists				
Montelukast	Blocks activity of leukotrienes (inflammatory mediators) by means of receptor antagonism	10 mg tablets 10 or 20 mg tablets	10 mg q HS 20 mg bid	Alternative therapy for persistent asthma in patients who have shown good response prior to pregnancy
Zafirlukast				
Theophylline	Bronchodilator (? Anti-inflammatory effects)	Liquids, sustained-release tablets, and capsules	400–800 mg/day to achieve serum concentration of 5–12 µg/mL	Alternative therapy for persistent asthma during pregnancy

Table 38.2 Estimated comparative daily adult regimens for inhaled corticosteroids.
(From NAEPP Expert Panel Report 2004.)

Drug	Low daily dose (μg)	Medium daily dose (μg)	High daily dose (μg)
<i>Beclomethasone HFA</i> 40 or 80 $\mu\text{g}/\text{puff}$	80–240	240–480	>480
<i>Budesonide DPI</i> 200 $\mu\text{g}/\text{inhalation}$	200–600	600–1200	>1200
<i>Flunisolide</i> 250 $\mu\text{g}/\text{puff}$	500–1000	1000–2000	>2000
<i>Fluticasone</i> MDI: 44, 110, 250 $\mu\text{g}/\text{puff}$ DPI*: 50, 100, or 250 $\mu\text{g}/\text{inhalation}$	88–264 100–300	264–660 300–600	>660 >600
<i>Triamcinolone acetonide</i> 100 $\mu\text{g}/\text{puff}$	400–1000	1000–2000	>2000

* Also available combined with salmeterol (50 $\mu\text{g}/\text{inhalation}$) at 100, 250, or 500 $\mu\text{g}/\text{inhalation}$.

expeditious acute management is necessary for both the health of the mother and that of the fetus.

Because of progesterone-induced hyperventilation, normal blood gases during pregnancy reveal a higher P_{O_2} (100–106 mmHg) and a lower P_{CO_2} (28–30 mmHg) than in the non-pregnant state. The changes in blood gases that occur secondary to acute asthma during pregnancy will be superimposed on the “normal” hyperventilation of pregnancy. Thus, a $P_{CO_2} > 35$ or a $P_{O_2} < 70$ associated with acute asthma will represent more severe compromise during pregnancy than will similar blood gases in the non-gravid state.

The recommended pharmacologic therapy of acute asthma during pregnancy is summarized in Table 38.4. Intensive fetal monitoring as well as maternal monitoring is essential. In addition to pharmacologic therapy, supplemental oxygen (initially 3–4 L/min by nasal cannula) should be administered, adjusting F_{iO_2} to maintain at $P_{O_2} \geq 70$ and/or O_2 saturation by pulse oximetry > 95%. Intravenous fluids (containing glucose if the patient is not hyperglycemic) should also be administered, initially at a rate of at least 100 mL/h.

Systemic corticosteroids (approximately 1 mg/kg) are recommended for patients who do not respond well (FEV_1 or peak expiratory flow rate [PEF] < 70% predicted) to the first beta-agonist treatment as well as for patients who

Table 38.3 NAEPP 2004 Recommendations for preferred step therapy for persistent asthma during pregnancy.

Step 1
Low-dose inhaled corticosteroids*

Step 2
Medium-dose inhaled corticosteroids*
or
Low-dose inhaled corticosteroids*
+ Long-acting beta-agonist†

Step 3
Medium-dose inhaled corticosteroids*
+ Long-acting beta-agonist†

Step 4
High-dose inhaled corticosteroids*
+ Long-acting beta-agonist†

Step 5
High-dose inhaled corticosteroids*
+ Long-acting beta-agonist†
+ Oral corticosteroids at lowest effective dose

* Budesonide is the preferred inhaled corticosteroid during pregnancy because of the availability of more reassuring human gestational safety data.

† Salmeterol is the preferred long-acting beta-agonist during pregnancy because of longer availability in the USA.

have recently taken systemic steroids and for those who present with severe exacerbations (FEV_1 or $PEF \leq 50\%$ of predicted). Patients with good responses to emergency therapy (FEV_1 or $PEF \geq 70\%$ predicted) can be discharged home, generally on a course of oral corticosteroids. Inhaled corticosteroids should also be continued or initiated upon discharge until review at medical follow-up. Hospitalization should be considered for patients with an incomplete response (FEV_1 or $PEF \geq 50\%$ but $< 70\%$ predicted). Admission to an intensive care unit should be considered for patients with persistent FEV_1 or $PEF \leq 50\%$ predicted, $PCO_2 > 42$, or sensorium changes.

FOLLOW-UP

Careful follow-up by physicians experienced in managing asthma is an essential aspect of optimal gestational asthma management. Asthmatic women

Table 38.4 Pharmacologic management of acute asthma during pregnancy.

-
- 1 Beta₂-agonist bronchodilator (nebulized or metered-dose inhaler)
 - Up to 3 doses in first 60–90 min
 - Every 1–2 h thereafter until adequate response
 - 2 Nebulized ipratropium (may be repeated every 6 h)
 - 3 Systemic corticosteroids (with initial therapy in patients on regular corticosteroids and with severe exacerbations and for those with incomplete response to initial therapy)
 - ~1 mg/kg every 6–8 h
 - May be given orally; intravenously for severe exacerbation
 - Taper as patient improves
 - 4 Consider intravenous aminophylline (generally only if patient requires hospitalization). If it is to be used
 - 6 mg/kg loading dose
 - 0.5 mg/kg/h initial maintenance dose
 - Adjust rate to keep theophylline level between 5–12 µg/mL
-

requiring regular medication should be evaluated at least monthly. In addition to symptomatic and auscultatory assessment, objective measures of respiratory status (optimally spirometry, minimally PEF) should be obtained on every clinic visit. In addition, patients with more severe or labile asthma should be considered for home PEF monitoring. All pregnant patients should have a written action plan for increased symptoms and facilitated access to their physician for uncontrolled symptoms.

CONCLUSIONS

Asthma is a common medical problem during pregnancy. Optimal diagnosis and management of asthma during pregnancy should maximize maternal and fetal health.

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Epilepsy

Neil K. Kochenour

INTRODUCTION

Management of the woman with epilepsy begins preconceptionally. At that time her antiepileptic drugs (AEDs) should be evaluated for their need, the minimum dosage required to prevent seizures, and the teratogenic potential of the drugs. In addition, adequate folate intake should be recommended during the preconceptional period. During pregnancy the patient should be treated with the lowest effective dosage and, if possible, a single AED. After delivery, vitamin K should be given to the neonates of women on AEDs during pregnancy, and consideration should be given to supplemental vitamin K administration to pregnant women receiving AEDs during the last month of pregnancy.

PATHOPHYSIOLOGY

Epilepsy complicates approximately 0.3–0.5% of pregnancies. Approximately 45% of these patients will experience an increase in seizure frequency during pregnancy, which is most often attributable to a reduction in the plasma concentration of anticonvulsant drugs. In some, emotional stress seems significant. In general, reasons for changes in anticonvulsant drug levels include fluid retention, electrolyte changes, respiratory alkalosis, and hormonal influences. Additionally, a number of physiologic changes that occur during pregnancy are known to affect the pharmacokinetics of drugs. Decreased motility of the gastrointestinal tract may change the bioavailability of orally administered dosage forms. Significant increases in glomerular filtration rate influence the renal clearance rates of many drugs, and hormonal changes may affect hepatic enzyme systems responsible for drug metabolism. Women who report seizure activity within 2 years of pregnancy are significantly more likely to experience antenatal, intrapartum, and postpartum seizures when compared with women whose last seizure was more than 2 years before pregnancy.

Whatever the underlying cause of the increase in seizure frequency, potential fetal damage secondary to hypoxia and the added maternal risk resulting from seizures necessitate close observation and careful management. Studies

to date have demonstrated no difference in the prevalence of obstetric complications, adverse neonatal outcomes, or congenital malformations when pregnancies in which the mother had one or more antepartum seizures when compared with those who had no seizures.

TERATOGENICITY OF ANTICONVULSANTS

There is considerable controversy concerning the teratogenicity of anticonvulsant drugs. The overall rate of congenital abnormalities in association with maternal intake of AEDs is 5–6%. This is twice the expected rate of 2.5–3.0% in the general population. In addition, children of mothers with epilepsy, treated or untreated with AEDs, tend to have slightly more minor anomalies than do children of fathers with epilepsy, or control subjects. Trimethadione has been shown to result in spontaneous abortions in a high percentage of pregnancies and fetal malformations in the majority of remaining pregnancies. Therefore its use is contraindicated during pregnancy and it probably should not be given to women of childbearing age. To date, no information is available as to which of the major AEDs (phenytoin, carbamazepine, valproate, phenobarbital) is the most teratogenic and causes more major malformations. Very little is known about the use of some newer anticonvulsants such as topiramate, zonisamide, and oxcarbazepine during pregnancy. Lamotrigine is a relatively new anticonvulsant therapy. Although lamotrigine is not indicated for use in pregnancy, women with epilepsy may require or be unintentionally exposed to the drug during pregnancy. The manufacturer GlaxoSmithKline has maintained a Pregnancy Registry for approximately 10 years. The number of pregnancies exposed to lamotrigine monotherapy to date is insufficient to reach definitive conclusions regarding the possible teratogenic risk of this drug. Polytherapy including valproate involving first trimester exposure to lamotrigine and valproate demonstrated a 10% incidence of major malformations whereas only approximately 3% of infants exposed to lamotrigine and at least one other AED excluding valproate in the first trimester demonstrated a major birth defect. Valproate and carbamazepine have been associated with an approximately 1% risk of spina bifida. Because no agreement has been reached regarding which AED is the most teratogenic, a reasonable approach is that the AED that stops seizures in a given patient should be used. If possible, only one AED should be used during pregnancy. Besides genetic background, polytherapy is a primary factor associated with a higher incidence of heart defects, cleft lip and palate, and dysmorphic features with retardation noted in offspring of mothers with epilepsy. The incidence of major congenital malformations increases with increasing number of anticonvulsant medications used to control seizures. Exposure to polytherapy and valproate during pregnancy are associated with significantly reduced verbal intelligence in the offspring. Carbamazepine monotherapy with maternal serum levels within the recom-

mended range does not impair intelligence in prenatally exposed offspring. It should be remembered that 95% of infants born to mothers receiving AED treatment will be normal.

MANAGEMENT

The treatment of the pregnant epileptic patient should ideally begin preconceptionally. At this time, her seizure status should be assessed to ascertain whether or not she truly needs an anticonvulsant drug. If she has been seizure-free for a long interval on minimal dosage of anticonvulsant drugs and has a negative electroencephalogram (EEG), it may be reasonable to attempt anticonvulsant withdrawal before conception. Risk for relapse increases when the history includes clonic-tonic grand mal convulsions, prolonged seizures, breaking through AED treatment, or seizure control achieved with a combination of two or three drugs. One should, therefore, hesitate in withdrawing AED treatment from women who are planning pregnancy if their history includes the above risks for relapse. The current recommendation is that AEDs, if withdrawn, should be withdrawn at least 6 months prior to pregnancy. When possible, monotherapy should be used rather than polytherapy. After monotherapy is established, the lowest plasma AED level that prevents seizures should be determined.

Several observations can serve as guidelines for management throughout pregnancy.

- 1 Steady-state plasma concentrations of most anticonvulsants decrease as pregnancy progresses.
- 2 These changes may be associated with a loss of seizure control, requiring an increase in anticonvulsant medications.
- 3 Patients appear to have a threshold concentration of drug below which seizure control is lost. In other words, seizure control may be complete in the given patient despite drug concentrations below the quoted therapeutic range.
- 4 The use of divided doses or slow-released preparations results in lower peak levels and may reduce the risk of malformations.
- 5 For valproate, the use of a single daily dose is not advisable because the adverse effects are believed to be the result of high peak serum level.
- 6 Total serum AED levels and, if possible, free AED fractions should be measured at regular intervals throughout pregnancy.

TREATMENT

Preconceptional

- 1 Ascertain the patient's need for anticonvulsant medications.
- 2 Determine the level of anticonvulsant medication at which the patient is seizure-free.

- 3 Attempt monotherapy wherever possible.
- 4 The use of divided doses or slow-released preparations results in lower peak levels and may reduce the risk of malformations.
- 5 Discuss the risks of anticonvulsant medications to the fetus.
- 6 Recommend folate supplementation (1 mg/day) beginning before conception.

Antenatal

- 1 Maintain the concentration of anticonvulsant medication(s) at the level(s) required by the patient.
- 2 Obtain plasma anticonvulsant levels every 3–4 weeks, or if a seizure occurs, if potential drug interaction is suspected, or if signs of toxicity develop.
- 3 Raise dosage if necessary to maintain effective anticonvulsant activity. Dosage increments may need to be small (i.e. the use of 30-mg rather than 100-mg phenytoin capsules).
- 4 Assess drug toxicity clinically after an appropriate interval based on the estimated time to reach a steady state.
- 5 If seizure control is not maintained and the anticonvulsant dose has been increased until toxic effects are apparent (Table 39.1), add additional anticonvulsant medication. Prescribe supplements containing 1 mg folic acid to all patients on anticonvulsant medication and follow their complete blood counts (CBCs), because folic acid deficiency anemia is frequent in this group of patients.

Table 39.1 Frequently prescribed anticonvulsants.

For grand mal and focal psychomotor seizures	Adult daily dosage (mg)	Therapeutic level ($\mu\text{g/mL}$)	Toxicity
Carbamazepine (Tegretol®)	800–1200	4–16	Ataxia, drowsiness, nystagmus, agitation
Phenytoin (Dilantin®)	300–400	10–20	Ataxia, slurred speech, vertigo, nystagmus, seizures
Phenobarbital	90–120	15–40	Ataxia, drowsiness
Primidone (Mysoline®)*	750–1500	5–15	Ataxia, vertigo, nystagmus

*Primidone is metabolized to phenobarbital, and combined use of phenobarbital and primidone should be avoided.

- 6 Offer prenatal diagnosis to patients receiving AEDs.
- 7 Consider administration of vitamin K (20 mg/day) prophylactically to the AED-treated mother during the last month of pregnancy as a means of protecting the infant against severe postnatal bleeding caused by a deficiency of vitamin K-dependent clotting factors II, VII, IX, and X. The newborn should receive 1 mg vitamin K intramuscularly at birth as a prophylactic measure.
- 8 Epilepsy is not usually considered an indication for the induction of labor.

First seizure during pregnancy

For the patient in whom seizures first develop during pregnancy, a detailed neurologic history and examination are essential. Diagnostic studies, including electroencephalography, skull X-ray, metabolic studies including serum calcium level, and fasting and postprandial blood glucose determinations should be performed on all patients. A lumbar puncture and computed tomography or magnetic resonance imaging are often indicated. Based on these studies and evidence of other neurologic signs or symptoms, angiographic studies may be appropriate.

Postpartum

- 1 Administer 1 mg vitamin K intramuscularly to all newborns of patients receiving AEDs.
- 2 Examine the newborn carefully for signs of fetal teratogenic effects.
- 3 Reduction of anticonvulsant medication may be required in the postpartum period. Check the patient every 2–3 weeks after delivery.
- 4 Most anticonvulsant medications are transferred to breast milk, but the concentrations are low and no adverse effects have been demonstrated. Thus, administration of anticonvulsant medications to the mother is not a contraindication to breastfeeding.

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Chronic hypertension

Baha M. Sibai

INTRODUCTION

According to data derived from the National Health and Nutrition Examination Survey, 1988–1991, the prevalence of chronic hypertension among women of childbearing age increases from 0.6–2.0% for women 18–29 years old to 4.6–22.3% for women 30–39 years old. The lower prevalences are for white people and higher rates are for African-Americans.¹ Because of the current trend of childbearing at an older age, it is expected that the incidence of chronic hypertension in pregnancy will continue to rise. During the new millennium, and estimating a prevalence of chronic hypertension during pregnancy of 3%, at least 120,000 pregnant women per year (3% of 4 million pregnancies) with chronic hypertension will be seen in the USA.²

DEFINITION AND DIAGNOSIS

In pregnant women, chronic hypertension is defined as elevated blood pressure that is present and documented before pregnancy. In women whose pre-pregnancy blood pressure is unknown, the diagnosis is based on the presence of sustained hypertension before 20 weeks' gestation, defined as either systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg on at least two occasions measured at least 4 h apart.

Women with chronic hypertension are at increased risk of superimposed pre-eclampsia. The diagnosis of superimposed pre-eclampsia should be made in the presence of any of the following findings:

- 1 In women with chronic hypertension and without proteinuria early in pregnancy (less than 20 weeks' gestation), pre-eclampsia is diagnosed if there is new onset proteinuria (≥ 0.5 g protein in a 24-h specimen).
- 2 In women with pre-existing proteinuria before 20 weeks' gestation, the diagnosis is confirmed if there is an exacerbated increase in blood pressure to the severe range (systolic pressure ≥ 180 mmHg or diastolic pressure ≥ 110 mmHg), particularly if associated with either headaches, blurred vision, or epigastric pain; or if there is significant increase in liver

enzymes (unrelated to methyldopa) or if the platelet count is less than 100,000/mm.

ETIOLOGY AND CLASSIFICATION

The etiology as well as the severity of chronic hypertension is an important consideration in the management of pregnancy. Chronic hypertension is subdivided into primary (essential) and secondary. Primary hypertension is by far the most common cause of chronic hypertension seen during pregnancy (90%). In 10% of cases, chronic hypertension is secondary to one or more underlying disorders such as renal disease (glomerulonephritis, interstitial nephritis, polycystic kidneys, renal artery stenosis), collagen vascular disease (lupus, scleroderma), endocrine disorders (diabetes mellitus with vascular involvement, pheochromocytoma, thyrotoxicosis, Cushing disease, hyperaldosteronism), or coarctation of the aorta.

Chronic hypertension during pregnancy can be subclassified as either mild or severe, depending on the systolic and diastolic blood pressure readings. Systolic and diastolic (Korotkoff phase V) blood pressures of at least 180 mmHg and/or 110 mmHg, respectively, constitute severe hypertension.

For management and counseling purposes, chronic hypertension in pregnancy is also categorized as either low-risk or high-risk (Fig. 40.1).³ The patient is considered to be at low risk when she has mild essential hypertension without any organ involvement.

MATERNAL AND PERINATAL RISKS

Pregnancies complicated by chronic hypertension are at increased risk for superimposed pre-eclampsia and abruptio placentae. The reported rates of pre-eclampsia in the literature in mild hypertension range from 10% to 25% (Table 40.1). The rate of pre-eclampsia in women with severe chronic hypertension approaches 50%. Sibai and associates studied the rate of superimposed pre-eclampsia among 763 women with chronic hypertension followed prospectively at several medical centers in the USA.⁶ The overall rate of superimposed pre-eclampsia was 25%. The rate was not affected by maternal age, race, or presence of proteinuria early in pregnancy. However, the rate was significantly greater in women who had hypertension for at least 4 years (31% vs 22%), in those who had had pre-eclampsia during a previous pregnancy (32% vs 23%), and in those whose diastolic blood pressure was 100–110 mmHg when compared with those whose diastolic blood pressure was below 100 mmHg at baseline (42% vs 24%).

The reported rate of abruptio placentae, in women with mild chronic hypertension, has ranged from 0.7 to 1.5% (Table 40.1). The rate in those with severe or high-risk hypertension may be 5–10%.⁷ In a recent multicenter study that included 763 women with chronic hypertension, the overall rate of abruptio

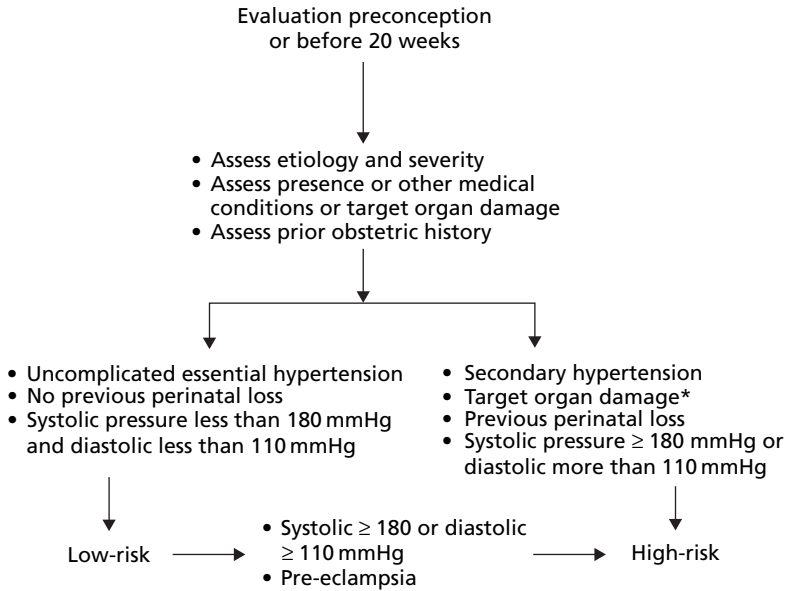


Fig. 40.1 Initial evaluation of women with chronic hypertension. * Left ventricular dysfunction, retinopathy, dyslipidemia, maternal age above 40 years, microvascular disease, stroke.

Table 40.1 Rates of adverse pregnancy outcome in observational studies describing mild chronic hypertension in pregnancy.

	Pre-eclampsia (%)	Abruptio placentae (%)	Delivery at <37 weeks (%)	SGA (%)
Sibai <i>et al.</i> ³ (n = 211)	10	1.4	12.0	8.0
Rey & Couturier ⁴ (n = 337)	21	0.7	34.4	15.5
McCowan <i>et al.</i> ⁵ (n = 142)	14	NR	16	11.0
Sibai <i>et al.</i> ⁶ (n = 763) ³	25	1.5	33.3	11.1

NR, not reported; SGA, small for gestational age.

placentae was reported at 1.5% and the rate was significantly higher in those who developed superimposed pre-eclampsia than in those without this complication (3% vs 1%; $P = 0.04$). However, the rate was not influenced by either maternal age, race, or duration of hypertension.⁸ In addition, the results of a

systematic review of nine observational studies revealed that the rate of abruptio placentae is doubled (OR, 2.1; 95% CI, 1.1–3.9) in women with chronic hypertension compared with either normotensive or general obstetric population.⁸

Fetal and neonatal complications are also increased in women with chronic hypertension. The risk of perinatal mortality is increased 3–4 times compared with the general obstetric population. The rates of premature deliveries and small-for-gestational age infants are also increased in women with chronic hypertension (Table 40.1).

TREATMENT

Most women with chronic hypertension during pregnancy have mild essential uncomplicated hypertension and are at minimal risk for cardiovascular complications within the short time frame of pregnancy. Several retrospective and prospective studies have been conducted to determine whether antihypertensive therapy in these women would improve pregnancy outcome. An overall summary of these studies revealed that, regardless of the antihypertensive therapy used, maternal cardiovascular and renal complications were minimal or absent. Based on the available data, there is no compelling evidence that short-term antihypertensive therapy is beneficial for the mother in women with low-risk hypertension except for a reduction in the rate of exacerbation of hypertension.

Antihypertensive therapy is necessary in women with severe hypertension to reduce the acute risk of stroke, congestive heart failure, or renal failure. In addition, control of severe hypertension may also permit pregnancy prolongation and possibly improve perinatal outcome. However, there is no evidence that control of severe hypertension reduces the rates of either superimposed pre-eclampsia or abruptio placentae.

There are many retrospective and prospective studies examining the potential fetal–neonatal benefits of pharmacologic therapy in women with mild essential uncomplicated hypertension (low-risk): some compared treatment with no treatment or with a placebo, others compared two different antihypertensive drugs, and others used a combination of drugs. Only four of these studies were randomized trials that included women enrolled prior to 20 weeks' gestation. Only two trials had a moderate sample size to evaluate the risks of superimposed pre-eclampsia and abruptio placentae. Therefore, treatment of mild chronic hypertension remains controversial.

MANAGEMENT

The primary objective in the management of pregnancies complicated with chronic hypertension is to reduce maternal risks and achieve optimal perinatal survival. This objective can be achieved by formulating a rational approach

that includes preconceptual evaluation and counseling, early antenatal care, timely antepartum visits to monitor both maternal and fetal well being, timely delivery with intensive intrapartum monitoring, and proper postpartum management.

Evaluation and classification

Management of patients with chronic hypertension should ideally begin prior to pregnancy, whereby evaluation and work-up are undertaken to assess the etiology, the severity, as well as the presence of other medical illnesses, and to rule out the presence of target organ damage of long-standing hypertension. An in-depth history should delineate in particular the duration of hypertension, the use of antihypertensive medications, their type, and the response to these medications. Also, attention should be given to the presence of cardiac or renal disease, diabetes, thyroid disease, and a history of cerebrovascular accident or congestive heart failure. A detailed obstetric history should include maternal, as well as neonatal, outcome of previous pregnancies with stresses on history of development of abruptio placentae, superimposed pre-eclampsia, preterm delivery, small-for-gestation infants and intrauterine fetal death.

Laboratory evaluation is obtained to assess the function of different organ systems that are likely to be affected by chronic hypertension, and as a baseline for future assessments. These should include the following for all patients: urine analysis, urine culture and sensitivity, 24-h urine evaluations for protein, electrolytes, complete blood count, and glucose tolerance test.^{2,8}

Low-risk hypertension

Women with low-risk chronic hypertension without superimposed pre-eclampsia usually have a pregnancy outcome similar to that in the general obstetric population. In addition, discontinuation of antihypertensive therapy early in pregnancy does not affect the rates of pre-eclampsia, abruptio placentae, or preterm delivery in these women. The author's policy is to discontinue antihypertensive treatment at the first prenatal visit because the majority of these women will have good pregnancy outcome without such therapy. Although these women do not require pharmacologic therapy, a careful management is still essential (Fig. 40.2). At the time of initial and subsequent visits, the patient is educated about nutritional requirements, weight gain, and sodium intake (maximum of 2.4 g/day sodium). During each subsequent visit they are observed very closely for early signs of pre-eclampsia and fetal growth retardation.²

The development of severe hypertension, pre-eclampsia, or abnormal fetal growth requires urgent fetal testing with non-stress test or biophysical profile. Women who develop severe hypertension, those with documented fetal growth retardation by ultrasound examination, and those with superimposed

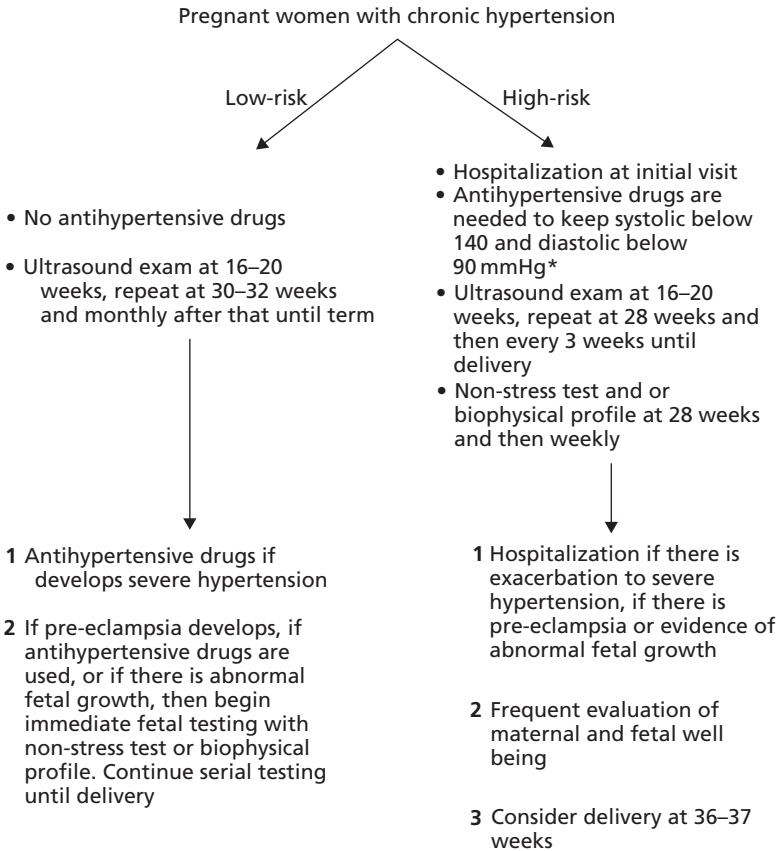


Fig. 40.2 Antepartum management of chronic hypertension. * For women with target organ damage. (From Sibai BM, 2002.²)

pre-eclampsia at or beyond 37 weeks require hospitalization and delivery. In the absence of these complications, the pregnancy may be continued until 40 weeks' gestation.

High-risk hypertension

Women with high-risk chronic hypertension are at increased risk for adverse maternal and perinatal complications. Women with significant renal insufficiency (serum creatinine over 1.4 mg/dL), diabetes mellitus with vascular involvement (class R/T), severe collagen vascular disease, cardiomyopathy or coarctation of the aorta should receive thorough counseling regarding the

adverse effects of pregnancy before conception. These women should be advised that pregnancy may exacerbate their condition with the potential for congestive heart failure, acute renal failure requiring dialysis, and even death. In addition, perinatal loss and neonatal complication are markedly increased in these women. All such women should be managed by or in consultation with a subspecialist in maternal–fetal medicine, as well as in association with other medical specialists as needed.

Women with high-risk hypertension may require hospitalization at the time of first prenatal visit for evaluation of cardiovascular and renal status and for regulation of antihypertensive medications, as well as other prescribed medications (Fig. 40.2). Women receiving atenolol, ACE inhibitors, or angiotensin II receptor antagonists should have these medications discontinued under close observation. Antihypertensive therapy, with one or more of the drugs listed in Table 40.2, are subsequently used in all women with severe hypertension. In women without target organ damage, the aim of antihypertensive therapy is to keep systolic blood pressure (BP) between 140 and 150 mmHg and diastolic BP between 90 and 100 mmHg. In addition, antihypertensive therapy is indicated in women with mild hypertension plus target organ damage because there are short-term maternal benefits from lowering blood pressure in such women. In these women, the author recommends keeping systolic BP below 140 mmHg and diastolic BP below 90 mmHg. In some women, blood pressure may be difficult to control initially, demanding the use of intravenous therapy with hydralazine or labetalol or oral short-acting nifedipine with dosage as described in Table 40.2. For maintenance therapy, one may choose either oral

Table 40.2 Drugs used to treat hypertension in pregnancy.

Drug	Starting dose	Maximum dose
<i>Acute treatment of severe hypertension</i>		
Hydralazine	5–10 mg i.v. every 20 min	30 mg*
Labetalol†	20–40 mg i.v. every 10–15 min	220 mg*
Nifedipine	10–20 mg oral every 30 min	50 mg*
<i>Long-term treatment of hypertension</i>		
Methyldopa	250 mg b.i.d.	4 g/day
Labetalol	100 mg b.i.d.	2400 mg/day
Nifedipine	10 mg b.i.d.	120 mg/day
Thiazide diuretic	12.5 mg b.i.d.	50 mg/day

*If desired blood pressure levels are not achieved, switch to another drug.

†Avoid labetalol in women with asthma or congestive heart failure.

methyldopa, labetalol, slow-release nifedipine, or a diuretic. My first drug of choice for control of hypertension in pregnancy is labetalol starting at 100 mg twice daily to be increased to a maximum of 2400 mg/day. If maternal BP is not controlled with maximum doses of labetalol, a second drug such as a thiazide diuretic or nifedipine may be added. For women with diabetes mellitus and vascular disease, the preference is oral nifedipine. Oral nifedipine and/or a thiazide diuretic is the drug of choice for young African-American women with hypertension because these women often manifest a low renin-type hypertension or salt-sensitive hypertension. If maternal blood pressure is adequately controlled with these medications, the patient can continue with the same drug after delivery.

Early and frequent prenatal visits are the key for successful pregnancy outcome in women with high-risk chronic hypertension. These women need close observation throughout pregnancy and may require serial evaluation of 24-h urine protein excretion and complete blood count with metabolic profile at least once every trimester. Further laboratory testing can be performed depending on the clinical progress of the pregnancy. Fetal evaluation is as recommended in Fig. 40.2.

The development of uncontrolled severe hypertension, pre-eclampsia, or evidence of fetal growth retardation requires maternal hospitalization for more frequent evaluation of maternal and fetal well being. The development of any of these complications at or beyond 34 weeks' gestation should be considered an indication for delivery. In all other women, consider delivery at 36–37 weeks' gestation after documenting fetal lung maturity.

CONCLUSIONS

Chronic hypertension in pregnancy is associated with increased rates of adverse maternal and fetal outcomes, both acute and in the long term. These adverse outcomes are particularly seen in women with uncontrolled severe hypertension, in those with target organ damage, and those who are non-compliant with prenatal visits. In addition, adverse outcomes are substantially increased in women who develop superimposed pre-eclampsia or abruptio placentae. Women with chronic hypertension should be evaluated either prior to conception or at the first prenatal visit. Depending on this evaluation, they can be divided into categories of either "high-risk" or "low-risk" chronic hypertension. High-risk women should receive aggressive antihypertensive therapy, lifestyle changes, and frequent evaluations of maternal and fetal well being.

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Immunizations

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INTRODUCTION

Maternal immunization should be viewed as an opportunity to enhance the pregnant woman's protection against disease and at the same time protect the neonate with maternal passive antibodies for the first 3–6 months of life. Previously, immunization during pregnancy was thought to potentially cause harm to the fetus; however, if live-virus vaccines are not used during pregnancy, there are no data proving harm to the fetus from other vaccines. The appropriate attitude should be to review the woman's vaccination record and plan to administer appropriate vaccines which will help to protect against disease based on time of year (for influenza), risk status, and immunization history. When vaccines are given at the appropriate time during pregnancy, the mother will generate immunoglobulin G (IgG), which will be transferred to the fetus with resultant protection for the first 3–6 months of life.

A great opportunity exists to bring the woman's vaccine status to recommended levels when she presents for preconceptional counseling. At that time, both live-virus vaccines and killed or attenuated vaccines may be considered. Pregnancy should be deferred for 1 month after administration of any of the live-virus vaccines but pregnancy may be initiated at any time with any of the attenuated vaccines.

Although no risk from earlier immunization has been proven, the risk of spontaneous abortion may be greater and temporal immunization could be alleged to be the cause.

Women of childbearing age should be immunized against poliomyelitis, measles, mumps, rubella, varicella, tetanus, and diphtheria prior to becoming pregnant. Unfortunately, many women have not received the basic immunization series. This is particularly true for immigrants from developing countries where immunizations are not administered in a standardized manner. For these individuals, one must view them as vaccine naïve and start with basic series of vaccination. Women who are pregnant should be considered for vaccines as shown in Table 41.1.

Table 41.1 Vaccines suitable for pregnant women.

Agent	Type of agent
Hepatitis A	Killed virus
Hepatitis B	Recombinant vaccine
Influenza	Killed virus
Pneumococcal	Polysaccharide
Tetanus–diphtheria	Toxoid

HEPATITIS A

Hepatitis A vaccine is underutilized by clinicians of both pregnant and non-pregnant women. Hepatitis A continues to be one of the most frequently reported vaccine-preventable diseases in the USA despite being on the market since 1995. Sporadic outbreaks occur in the USA every year. Additionally, many pregnant women travel to hepatitis A endemic areas such as Mexico, Caribbean countries, South America, Africa, Eastern Europe and Asia.¹

Pregnant women are at increased risk of infection with hepatitis A virus if a member of their family becomes ill with hepatitis A, if they work in an area with infected persons or if they are employed in an area with high hepatitis A infection rates such as daycare or institutional facilities.

The Advisory Committee for Immunization Practices (ACIP) recommended hepatitis A vaccine for persons at high risk for infections, including the following groups:²

- 1 Travelers to countries with high rates of infection (countries already mentioned)
- 2 Men who have sex with men
- 3 Injecting drug users
- 4 Persons with clotting factor disorders
- 5 Persons with chronic liver disease of any type
- 6 Children who live in communities with high rates of disease

Additional indications may include:

- 1 A desire to be protected from hepatitis A virus disease
- 2 Prophylaxis because of a local outbreak of disease

Fecal–oral transmission is the predominant mode of spread. Hepatitis A virus is excreted in the stools of infected persons for 1–2 weeks before and 1 week after the onset of the illness. The viremic phases of hepatitis A infections are short and there is no chronic fecal carrier state. Because of the short viremic phase, maternal–neonatal transmission is not a recognized epidemiologic entity.

The recommended regimen consists of two doses with the second dose given 6–12 months after the first dose. For postexposure prophylaxis, hepatitis A vaccine and hepatitis A immunoglobulin 0.02 mg/kg i.m. is administered. Pregnant women can safely receive both hepatitis A vaccine and hepatitis immunoglobulin.

HEPATITIS B

Hepatitis B virus (HBV) infection during pregnancy can result in severe disease for the mother, fetal loss, or chronic infection for either the mother or the neonate. HBV infection results in a viremia that lasts for weeks to months and 1–5% of adult patients develop chronic infection and a persistent viremic carrier state with or without active liver disease. Unfortunately, neonates and children are much more susceptible to chronic infection with as many as 90% of infected neonates, 50% of infected infants, and 20% of infected young children developing chronic infection.³

HBV infections have been a hazard to persons who are exposed to infected blood and blood products. HBV transmission is not limited to blood or/and blood products; sexual transmission of HBV is recognized as a major mode of spread in the USA. HBV has been found in blood, semen, cervicovaginal secretions and cells, saliva, colostrum, and other body fluids.

Maternal–fetal transmission rates depend on the presence of HBsAg and HBeAg. If both antigens are present the perinatal transmission rate is 90%; whereas if only HBsAg is present the transmission rate is 10%. Because the majority of neonatal and infant HBV infections are the result of maternal–fetal transmission, the obstetrician is a critical link in the strategy to prevent perinatal transmission. All pregnant women should have routine prenatal screening for HBsAg early in pregnancy. Patients who are HBsAg negative but meet any of the following high-risk criteria should receive HBV vaccine during pregnancy. High-risk indications for pre-exposure HBV immunizations are as follows:⁴

- 1 All infants in the hospital nursery
- 2 Preadolescents (starting at age 10 years), adolescents, and young adults
- 3 Persons with occupational risks:
 - Healthcare workers
 - Public service workers
- 4 Persons with lifestyle risks:
 - Heterosexual persons with multiple partners (more than one partner in the preceding 6 months)
 - Diagnosis of any sexually transmitted disease
 - Intravenous drug abusers
- 5 Special patient groups:
 - Persons with hemophilia

- Patients undergoing dialysis
- 6 Environmental risk factors:
 - Household and sexual contacts of HBV
 - Patients and staff of institutionalized carrier facility
 - Prison inmates
 - Immigrants and refugees
 - International travelers to endemic areas

Pregnant women who are HbsAg negative but have any of the high-risk factors should receive the HBV vaccination series (0, 1, and 6 months). Infants born to HBsAg negative mothers should receive a birth dose of HBV vaccine while in the hospital, with the second dose 1 month later, and the third dose 6–12 months later.

Infants of women who are HbsAg positive should receive hepatitis B immunoglobulin (HBIG) 0.5 mL intramuscularly and HBV vaccine at the same time but at a different site within 12 h of birth. The site for injection in the neonate is the anterolateral muscle of the thigh. The efficacy is more than 90%.

INFLUENZA

Influenza is an acute respiratory disease characterized by the abrupt onset of constitutional and respiratory signs and symptoms (fever, myalgia, headache, severe malaise, non-productive cough, sore throat, and rhinitis). Influenza illness typically resolves after 5–7 days for most people. However, influenza can exacerbate underlying medical conditions leading to secondary bacterial pneumonia.⁵

Pregnant women have been the victims of influenza-associated deaths. During the pandemics of 1918–1919 and 1957–1958, pregnancy-related deaths were significantly greater than for non-pregnant women. A study of 17 interpandemic influenza seasons demonstrated the relative risk for hospitalization for selected cardiorespiratory conditions among women enrolled in Medicaid increased from 1.4 during 14–20 weeks' gestation to 4.7 during 37–42 weeks' gestation in comparison with women who were 1–6 months postpartum.⁶ Women in the third trimester of pregnancy were hospitalized at a rate (250 per 100,000 pregnant women) comparable with that of non-pregnant women who had high-risk conditions.

The influenza season in the northern hemisphere runs from October through March. ACIP has advised that all pregnant women during the influenza season be immunized with trivalent inactivated vaccine (TIV) once each year. During the 2003–2004 influenza season, which was occurring at epidemic proportions in some geographic regions, it became clear that influenza immunization in the first trimester was indicated. Studies have demonstrated no adverse fetal effects associated with influenza vaccine. Influenza vaccine needs to be repeated yearly. The following high-risk conditions are indication for influenza vaccine:⁷

- 1 Adults aged 50 years or older
- 2 Persons aged 6 months to 50 years with medical problems such as heart disease, lung disease, diabetes mellitus, renal disease, immunosuppression, and persons who live in assisted care facilities
- 3 All healthcare workers
- 4 Pregnant women during the influenza season
- 5 International travelers
- 6 Anyone who wishes to reduce the likelihood of becoming ill with influenza
- 7 All infants 6 months to 2 years of age

Influenza vaccine does not affect the safety of mothers who are breastfeeding their infants. Breastfeeding does not adversely affect either the mother's or infant's immune response and is not a contraindication to influenza vaccine.

PNEUMOCOCCAL VACCINE

Streptococcal pneumoniae infections are a major cause of pneumonia, meningitis, and otitis media in young children, elderly adults, and persons who are immunodeficient. *Streptococcal pneumoniae* may act as a primary pathogen or become a secondary invader following influenza or *Mycoplasma pneumoniae* infection. It is estimated that pneumococcal disease causes 3000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and 7,000,000 cases of otitis media in the USA annually.^{8,9} Approximately 150,000 persons are hospitalized with pneumococcal pneumonia, with 10,000 deaths annually in the USA. Maternal mortality is estimated to be 2–3% in pregnant women with severe disease, with fetal mortality approaching 30%.

Because there are no data on the increased incidence or severity of pneumococcal infection during pregnancy, ACIP does not include routine pregnancy as an indication for pneumococcal polysaccharide vaccine (PPV). However, pneumococcal polysaccharide 23-valent vaccine is recommended for individuals including pregnant women with any of the high-risk medical conditions listed below:^{10,11}

- 1 Adults aged 65 years or older
- 2 Alaskan natives
- 3 American Indians
- 4 Organ transplant recipients
- 5 Smokers
- 6 Persons aged 2–64 years with the following chronic illnesses:
 - Cardiac disease
 - Pulmonary disease
 - Liver disease
 - Alcoholism

- Diabetes mellitus
- Anatomic or functional asplenia
- Sickle cell disease
- Immunocompromised status
- Chronic renal disease

7 Pregnant women with any of the listed high-risk conditions

PPV can be administered at any time during pregnancy. Patients remember PPV as the “pneumonia shot” to differentiate it from influenza vaccine or the “flu shot.” One-time revaccination is recommended 5 years later for persons with high-risk conditions. If the first dose is given during pregnancy, it may be repeated at age 50 and again at age 65 years.

There are some data to suggest that passive transfer of maternal pneumococcal antibodies to the fetus will reduce the risk of otitis media in the infant for the first 3–6 months of life. Pregnant women show good antibody response and no significant side-effects of the vaccine except some soreness at the infection site. This is another example of a vaccine which has been on the market since 1983, that is underutilized in protecting pregnant women. This vaccine has been used extensively in pregnancy.

TETANUS–DIPHTHERIA

Tetanus–diphtheria toxoid (Td) vaccine is indicated routinely for pregnant women who been previously vaccinated or who have never received Td vaccine. Td vaccine protects the mother during pregnancy and passive antibodies protect the neonate from neonatal tetanus. Neonatal tetanus kills 250,000 infants/year worldwide.¹²

Pregnant women should be routinely asked when they received their last Td vaccine. If they do not know or cannot remember then a booster dose of Td should be given.

Immigrants and refugees who come to the USA are infrequently fully immunized and should receive the complete primary series. The schedule of vaccination is at 0, 1–2 months, and 6–12 months. Frequently, the first two doses can be given during the prenatal period.

The antigens listed in Table 41.2 can be used to vaccinate pregnant women under special circumstances.

POLIOMYELITIS

Successful immunization programs have eliminated illness caused by wild poliovirus and the last case in the USA was reported in 1978. Worldwide eradication is a public health goal. The risk for poliomyelitis is related to international travel to areas where polio still exists. Pregnant women do not need to receive polio vaccination unless they are exposed to a risk factor for disease.¹³

Table 41.2 Antigens used to vaccinate pregnant women in special circumstances.

Agent or antigens	Type of agent
Poliomyelitis	Inactivated or live virus
Varicella	Live attenuated
Meningococcal	Polysaccharide
Yellow fever	Live attenuated
Measles, mumps, rubella	Live attenuated
Smallpox	Live attenuated

Two polio vaccines are available: enhanced-potency inactivated polio vaccine and oral live-virus vaccine. For pregnant women who have completed their primary series of polio vaccination more than 10 years earlier, a one-time booster of enhanced-potency inactivated polio vaccine is recommended. If less than 4 weeks are available for immunization and immediate protection is needed, a single dose of oral polio vaccine may be given.

VARICELLA VACCINE

Varicella vaccine is a live attenuated virus vaccine and is not recommended during pregnancy. Pregnant women should be asked if they have had varicella (chickenpox), and the answer is usually yes as more than 95% will be serologically positive for varicella IgG. If the patient is uncertain, a varicella IgG should be obtained. If the patient is seronegative, then she should receive the first of two immunizing doses immediately postpartum with the second dose given 4–8 weeks later. Remember the second dose as it is easy to forget to complete the immunization series.^{14,15}

MENINGOCOCCAL POLYSACCHARIDE VACCINE

Neisseria meningitidis causes rare but serious infections in pregnancy. Major manifestations of meningococcal disease are acute meningococemia and meningitis.

Meningococcal polysaccharide vaccine is a quadrivalent vaccine against disease caused by serotypes A, C, Y and W-135. Because it is a polysaccharide vaccine, there is no risk of infectivity. The vaccine is effective in controlling epidemics.¹⁶

Meningococcal vaccine is not recommended for routine use but is recommended for specific medical indications: adults with terminal complement deficiencies, anatomic or functional asplenia, international travelers to countries where the disease is endemic (sub-Saharan Africa, Mecca, Saudi Arabia). College freshman are a group at high risk.

Meningococcal vaccine is administered as a single 0.5 mL subcutaneous dose. This vaccine can be given at any time during pregnancy when indicated.

YELLOW FEVER

Yellow fever vaccine is a live attenuated preparation made from the 17 D yellow fever strain and is grown on chick embryos. The safety of yellow fever vaccine during pregnancy has not been established and the vaccine should be administered only if travel to an endemic area is unavoidable and if an increased risk for exposure exists. Because yellow fever vaccination is a requirement for entry into certain countries, any physician who elects not to immunize a pregnant woman should provide her with a letter of explanation.¹⁷

MEASLES, MUMPS, AND RUBELLA

Measles, mumps, and rubella (MMR) vaccines are live attenuated viruses, which are not given to pregnant women or to non-pregnant women who plan to become pregnant within 1 month of the vaccination. The immediate postpartum period is a good time to administer MMR for initiation or boosting of immunity.

All pregnant women should be screened for immunity to rubella with a rubella IgG serology. If the patient is rubella seronegative, MMR should be administered postpartum. MMR vaccination is compatible with breastfeeding.

SMALLPOX (VACCINIA VACCINE)

Smallpox vaccine is not recommended for use in pregnancy unless an outbreak of smallpox occurs. Currently, international concern is heightened regarding the potential use of smallpox (variola) as a bioterrorism agent.^{9,18}

Currently, the only smallpox vaccine available from the Centers for Disease Control (CDC) is Dryvax® (Wyeth Laboratories, Inc., Marietta, PA), a live-virus preparation using vaccinia virus. A reformulated vaccine produced by cell culture technique is being developed.

Vaccinia vaccines should not be administered to pregnant women for non-emergency indications. However, vaccinia vaccine is not known to cause congenital malformations.¹⁹

IMMUNOGLOBULINS

All immunoglobulin preparations are of the IgG class and may contain small amounts of other classes. Immunoglobulin for clinical use is administered intramuscularly or intravenously. Indications for use of immunoglobulin are listed in Table 41.3.⁴

CONCLUSIONS

Obstetricians and other healthcare workers who provide services to pregnant women should be aware of the requirements for maternal immunization:

Table 41.3 Indications for immunoglobulins in pregnancy. (From American College of Physicians, 1994: 86.⁴)

Infection or condition	Indication	Preparation	Dose
Rh negative	Prevent isoimmunization	Ig	250 mg at 28 weeks and postpartum
Botulism	Treatment or prophylaxis for ingestion of botulinus toxin	Equine antibodies	Consult CDC (404-639-6370)
Hepatitis A	Family contacts, sexual contacts, daycare outbreak, international travel	Ig	0.02 mL/kg i.m. protects 2 months 0.06 mL/kg i.m. protects 6 months
Hepatitis B	Percutaneous or mucosal exposure Sexual contacts of person with acute or chronic HBV	HBIG HBIG	0.5 mL i.m. at birth, vaccinate with HBV vaccine 0.06 mL/kg i.m. vaccinate with HBV vaccine
Measles	Non-immune contacts of acute cases exposed less than 6 days previously	Ig	0.25 mL/kg i.m. up to 15 mL for normal; 0.5 mL/kg up to 15 mL for immunocompromised
Rabies	Persons exposed to rabid or Potentially rabid animals	HRiG	20IU/kg i.m.
Varicella-zoster	Immunosuppressed, pregnant or newborn contact	VZIG	125 IU/10 kg; up to 625 IU i.m.

HBV, hepatitis B virus; HBIG, hepatitis B immunoglobulin; HRiG, human rabies immunoglobulin; Ig, immunoglobulin; VZIG, varicella-zoster immunoglobulin.

- 1 Non-live virus can be given at any time during pregnancy
- 2 Live-virus vaccines should usually be deferred until the postpartum period or preconceptionally
- 3 All pregnant women should be screened for rubella IgG and HBsAg routinely
- 4 All pregnant women should be asked about their last Td vaccine and whether they have ever had chickenpox
- 5 Hepatitis A and HBV vaccines can be administered during pregnancy to women who have the listed indications

- 6 PPV is underutilized and should be administered at any time during pregnancy for those women who have the risk factors listed
- 7 Contraindications to vaccination are few. They include:
 - Allergic reaction to previous vaccination with same antigen
 - Acute illness
 - Egg allergy for influenza and yellow fever vaccine
 - Neomycin allergy for MMR and varicella vaccines

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Cytomegalovirus

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INCIDENCE

Cytomegalovirus (CMV) infection is the most common vertically transmitted viral infection in developed countries. Perinatal infection can occur *in utero*, intrapartum, and through breast milk. Transmission of CMV is observed more frequently during primary versus recurrent maternal infection. Primary CMV infection of the mother during pregnancy resulted in congenital infection for 30–40% of their infants, while less than 1% of infants born to mothers with recurrent CMV infection will have evidence for perinatal infection.¹ Overall, approximately 1–2% of all newborns are CMV infected, about half because of primary infection of the mother during pregnancy and the other half because of reactivation of a prior infection of the mother.

The majority of adults have antibodies to CMV. The virus can be detected in cervical specimens of 3–5% of pregnant women. CMV DNA was found more commonly in placentas at later gestational ages (30.5%) than in those of earlier gestational ages (18%) after second trimester deliveries as a result of maternal complications.²

Women with primary CMV infection are usually asymptomatic, but approximately 10% of women have an infectious mononucleosis-like disease with a negative heterophil antibody test. Congenital infection is likely when CMV can be cultured from the urine of the infant within the first week of life. Primary infection during any trimester can lead to intrauterine infection, but the first half of pregnancy holds the highest risk. Intrauterine CMV infection is not known to cause defects in organ development, as seen with congenital rubella infection. Most disease manifestations of congenital CMV infection are a result of tissue invasion by the virus and inflammatory response.³ Between 85% and 90% of congenitally infected infants are clinically asymptomatic and only 5–10% of those infants who are asymptomatic at birth will later have evidence of abnormal development. Most commonly observed are unilateral or bilateral hearing impairment, usually within the first 2 years of life.⁴ Infants who are symptomatic at birth, however, can present with the most severe forms of

impairment in the neonatal period such as thrombocytopenia, hepatosplenomegaly, chorioretinitis, deafness, microencephalopathy, cerebral calcification, mental retardation, or early death, often resulting from disseminated intravascular coagulation, hepatic failure, and sepsis.

While overall infection rates of infants whose mothers have reactivation of CMV are very low, cervical shedding of CMV during the third trimester or at birth versus only in the first or second trimester poses a three- to fourfold increased risk for infection of the infant.⁵

It has been estimated that among the 1–2% of infected newborns, as many as 10–20% may ultimately develop some impairment resulting from CMV infection. Postnatal CMV infection of the infant through breastmilk does not lead to visceral or neurologic sequelae.⁶

In the USA, an estimated 8000 neonates have health problems each year as a result of congenital CMV infection,⁷ while the incidence of severely symptomatic disease in the newborn period is low, approximately 1 in 20,000 births.

CMV infections are also important for patients with immunosuppression, cancer, and acquired immunodeficiency syndrome (AIDS). In these individuals, pulmonary, eye, or systemic CMV disease may contribute to morbidity or death.

DIAGNOSIS

The great majority of CMV infections in women are asymptomatic and can be identified only by prospective serial antibody determinations or repeat cervical cultures. At present, this approach is of value only for research purposes.

After primary CMV infection, virus replication may persist for many months and can be reactivated months or years later, with intermittent CMV shedding from the cervix and other body sites. To document the cause of the disease, isolating CMV from the throat, urine, and cervix is the most reliable approach. Higher than average cervical CMV prevalence was found in women attending STD clinics.^{8,9} In HIV-positive women, cervical shedding of CMV as determined by polymerase chain reaction (PCR) was associated with detection of HIV-1 DNA in cervical secretions.¹⁰ Tests for immunoglobulin M (IgM)-specific CMV antibody are available. The presence of IgM-specific CMV antibody correlates quite well with infection but, as with virus isolation, cannot document primary infection because IgM antibody is detected with approximately 90% of primary infections but may also appear with recurrent infections.

Infected infants excrete CMV from the nasopharynx and urine for a number of months after birth, which can be cultured or detected by PCR.

MANAGEMENT

When infection with CMV is asymptomatic, no intervention is currently advised. Routine serial serologic tests are not recommended because of the low

yield of seroconversions, and the inability to distinguish an infected and damaged fetus from an uninfected or undamaged fetus. Research is being conducted on the value of amniocentesis for documenting *in utero* infection when the mother has serologic evidence of infection. The presence of CMV in amniotic fluid (which is detected by culture or PCR), however, does not necessarily indicate that the fetus is damaged. In a recent study, amniotic fluid, not fetal blood, was shown to be the preferred specimen type for the prenatal diagnosis of CMV infection. In a recent study, PCR with amniotic fluid had a sensitivity of 100%, a specificity of 83.3%, a positive predictive value of 40%, and a negative predictive value of 100% for congenital CMV infection. Rapid virus isolation from the same amniotic fluid was found to be only 50% sensitive and fewer than 10% of women seropositive for IgM by enzyme immunoassay had a congenitally infected fetus or newborn infant.¹¹

If a woman has primary infection with CMV that is detected because of infectious mononucleosis-like symptoms, there is a 30% chance her child will be infected and thus, at most, a 6–7% chance her child will have some damage resulting from this infection. In about half of the cases the damage will be evident at birth. No treatment is available, but therapeutic abortion can be considered. There can be a role for amniocentesis and amniotic fluid PCR for CMV to assess *in utero* infection. A negative test should rule out fetal infection. A positive test however, would not necessarily indicate that the fetus is damaged. It should be remembered that the 6–7% rate of infection is a maximum estimate and includes the risk of deafness. In addition, serial sonography can be useful to evaluate the fetal status. Ultrasound has a 40% sensitivity of detecting symptomatic infection (fetal hydrops/ascites, growth restriction, central nervous system abnormalities).

Women who have had a child with congenital cytomegalic disease should be advised that it is quite likely that subsequent children will be born excreting virus, but that the great majority of these children will be normal. Women who have antibody (IgG) to CMV before being pregnant can be assured that it is very unlikely that subsequent children will have sequelae resulting from congenital CMV infection.

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Herpes simplex

Jeanne S. Sheffield

INTRODUCTION

Genital herpes simplex virus (HSV) infection is one of the most common viral sexually transmitted diseases worldwide. More than 50 million adolescents and adults in the USA are currently affected. NHANES III (1988–1994) reported a 24.2% seroprevalence rate for women aged 12 years or more, an increase of 32% from the previous two decades. The majority of these seropositive women are unaware of their status. As the incidence of this sexually transmitted disease continues to rise, and as the greatest incidence of HSV infections occur in women of reproductive age, the risk of maternal transmission of the virus to the fetus or neonate has become a major health concern.

PATHOPHYSIOLOGY

HSV-1 and HSV-2 are two of the eight viruses in the human herpesvirus family. They are DNA viruses with considerable homology — antibodies to one virus provide some cross-protection against the other virus. Both HSV-1 and HSV-2 cause clinical maternal and neonatal disease. Whereas most orolabial lesions are secondary to HSV-1, genital lesions may be caused by either virus. In the last two decades, we have seen an increase in genital HSV-1 lesions, now accounting for 20–30% of genital lesions in many demographic groups.

Transmission of HSV-1 and HSV-2 is primarily from genital–genital contact, although oral–genital transmission of HSV-1 has increased in frequency. Vertical transmission to a fetus or neonate will be discussed in a subsequent section. The incubation period averages 4 days (range 2–12 days). The virus replicates at the point of entry and then enters the nervous system. It is transported along axons to the sensory neuron cell body and the virion remains there for the life of the host. Periodic reactivation is common and may lead to clinically apparent disease or asymptomatic infection.

First episode primary infection

The initial HSV-2 genital outbreak in the setting of no pre-existing HSV-1 anti-

bodies (or HSV-1 genital infection with no pre-existing HSV-2 antibodies) may be associated with severe symptoms. A “classic” presentation is of multiple papules progressing to vesicles which subsequently rupture to form shallow ulcers. These are painful and often associated with tender regional lymphadenopathy. Systemic symptoms including myalgias, headache, fever and malaise occur in 50–60% of primary infections. The lesions resolve over 2–3 weeks. Many women do not present with the “classic” appearance of the HSV lesions — instead, a painful abraded area or knife-slit may be present.

First episode non-primary infection

An initial HSV-2 genital infection in the setting of pre-existing HSV-1 antibodies (or the converse) usually presents with fewer lesions, a shorter duration of disease, decreased viral shedding and fewer systemic symptoms. This is caused by partial cross-protection of the pre-existing antibodies.

Recurrent infection

The majority of women experience clinical or subclinical recurrences throughout their lives, especially in the first few years after infection. Most recurrent HSV episodes are asymptomatic. If lesions are present, the duration is short (7–10 days), the lesions are limited in size and number, and systemic symptoms are infrequent. Prodromal symptoms of tingling, burning, or pruritus are occasionally reported. HSV-1 recurs less often than HSV-2. The periodic reactivation may be caused by stress, illness, fever, or ultraviolet light although often an exacerbating factor is not identified. During the course of a pregnancy, 5–10% of women with a history of HSV will have a symptomatic recurrence.

Asymptomatic viral shedding

Women seropositive for HSV have subclinical viral shedding 20–30% of days tested. Although the viral load is often low, sexual and neonatal transmission may occur with asymptomatic shedding, particularly in the first year after acquisition of HSV-2.

Neonatal HSV infection

The incidence of neonatal HSV is reported to be 1 in 3200 deliveries, with 1500 cases annually in the USA. Eighty-five percent of neonatal herpes infections result from transmission of virus at delivery. The majority of these cases occur in neonates born to women who have subclinical viral shedding at delivery and who often have no history of disease, making transmission prevention a difficult task. *In utero* infection occurs in approximately 5% of neonatal HSV cases. Transplacental and hematogenous spread of the virus prior to delivery may result in neurologic abnormalities, cutaneous scarring, chorioretinitis, and microcephaly. This is a rare occurrence, appearing in 1 in 300,000 infants. A

number of factors influence transmission. Infants born to mothers who have a first episode primary HSV infection near delivery have the greatest risk of neonatal HSV (no protective antibodies crossing the placenta). The risk of transmission from asymptomatic shedding in a woman with recurrent HSV is much lower, approximately 1 in 10,000 deliveries. The longer the duration of rupture of membranes, the use of fetal scalp electrodes, and the mode of delivery also influence neonatal transmission.

Two-thirds of neonatal HSV infection is caused by HSV-2 and the remaining third by HSV-1 infection. Neonatal disease manifests in three main ways. First, a localized infection of the skin (vesicular or bullous), eyes and mucous membranes may occur. Localized central nervous system disease (encephalitis) is also seen, associated with higher mortality rates. Finally, disseminated disease involving multiple organs, particularly the liver and lungs, may occur. This manifestation carries the highest mortality risk.

DIAGNOSIS

The diagnosis of HSV infection is often made clinically. However, clinical identification is insensitive and non-specific secondary to frequent non-classical presentations. As a confirmed diagnosis is vital for counseling and prevention of transmission, laboratory testing should be performed.

Isolation of virus by cell culture is the most sensitive test widely available. The sensitivity approaches 80% in women with early lesions. Unroofing a vesicle and expressing the fluid provides the greatest yield. As lesions begin to heal, the sensitivity decreases. False-negative cultures are not uncommon in recurrent lesions and healing lesions because of a low viral load. The benefit of cell culture is the sensitivity and ability to type the virus.

Type-specific serology is also available. Antibodies begin to develop within 2–3 weeks of infection. Many commercially available kits are unable to differentiate between HSV-1 and HSV-2. Type-specific tests now available are based on antibodies formed to type-specific G-glycoproteins. These tests allow specific typing, useful for counseling.

The identification of cellular changes consistent with HSV on cytologic evaluation of a Tzanck or Papanicolaou smear is the least sensitive technique available and should not be used for screening procedures. Polymerase chain reaction (PCR) is highly sensitive but not widely available at this time.

Other genital ulcer diseases such as chancroid and syphilis may present with manifestations often confused with HSV. Evaluation for other sexually transmitted diseases is prudent.

MANAGEMENT

Antepartum management

Late pregnancy primary HSV has the highest likelihood for neonatal transmis-

sion. Counseling the woman who is HSV serology negative about safe sexual practices may lead to a decrease in acquisition of genital herpes in late pregnancy. Although some experts recommend screening, at this time universal screening of all pregnant women with type-specific serology is not recommended.

The diagnosis of HSV has both acute and long-term psychological and physical implications. Extensive counseling is necessary to inform the woman about the natural history of HSV, asymptomatic shedding, sexual and vertical transmission risks, recurrence rates, and preventative measures. She needs to be taught to recognize common manifestations in order to initiate early therapy and use preventative measures such as abstinence or latex condoms. The partner's HSV serologic status needs to be determined.

An active lesion in the antepartum period should be cultured to confirm the clinical diagnosis. If this is an initial lesion, type-specific serology should be performed to determine if this is a primary or non-primary infection. Systemic antivirals such as aciclovir and valaciclovir may be used to attenuate signs and symptoms of HSV, especially if this is a primary infection. However, these will not eradicate latent virus.

Aciclovir therapy in the latter part of pregnancy (36 weeks' gestation until delivery) has been shown to decrease the rate of clinical HSV recurrences at delivery and the rate of asymptomatic shedding at delivery. The American College of Obstetricians and Gynecologists (ACOG) states that prophylactic therapy should be considered, especially in the setting of a first episode of HSV during the current pregnancy. Of note, the Aciclovir in Pregnancy Registry is now closed. No increase in fetal anomalies was identified.

Intrapartum management

A woman with a history of HSV should be asked about prodromal symptoms and recent HSV lesions. A careful vulvar, vaginal, and cervical examination should be performed. Any suspicious lesion should be cultured. Currently, cesarean delivery is indicated if the woman has an active lesion or if prodromal symptoms are present. Although the risk of neonatal transmission is low in the setting of a recurrent lesion, it does occur and cesarean delivery should still be offered. However, a cesarean delivery does not eliminate the risk. Ten to fifteen percent of infants with HSV are born to women who have had a cesarean delivery. If a lesion is present distant from the vulva, vagina, or cervix, the risk of neonatal transmission is very low. The non-genital lesions should be covered with an occlusive dressing and a vaginal delivery allowed. Cesarean delivery should not be performed in a woman with a history of HSV but not active lesions or prodromal symptoms.

The management of the woman presenting with an active HSV lesion and ruptured membranes is controversial. In a term infant, cesarean delivery

should be effected regardless of how long the membranes have been ruptured. In the setting of preterm premature rupture of membranes, especially in a pregnancy remote from term, expectant management should be allowed as the risk of prematurity complications outweighs the unproven benefit of immediate delivery. When labor then ensues, she should be examined; if the lesion has resolved, vaginal delivery is possible.

Postpartum management

The woman with HSV, especially if she has an active lesion, may transmit the virus to her infant through direct contact. Meticulous hand washing is important. Breastfeeding is allowed as long as there is not a herpes lesion on the breast. Aciclovir is transmitted in the breast milk but not at levels deemed detrimental to the neonate.

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Influenza

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INTRODUCTION

Influenza infection, while clinically recognized for centuries, remains a significant contributor to morbidity and mortality from febrile respiratory illness. Occurring annually, this viral infection affects all age groups and has caused approximately 36,000 deaths/year in the USA, 1990–1999. While children and adults aged 65 years and older are at highest risk for serious complications and death, other high-risk groups have been identified, including pregnant women.

The data regarding influenza infection and pregnancy are limited. Early studies from the 1918 and 1957 influenza pandemics reported higher risks of complications such as abortion, stillbirth, low birth weight, congenital anomalies, and maternal mortality rates (as high as 30%) in pregnant women compared with the general population. However, recent studies over the last two decades have contradicted the frequency of these early findings. It is now thought that a small increase in overall complication rates and congenital anomalies is associated with influenza. Although the virus can cross the placenta, fetal infection is rare.

PATHOPHYSIOLOGY

Influenza is a myxovirus with three antigenic types: A, B, and C. Only influenza A and B cause clinically significant disease. Influenza A is further subtyped using two surface glycoproteins, hemagglutinin (H) and neuraminidase (N). Hemagglutinin is a viral attachment protein and mediates viral entry. The neuraminidase enzyme facilitates viral spread. The annual antigenic variation noted worldwide is secondary to either antigenic drift or shift. Antigenic drift occurs when mutations accumulate in the N or H antigen. It is a slow, often subtle process and the mutations directly affect vaccine efficacy. Antigenic shift, seen only in influenza A, involves replacement of the current either H or N antigen with a new subtype. This shift to a novel antigen subtype is responsible for the intermittent worldwide influenza pandemics.

CLINICAL FEATURES

The influenza virus is spread through respiratory droplets and direct contact with recently contaminated articles. The incubation period ranges from 1 to 4 days. Adults often shed virus the day before symptoms develop until 5 days after symptom onset. Although many cases of influenza are asymptomatic, adults may present with a sudden onset of fever and rigors, diffuse myalgias, malaise, headache, and a non-productive cough. Sore throat, rhinitis, abdominal pain, nausea and vomiting may also be present. Tachycardia and tachypnea are common, especially in pregnant women. Although most symptoms resolve within a few days, the cough and malaise may persist for more than 2 weeks.

Physiologic changes in pregnancy such as an elevated diaphragm, increased oxygen consumption, and decreased functional residual capacity may worsen the pulmonary complications of influenza (i.e. pneumonia). Secondary bacterial infections, particularly pneumonia, are not uncommon. Myocarditis has also been reported. Death, although rare, can be a consequence of influenza in patients with underlying chronic disease.

DIAGNOSIS

During the influenza “season,” the diagnosis is usually made using clinical features. Diagnostic tests are best performed within 72 h of onset of illness, as viral shedding is greatest at this time. Viral culture of throat washings and nasopharyngeal secretions allow subtyping of the virus, important for epidemiologic evaluation and vaccine development. Serology, polymerase chain reaction (PCR), and immunofluorescence testing is also available. Finally, rapid antigen tests, although of lower sensitivity than viral culture, are readily available and allow rapid viral detection of nasopharyngeal secretions.

TREATMENT

Hospitalization of the pregnant woman with influenza depends on the severity of symptoms and any associated complications. The patient should be evaluated for evidence of pneumonia and other complications as the clinical findings dictate. A 12-lead electrocardiogram should be performed in the presence of marked maternal tachycardia. Fetal well being needs to be assessed if the fetus is viable. If influenza is suspected, initiate respiratory and contact isolation procedures along with strict hand hygiene.

Four antiviral medications are currently marked for use during influenza outbreaks. Amantadine and ramantadine are adamantanes with activity against influenza A only. Their use in pregnancy has been reported with no adverse outcomes to date. Optimally, treatment should begin within 48 h of symptom onset. However, as pregnant women have higher complication rates, treatment should be started at any time to decrease the duration and severity of illness. The neuroaminidase inhibitors, zanamivir and oseltamivir, are effec-

tive against influenza A and B. The safety of these drugs has not been established in pregnancy and they should be used only if the potential benefit justifies the potential risk (e.g. patient with influenza B at high risk for complications).

FOLLOW-UP

The pregnant woman should be followed for evidence of secondary complications during the acute illness. Once clinically improved, vaccination is recommended to decrease the likelihood of reinfection with another influenza A subtype or with influenza B.

PREVENTION

Vaccination is the primary method to prevent influenza and its severe complications. Each year, a new vaccine formulation consisting of two influenza A subtypes and one influenza B virus is determined based on typing of current virus worldwide. The efficacy of the vaccine is variable depending on how well the vaccine antigens correlate with the virus circulating in a specific community. Pregnant women respond to vaccination with increases in antibody titers similar to non-pregnant women.

There are two vaccine preparations available: an inactivated vaccine and a live attenuated vaccine. Only the inactivated influenza vaccine is recommended in pregnancy. Although currently the multidose vials of this vaccine are known to contain thimerosal (a mercury-containing preservative), new formulations are now being made without this compound and should be used in pregnant women. However, if unavailable, there is little theoretical risk as the amount of mercury in the old formulations is less than 25 µg/dose.

As pregnant women are at risk of severe illness from influenza and as there is no evidence that influenza vaccination is harmful to the pregnancy, the 2004 Advisory Committee on Immunization Practices (ACIP) now recommends vaccination for all pregnant women in *any* trimester. This has changed from the 2003 guidelines which excluded women in the first trimester. Breastfeeding is allowed in women recently vaccinated.

Secondary prevention strategies such as hand hygiene, respiratory and contact isolation, and prophylaxis of contacts should also be implemented.

CONCLUSIONS

Influenza remains a common problem in the pregnant population. Rapid diagnosis, treatment of complications, and implementation of both primary and secondary prevention strategies all contribute to keeping the overall morbidity and mortality in this population low.

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West Nile virus

Ronald Gibbs and Joel K. Schwartz

INTRODUCTION

Prior to 1999, West Nile virus was limited to Africa, Asia, the Middle East and Europe.¹ It is unknown how the virus entered North America. Since the virus entered the USA in New York in the summer 1999, the number and severity of cases has continued to increase as the virus has spread in a westward direction. Most West Nile virus infections are mild and clinically asymptomatic. One in 150 persons infected develops meningitis, encephalitis, or both.² From 1999 to 2001, there were a total of 149 cases reported to the Centers for Disease Control (CDC), with 18 deaths.³ In 2002, there were 4156 cases reported to the CDC, from which 284 people died.⁴ In 2003, there were 9858 reported cases, from which there were 2864 cases of neuroinvasive disease and 264 deaths.⁵ Researchers are unsure as to whether the increasing incidence rate in the USA is a result of an increase in virulence or characteristics peculiar to the affected population.⁶

PATHOPHYSIOLOGY

West Nile virus is a single-stranded RNA virus which is associated with other viruses that cause human encephalitis from the genus *Flavivirus*, which contains the Japanese encephalitis antigenic complex. There are 12 known members of this complex including the Japanese encephalitis and St. Louis encephalitis viruses. There are two genetic lineages of West Nile virus; however, only lineage 1 has been linked to human disease in the USA. West Nile virus is an arthropod-borne virus (arbovirus). These viruses are maintained in nature through biologic transmission between susceptible vertebrate hosts by blood-feeding arthropods. Mosquitoes, primarily members of the *Culex* species, are the maintenance vectors for West Nile virus. The virus is amplified during periods of adult mosquito blood-feeding by continuous transmission between mosquito vectors and bird reservoir hosts. There have been over 138 bird reservoir hosts identified through 2003. Humans and horses are likely incidental hosts because the infectious-level viremia necessary for continuous transmis-

sion is not reached. West Nile virus rarely causes illness in dogs and cats, although there was significant sero-evidence of dog infection during the New York City outbreak of 1999. There is no documented evidence of person–person or animal–person transmission, although there does exist one case from Michigan in 2002 of possible transmission through breast milk.

DIAGNOSIS

The incubation period following mosquito bite ranges from 3 to 14 days. Most human infections are not clinically apparent. One in five infected persons develops mild febrile illness with symptoms generally lasting 3–6 days. Other symptoms that may accompany fever are malaise, anorexia, nausea, vomiting, eye pain, headache, myalgia, rash, and lymphadenopathy. Severe infection results in serious neurologic disease, including symptoms of ataxia and extrapyramidal signs, cranial nerve abnormalities, myelitis, optic neuritis, polyradiculitis, and seizures. Encephalitis has been more frequently reported than meningitis.⁷ Severe infection requiring hospitalization is often accompanied by severe muscle weakness ranging to flaccid paralysis. This condition has been confused with Guillain–Barré syndrome. Advanced age is the greatest risk factor for severe neurologic disease and death. Because of its relative immunosuppressive state, pregnancy may predispose to more severe maternal infection. Approximately 70 women have contracted West Nile virus during pregnancy, with one known case of intrauterine transmission.⁸ The consequences of West Nile virus infection during pregnancy have not been well defined.

Practitioners should have a high index of clinical suspicion in patients with meningitis, encephalitis, acute flaccid paralysis, unexplained fever in the summer or fall, or in an area of ongoing infection. Diagnosis is based on detection of virus-specific immunoglobulin M (IgM), antibody capture enzyme-linked immunosorbent assay (ELISA) of either serum or cerebrospinal fluid (CSF) specimens from infected patients at the time of clinical presentation. Serum IgM antibody may persist for more than a year. It is possible that a positive serum IgM antibody may represent old infection and be unrelated to a patient's clinical presentation. In patients from endemic areas with IgM antibody detected in serum, a convalescent serum sample should be collected 14–21 days after illness onset to confirm acute infection by showing an increase in neutralizing antibody.² Persons recently vaccinated with yellow fever or Japanese encephalitis vaccines or persons recently infected with a related flavivirus may have positive results on IgM antibody tests. IgM antibody does not cross the blood–brain barrier. The detection of IgM antibody in a CSF specimen likely represents an acute central nervous system infection. Amniotic fluid, chorionic villi, fetal serum, or products of conception can be tested for evidence of West Nile virus infection.⁹ The sensitivity, specificity, and predictive values are not known.

TREATMENT

Treatment of West Nile virus consists of supportive therapy based on the severity of disease. More severe cases, particularly in older patients, require hospitalization and intravenous fluids. Respiratory support may be needed in patients with flaccid paralysis. Precautions should be taken to prevent secondary infections in severely ill patients. Ribavirin in high doses and interferon- α 2b have shown favorable results *in vitro*. One comatose patient treated with both ribavirin and interferon- α 2b did not improve.¹⁰ No controlled trials have been completed on these medications or on the use of steroids, antiseizure drugs, or osmotic agents for the treatment of West Nile virus encephalitis.

COMPLICATIONS

There is little information regarding the long-term morbidity following severe infection. Many patients continue with significant morbidity. Many patients do not return to their original functional level. Following the 1999 outbreak in New York City, the most common persistent symptoms were fatigue (67%), memory loss (50%), difficulty walking (49%), muscle weakness (44%), and depression (38%).¹¹ In pregnant women with laboratory tests indicating infection with West Nile virus, a detailed fetal ultrasound examination for structural abnormalities should be considered no sooner than 2–4 weeks after illness presentation in the mother. Clinical evaluation of infants born to infected mothers is recommended.

PREVENTION

Whenever possible, pregnant women should avoid being outdoors during dusk or dawn, which are peak mosquito feeding times of day. If pregnant women are going to be outdoors, they should wear long-sleeved shirts and long pants when possible. Pregnant women who live in areas with West Nile virus infected mosquitoes should apply insect repellent. The most widely used repellent is DEET (N,N-diethyl-3-methylbenzamide). DEET has been so widely used that both short-term and long-term testing has been performed. DEET is registered for direct application to skin, clothing, pets, tents, bedrolls, and screens. Products containing 10–50% DEET are sufficient. The percentage of DEET relates to the amount of protection time. For example, a product containing 20% DEET provides almost 4 h of protection. When used in conjunction with sunscreen, the sunscreen should be applied first followed by the repellent containing DEET. Permethrin is found in some repellents. It can be applied to clothing and tents, but not to skin. Citronella is not found to be as effective as DEET. The American Academy of Pediatrics recommends that repellents containing no more than 10% DEET be used on children, which protects for slightly more than 2 h.

CONCLUSIONS

There is minimal information regarding the risks of West Nile virus to pregnant women and the developing fetus. Pregnant women may be more susceptible because of their relative immunosuppressive state. In those patients with suspected illness, a serum or CSF IgM ELISA assay should be performed to confirm disease. Hospitalization and supportive therapy is recommended in patients with severe disease. The likelihood of transmission to the fetus is unknown as is the teratogenic potential. Pregnant women should avoid endemic areas and exposure, particularly during dusk and dawn. Repellents such as DEET are safe and effective means to reduce transmission by preventing mosquito bites.

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Human immune deficiency virus infection

Howard Minkoff

INTRODUCTION

The remarkable pace of antiretroviral drug development, starting in the 1990s, has transformed human immune deficiency (HIV) disease from a uniquely dreaded and rapidly fatal illness to one that can be controlled for increasingly long periods of time, perhaps decades. These same agents can be used to prevent the overwhelming majority of pediatric HIV infections. Both of these goals, maintaining women's health and preventing the mother-child transmission of HIV, can only be assured if women's healthcare providers are comfortable and rigorous in their efforts to identify HIV-infected women, assess the status of their illness, implement appropriate drug therapy, and monitor the success and toxicities that may be associated with the chosen agents.

EPIDEMIOLOGY

The number of HIV-infected individuals worldwide is now estimated to be close to 40 million, with approximately 1 million infected individuals residing in the USA. HIV is acquired through exposure of the host's blood or mucous membranes to infected blood or secretions. The most common means of transmission in the developing world is unprotected sexual activity. In the USA it continues to be spread by the sharing of contaminated needles as well as by unprotected sex. Exposure in the healthcare setting, of the patient by the doctor or vice versa, is a rare event if universal precautions are utilized. Transmission from mother to child may occur in the antepartum, intrapartum, or via breast milk in the postpartum period. Perinatal transmission occurs primarily (perhaps two-thirds to three-quarters of transmissions) in the intrapartum period. If a mother breastfeeds, there may be an ongoing transmission rate of 0.5% per month. Breast milk transmission occurs at the greatest rate during the first months of breastfeeding.

Risks for transmission include:

- Advanced disease (low CD4 count, high viral load, clinical illness)
- Delivery after ruptured membranes, particularly if there is chorioamnionitis

- Cigarette smoking, illicit drug use, and unprotected sexual intercourse with multiple partners during pregnancy may increase risk
- Preterm birth
- Vaginal delivery

PATHOPHYSIOLOGY

HIV is a single-stranded ribonucleic acid (RNA)-enveloped virus that has the ability to become incorporated into cellular deoxyribonucleic acid (DNA). HIV preferentially infects cells with the CD4 antigen, particularly helper lymphocytes and macrophages. At least two cell surface molecules, CXCR4 and CCR5, which are cytokine receptors, help HIV to enter the cells. After the virus enters the cell, its RNA is released from the nucleocapsid and is reverse-transcribed into proviral DNA. The provirus is inserted into the genome and then transcribed into RNA that is translated leading to the assembly of virions which are extruded from the cell membrane by budding. The virus is composed of core (p18, p24, and p27) and surface (gp120 and gp41) proteins, genomic RNA, and the reverse transcriptase enzyme surrounded by a lipid bilayer envelope. The virion contains three structural genes (*gag*, *pol*, and *env*) and a complex set of regulatory genes, including *tat*, *vif*, *nef*, *vpu*, and *ref*, which control the rate of virion production.

Once an individual is infected he/she will undergo a progressive debilitation of the immune system, rendering them susceptible to opportunistic infections (e.g. *Pneumocystis carinii* pneumonia and central nervous system toxoplasmosis) and neoplasias (e.g. Kaposi sarcoma) that rarely afflict patients with intact immune systems. When one of several specific opportunistic infections, neoplasia, dementia encephalopathy, or wasting syndrome, occurs or the CD4 count drops below 200 lymphocytes/mm³, the diagnosis of AIDS is assigned.

At the time of initial infection, there may be no symptoms or an acute mononucleosis-like syndrome may develop, sometimes accompanied by aseptic meningitis. There is an immediate, dramatic viremia (up to a billion viral particles turned over per day) and a rapid immune response with similar levels of T-cell turnover. After the initial viremia, the level of virus returns to a set-point. The level of virus in the plasma at that time correlates with long-term survival. Antibodies are usually detectable 1 month after infection and are almost always detectable within 3 months. After seroconversion has occurred, an asymptomatic period of variable length usually follows. The median clinical latency in the pre-highly active antiretroviral therapy (HAART) era was a little more than a decade with a few individuals (less than 5%) developing AIDS within 3 years.

Once an individual's immune system becomes sufficiently compromised they will be subject to clinical conditions ranging from fever, weight loss, malaise, lymphadenopathy, and central nervous system dysfunction to a variety of

infections. These conditions are usually a prelude to the opportunistic infections that are diagnostic of AIDS. Studies in the pre-HAART era found that the incidence rate of AIDS after seroconversion was over 2.5 per 100 person-years and was directly related to age (AIDS developed in younger individuals at a slower rate). However, the advent of ever more powerful and palatable regimens has had significant effects on surrogate markers of disease progression as well as rates of opportunistic infections and hospitalizations.

DIAGNOSIS

Recommend the HIV test to all prenatal patients. The American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control (CDC) recommend a policy of routine testing with an informed “right of refusal.” The standard approaches to the diagnosis of HIV (enzyme-linked immunoadsorbent assay [ELISA] and confirmatory Western blot) remain among the most reliable diagnostic tools used by obstetricians. Recently, these tests have been supplemented by rapid tests, including most recently a saliva-based test, that allow obstetricians to treat patients whose status was not known prior to the intrapartum period.

MANAGEMENT

- Refer the patient to social services for case management.
- Assess the patient’s immune status by determining a CD4 count each trimester.
- Assess viral load monthly until viral load is undetectable, then every 3 months.
- Screen for other sexually transmitted diseases, such as syphilis, gonorrhea, chlamydia, and hepatitis B.
- Provide appropriate vaccinations.
- Papanicolaou (Pap) smears should be performed with liberal recourse to colposcopy because of high human papillomavirus (HPV) carriage and dysplasia rates.

Antiretroviral therapy

Before starting therapy discuss:

- The risks of these drugs during pregnancy as well as benefits both for the infected woman and for reducing the risk for HIV-1 transmission to her infant
- A long-term treatment plan
- The importance of adherence to any prescribed antiretroviral regimen
- The availability of support services, mental health services, and drug abuse treatment that may be required

To reduce the potential for emergence of resistance, if therapy requires temporary discontinuation for any reason during pregnancy, all drugs should be

stopped and reintroduced simultaneously. Similarly women who must temporarily discontinue therapy because of pregnancy-related hyperemesis should not resume therapy until sufficient time has elapsed to ensure that the drugs will be tolerated.

In considering treatment, the first consideration is the treatment of maternal disease. A CD4 count of less than 350/ μ L, or a viral load greater than 100,000 copies are the usual thresholds for starting HAART in the non-pregnant population. If a woman does not reach the traditional criteria for starting HAART but has a detectable viral load (some providers use a threshold of greater than 1000 copies), there is still a role for HAART during pregnancy in order to decrease transmission and to reduce the need for cesarean section. Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10–12 weeks' gestation.

HAART is any regimen that results in maximal and durable reduction in viral load. Commonly used regimens consist of two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. First regimens should be "class sparing," (i.e. should not use both non-nucleosides and protease inhibitors).

Results of therapy are evaluated through plasma HIV RNA levels which are expected to indicate a 1.0 \log_{10} decrease at 2–8 weeks and no detectable virus (less than 50 copies/mL) at 4–6 months after. Failure of therapy at 4–6 months might be ascribed to non-adherence, inadequate potency of drugs, or suboptimal levels of antiretroviral agents, viral resistance, and other factors that are poorly understood. Patients whose therapy fails in spite of a high level of adherence to the regimen should have their regimen changed; this change should be guided by a thorough drug treatment history and the results of drug-resistance testing in collaboration with an HIV expert.

If no detectable virus is detected (some providers use a threshold of 1000 copies of virus) the ACOG 076 regimen alone can be used:

- 300 mg twice daily (or 200 mg three times daily), beginning at 14 weeks, given until labor
- *Intrapartum*: loading, 2 mg/kg over the first hour; maintenance, 1 mg/kg/h until delivery
- *Neonatal*: oral ZDV syrup, 2 mg/kg orally four times daily for 6 weeks per protocol supervised by a pediatrician
- *Monitoring*: complete blood count (CBC) twice every 2 weeks; then every month; liver function test each month; creatinine each month

For a woman not treated prior to labor, several effective regimens are available:

- Intrapartum intravenous ZDV, followed by ZDV for the newborn for 6 weeks.
- Oral ZDV and 3TC during labor, followed by oral ZDV/3TC for 1 week for the newborn.

- A single dose of nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 h. Recent data raises concerns about failure rates with this choice.
- The two-dose nevirapine regimen combined with intrapartum intravenous ZDV and 6-week ZDV for the newborn.

In the immediate postpartum period, the woman should have appropriate assessments (e.g. CD4⁺ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

Resistance testing

Recommendations for performing these tests in pregnant women are the same as for resistance testing of all other individuals: failing regimen, suboptimal suppression, and high likelihood of exposure to resistant strain based on community prevalence of knowledge of source. Get blood *before* switching from a failing regimen. Resistance testing is useful to rule a drug out, but cannot guarantee success of a new regimen.

Risks from drug exposure in pregnancy

Nevirapine (Viramune ©, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT)

Nevirapine should be used with caution in pregnant women with CD4⁺ lymphocyte counts of more than 250/mm³ who are starting combination therapy for preventing perinatal transmission but do not require therapy for own health. There is a significant risk of rash and hepatotoxicity. If used, monitor closely for liver toxicity in first 18 weeks of therapy. Women who enter pregnancy on nevirapine regimens and are tolerating well may continue therapy, regardless of CD4⁺ lymphocyte count.

Efavirenz (Sustiva©, DuPont Pharmaceuticals Co., Wilmington, DE)

Animal teratogenicity studies reveal anencephaly, anophthalmia, microphthalmia in the cynomolgus monkey.

Amprenavir

The liquid oral formulation of amprenavir contains high levels of propylene glycol and should not be used in pregnant women.

HAART

Some studies suggest a heightened risk of preterm birth or low birth weight associated with HAART, but many other studies do not.

Mitochondrial toxicity

Pregnant women receiving nucleoside analog drugs should have hepatic

enzymes and electrolytes assessed more frequently during the last trimester of pregnancy, and any new symptoms should be evaluated thoroughly. The combination of ddI and d4T should be avoided because of reports of several maternal deaths secondary to lactic acidosis with prolonged use.

Diabetes

New onset hyperglycemia has been reported in association with protease inhibitors.

Prophylaxis for opportunistic infections

Pneumocystis carinii pneumonia

Offered to women with CD4⁺ lymphocyte counts below 200/μL, unexplained fever (more than 100°F) for 2 weeks or more, or a history of oropharyngeal candidiasis. Prophylaxis may be discontinued for women on HAART with sustained elevations in their CD4⁺ lymphocyte count above 200/μL.

Trimethoprim-sulfamethoxazole (TMP-SMZ), one double-strength tablet daily, is the first choice for prophylaxis in pregnancy. Alternatives include aerosolized pentamidine 300 mg/month via Respigard II® (Marquest Medical Products, Inc., Englewood, CO) nebulizer, or oral dapsone 100 mg/day.

Mycobacterium avium complex

Prophylaxis for CD4 lymphocyte counts less than 50/μL or previous documented *Mycobacterium avium* complex infection. Azithromycin 1200 mg once weekly, is first choice for therapy. Clarithromycin should be avoided in pregnancy because of teratogenicity in animals.

Toxoplasma

TMP-SMZ will also provide prophylaxis against toxoplasma encephalitis in women who are seropositive for antibodies to *Toxoplasma gondii*. For women with previous toxoplasma encephalitis, an appropriate prophylaxis regimen should be offered throughout pregnancy.

Obstetric management

Cesarean section will lower transmission if virus is detectable. Evidence is unclear regarding any benefit when viral load is less than 1000 copies. The procedure is performed at 38 weeks with no amniocentesis; prophylactic antibiotics should be used.

If the patient is allowed to labor, avoid scalp electrodes and scalp pH if possible.

Delay amniotomy. Some data suggest a relationship between the duration of ruptured membranes and the vertical transmission rate of HIV. Use universal precautions and counsel against breastfeeding.

Table 46.1 Pharmacokinetics, toxicity data, and recommended use of antiretroviral drugs in pregnancy. (Modified from www.AIDSinfo.nih.gov)

Drug	Pk data in pregnancy	Concerns in human pregnancy	Recommended use in pregnancy
NRTI NNRTIs			
<i>Recommended agents</i>			
Zidovudine	Pk not significantly altered in pregnancy	Safe in short term	Preferred nucleoside for use in combination regimen in pregnancy based on efficacy studies, large experience. Should be included in regimen unless significant toxicity or stavudine use
Lamivudine	Similar pk in pregnancy to that observed in non-pregnant subjects. No change in dose indicated	Well-tolerated; no evidence of teratogenicity	Because of extensive experience with use of this drug in pregnancy in combination with zidovudine, recommended NRTI with zidovudine in HAART regimen
<i>Alternate agents</i>			
Didanosine	Similar pk in pregnancy and postpartum; no change in dose indicated	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine	Alternate NRTI for HAART regimens. Use with stavudine only if no other alternatives are available
Emtricitabine	No studies in pregnancy	None identified	Alternate NRTI for HAART regimens

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Drug	Pk data in pregnancy	Concerns in human pregnancy	Recommended use in pregnancy
Stavudine	Pk study in combination with lamivudine showed pk similar to that in non-pregnant subjects	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine with other agents	Alternate NRTI for HAART regimens. Use with didanosine only if no other alternatives are available. Do not use with zidovudine as may be antagonistic
<i>Insufficient data</i> Abacavir	Phase I/II study in progress	Potentially fatal hypersensitivity reactions in non-pregnant persons; rate in pregnancy unknown	Triple NRTI regimens including abacavir have been less potent virologically compared with PI-based HAART regimens. Should be used only when an NNRTI or PI-based HAART regimen cannot be used e.g. significant drug interactions. A study evaluating use among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development
Tenofovir	No studies. Phase I study in late pregnancy	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy	Because of lack of data on use in human pregnancy, tenofovir should be used as a component of maternal HAART regimen only if other options have been exhausted

Not recommended

Zalcitabine

Teratogenicity (hydrocephalus) in rats at $1000 \times$ human doses. Developmental toxicity seen in rodents at moderate to high doses

Given toxicity in non-pregnant adults and teratogenicity concerns, not recommended for use in pregnant women

NNRTIs

Recommended agents

Nevirapine

Increased risk of symptomatic, often rash-associated and potentially fatal, liver toxicity among women with CD4⁺ lymphocyte counts > 250/ μ L; unclear if pregnancy increases risk

Use with caution in pregnant women with CD4⁺ lymphocyte counts > 250; monitor closely for liver toxicity in first 6 weeks of therapy

Pk study of 12 women demonstrated similar pk during pregnancy compared with postpartum and compared with historical controls

Insufficient data

Delavirdine

Embryotoxic in rats and rabbits at 5–6 times human dose. Carcinogenic in mice. Teratogenic (ventricular septal defects) in rats

Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available

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Drug	Pk data in pregnancy	Concerns in human pregnancy	Recommended use in pregnancy
<i>Not recommended</i> Efavirenz	No studies in human pregnancy	Significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys exposed to therapeutic plasma levels during the first trimester. Case reports of neural tube defects in humans after first trimester exposure; relative risk unclear	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Use in the second half of pregnancy could be considered if other alternatives not available

Protease inhibitors

Recommended agents

Nelfinavir

Dosing at 750 mg t.i.d. produced variable and generally low levels in pregnant women. Adequate levels with 1250 mg b.i.d. in pregnancy.

No specific concerns identified

Given pk data and extensive experience with use in pregnancy compared to other PIs, preferred PI for HAART regimens in pregnancy

<p>Saquinavir/ritonavir</p> <p>Inadequate levels with saquinavir alone at 1200 mg b.i.d. Saquinavir 800 mg with ritonavir 100 mg, both b.i.d., produced adequate levels and was well-tolerated in study of 13 women</p>	<p>No specific concerns identified</p>	<p>Given pk data and moderate experience with use in pregnancy, can be considered a preferred PI for HAART regimens in pregnancy</p>
<p><i>Alternate agents</i></p> <p>Indinavir</p> <p>Two studies including six women total using a dose of 800 mg t.i.d. showed markedly lower levels during pregnancy compared with postpartum, although HIV RNA levels were suppressed to undetectable. Study underway evaluating pk of indinavir 800 mg with ritonavir 100 mg, both b.i.d.</p>	<p>Developmental toxicity in rats at human doses but no evidence of teratogenicity in rats, rabbits, or dogs. Theoretical concern re: neonatal hyperbilirubinemia with use in pregnancy, but minimal placental passage</p>	<p>Alternate PI if unable to use nelfinavir or saquinavir/ritonavir</p>
<p><i>Insufficient data</i></p> <p>Lopinavir/ritonavir</p> <p>Phase I/II safety and pk study in progress using lopinavir 400 mg and ritonavir 100 mg, both b.i.d.</p>	<p>No specific concerns identified in animal studies. Minimal experience in human pregnancy</p>	<p>Not recommended pending safety and pk studies. If used, monitor response closely</p>

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Drug	Pk data in pregnancy	Concerns in human pregnancy	Recommended use in pregnancy
Amprrenavir	No studies in human pregnancy	In rats and rabbits, increased skeletal variants, decreased ossification, and decreased birth weight noted at lower than human exposure. Oral solution contraindicated in pregnant women because of high levels of propylene glycol which may not be adequately metabolized during pregnancy	Data are insufficient regarding safety and pk in pregnancy to recommend use of capsules during pregnancy. Oral solution contraindicated
Fos-amprrenavir	No studies in human pregnancy	See amprrenavir	Data are insufficient regarding safety and pk in pregnancy to recommend use during pregnancy.
Atazanavir	No studies in human pregnancy	Theoretical concern re: increased indirect bilirubin levels which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low	Data are insufficient regarding safety and pk in pregnancy to recommend use during pregnancy
Fusion inhibitors			
<i>Insufficient data</i>			
Enfuvirtide	No studies in human pregnancy	No specific concerns based on animal studies; no experience in human pregnancy	Data are insufficient regarding safety and pk in pregnancy to recommend use during pregnancy

HAAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; pk, pharmacokinetics.

CONCLUSIONS

This chapter provides a very brief summary of a very complex topic. There are now 20 approved antiretroviral agents from which to craft drug regimens (Table 46.1). The choice of regimen and the starting point for initiating therapy should be tailored to the individual patient's needs and should be decided upon in collaboration with an HIV expert who will assume the ongoing care of the patient in the postpartum period. That same expert should be called upon to provide guidance in those cases in which adequate response to a first course of therapy is not obtained or the need for prophylaxis or treatment of opportunistic infections arises.

Obstetricians have made a remarkable contribution to the rapid advances in the field of HIV, including improved survival and reduced rates of mother-child transmission. However, challenges remain and the price of progress has been complexity. By assisting women to learn their serostatus, to get optimal therapy, and to be adherent to treatment, obstetricians will continue to earn their reputation as the principal advocates for the health of all pregnant women.

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www.AIDSINFO.nih.gov

Parvovirus B19 infection

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INTRODUCTION

The spectrum of clinical manifestations caused by parvovirus B19 infection, a single-stranded DNA virus, is unlikely to have been completely described. In the normal host, B19 infection can be manifest as an asymptomatic or subclinical infection, erythema infectiosum (EI) or fifth disease, or as an arthropathy. In patients with thalassemia or sickle cell disease, B19 infection can cause a severe, transient, red cell aplasia (transient aplastic crisis [TAC]). In the immunocompromised population, B19 infection can persist and manifest as chronic anemia. In the fetus, B19 infection is associated with anemia, non-immune hydrops, and demise.

PATHOPHYSIOLOGY

The rash of EI and B19 arthralgias are thought to be secondary to an immunologic phenomenon. The hematologic manifestations of B19 infection result from selective infection and lysis of erythroid precursor cells with interruption of normal red blood cell production. In the otherwise healthy but infected host, this infection produces a limited and clinically unapparent red cell aplasia. However, in the patient with chronic red cell destruction, dependent upon the ability to increase red blood cell production, B19 infection may lead to aplastic crisis.

The pathogenesis of fetal and congenital disease is thought to be fairly well understood. Infection of the fetus occurs through transplacental passage of the virus. The red cell aplasia is particularly devastating for the fetus, given the dramatic increase in red cell mass necessary to promote accelerated growth, as well as the shortened lifespan of the fetal red cell. There are some data also to support a viral effect upon myocardiocytes, but the clinical importance of fetal myocarditis is less certain. The pathogenic mechanism of hydrops is associated with severe fetal anemia, which may result in tissue hypoxia and increased capillary permeability, as well as increased cardiac output and increased umbilical venous pressure. High-output heart failure results, by virtue of these changes

alone or together with a myocarditis, is associated with increased hydrostatic pressure and decreased venous return, as a result of ascites and/or organomegaly, leads to further cardiac decompensation. Compromised hepatic function and placental hydrops likely play a part too.

EPIDEMIOLOGY

B19 is presumably transmitted person–person through direct contact with respiratory secretions, vertically from mother to fetus, and via parenteral transfusion with contaminated blood products or needles.

Cases of EI occur sporadically and as part of school outbreaks. The peak incidence of B19 infection occurs among school-aged children, with reported attack rates amongst susceptible students of 34–72%. Patients with EI are likely most contagious before the onset of the rash, and may remain contagious for a few days after appearance of the rash. During school outbreaks, reported attack rates amongst employees vary from 12% to 84%, with the highest rates in elementary school teachers, reflecting exposure to greater numbers of children or a greater likelihood of contacting respiratory secretions of younger children. When serologic criteria are used, the frequency of asymptomatic infection was greater than 50% in most studies. Healthcare workers are another susceptible population, with over 30% demonstrating seroconversion following exposure to children with TAC.

DIAGNOSIS

Seroprevalence

The seroprevalence of specific immunoglobulin G (IgG) antibodies increases with age, and is below 5% in those less than 5 years of age. The greatest increase in seroprevalence occurs between 5 and 20 years of age, increasing from 5% to 40%. Seroprevalence then increases more slowly, exceeding 75% by 50 years of age.

Specific IgM antibodies can be detected 10 days after inoculation, and IgG is detectable 2–3 days thereafter. Rash and/or arthropathy may develop approximately 18 days after inoculation. IgM antibodies persist typically for months, and IgG antibodies persist for years. Antibodies are detected by enzyme-linked immunoabsorbent assay (ELISA) or radioimmunoassay (RIA), and viral DNA by DNA hybridization studies.

An individual is susceptible in the absence of documented IgM and IgG. The presence of only IgG denotes an immune individual, who may have been infected as recently as 4 months previously. The presence of only IgM denotes a very recent infection, whereas the presence of both IgM and IgG is typical of a patient with recent (typically 7 days to 4 months) exposure.

FIFTH DISEASE

The most frequently recognized manifestation of B19 infection is the rash illness, EI. The most distinctive feature of EI, or slapped cheek disease, is an erythematous maculopapular rash that affects the cheeks and typically spares the remainder of the face. The trunk and extremities are also affected, and the rash may be pruritic. The rash occurs coincidentally with the production of specific antibodies, suggesting that it is an immune-mediated phenomenon.

Arthralgias, sometimes accompanied by inflammatory changes in affected joints, are a manifestation of acute B19 infection and can accompany EI, particularly in adults. Arthropathy, most often affecting wrists, hands and knees, can also be the sole manifestation of B19 infection. As with the rash, onset of arthropathy is accompanied by a rise in anti-B19 antibodies, suggesting an immunologic phenomenon.

Fifth disease and pregnancy

Sequelae

Many pregnant women are susceptible to B19 infection, as the reported seroprevalence in reproductive-aged and pregnant women is 35–55%. The infection rate during pregnancy is estimated at 1.1%. Transplacental transmission of B19 to the fetus may be common after maternal infection, but the frequency with which infection occurs is uncertain, and whether efficiency of transmission varies with gestational age is unknown. Many infants infected *in utero* are asymptomatic at birth.

Adverse pregnancy outcomes following B19 infection include fetal demise, non-immune hydrops, and congenital anomalies. It is difficult to say with certainty the proportion of all demises attributable to B19 infection. At present, it appears that the primary mechanism leading to fetal death is anemia and hydrops in those gestations before 20 weeks, with death usually in mid-trimester. The crude fetal death rate is less than 10%. In the USA, it is likely that less than 1% of all demises result from B19 infection. Although infection with B19 may be a common cause of non-immune hydrops especially during community outbreaks of EI, it does not follow that intrauterine B19 infection frequently causes hydrops. The most common outcome is normal seronegative newborns, followed by liveborn seropositive babies, and finally hydrops in less than 1%.

Experimental and natural infection with many of the parvoviruses is associated with birth defects, and there is some circumstantial evidence that intrauterine B19 infection may be etiologic in some cases of human birth defects, particularly CNS abnormalities. However, there are currently no data suggesting that B19 infection is an important etiologic agent of birth defects.

Management

Our knowledge of optimal management of B19 infection in pregnancy lags behind our understanding of the potential adverse consequences. As a result, there are considerable resources devoted to the pregnancy with this diagnosis, even though there are few data demonstrating efficacy of any particular therapeutic approach or intervention.

In the event that a pregnant patient presents with complaints potentially consistent with B19 infection, such as arthralgias, exposure to someone with EI, hydropic changes, or a demise on ultrasound, for example, blood should be sent for determination of anti-B19 IgM and IgG antibodies to determine immunity or risk. In the event of a school outbreak of EI, the decision to limit presumptive exposure for a pregnant school teacher should be individualized, as the risk of that teacher becoming infected and suffering a demise is less than 1.5%. Intrauterine B19 infection can be determined by polymerase chain reaction (PCR) DNA detection of viral B19 in amniotic fluid or fetal blood.

There are no studies to identify the optimal management of a pregnant patient with an acute B19 infection. Serial ultrasounds are often advocated, as the peak in fetal morbidity and mortality is 4–6 weeks postexposure, and as late as 3 months following onset of symptoms, but the yield of such intensive observation is low. Determination of fetal, middle cerebral artery Doppler velocimetry for detection of anemia has been studied. In the event that hydropic changes are noted on ultrasound, intrauterine transfusion following determination of severe fetal anemia can be accomplished until the fetus recovers from the infection. However, this intervention is not without its own inherent risk of fetal morbidity and mortality, and there are no trials that demonstrate improved survival following transfusion versus without transfusion. There are no B19 vaccines for B19 immunization available at this time, and the role of hyperimmune serum globulin in the prevention or modification of B19 infection is unclear.

CONCLUSIONS

Intrauterine B19 infection is a cause of fetal anemia, hydrops, and demise, and perhaps also of congenital abnormalities. The best strategy for surveillance of the infected pregnant patient is unclear, as are strategies to decrease infection rate and untoward outcomes.

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Syphilis

Vanessa Laibl and George D. Wendel, Jr

BACKGROUND AND INCIDENCE

The exact incidence of syphilis complicating pregnancy is unknown. It is known that the incidence of primary and secondary syphilis in the general population decreased significantly in the USA during the 1990s. However, between 2000 and 2002, the rate of primary and secondary syphilis in the general population increased. The 2002 rate of 2.4 cases per 100,000 persons is 9% higher than the previous year. The incidence of syphilis in women has continued to decrease, and this has heralded a decrease in the incidence of congenital syphilis. The objective for Healthy People 2010 is to reduce the incidence of syphilis to 0.2 cases per 100,000 persons.

Syphilis in pregnant women is often related to illicit drug use, especially cocaine, and the concomitant exchange of sex for drugs. Many of these drug users receive little to no prenatal care, which in turn leads to an increased risk of having an infant with congenital syphilis.

PATHOPHYSIOLOGY

Pregnancy itself probably does not affect the course of syphilis. However, syphilis may cause premature birth, stillbirth, and neonatal morbidity and mortality.

One of the most important consequences of maternal syphilis is congenital syphilis in the fetus and infant. Spirochetes readily cross the placenta to produce chronic infection in the fetus, although clinical disease is generally not evident before 18 weeks' gestation. The most common clinical findings in newborns with congenital syphilis are hepatosplenomegaly, osteochondritis or periostitis, jaundice or hyperbilirubinemia, petechiae, purpura, lymphadenopathy, and ascites or hydrops. Some of these anatomic pathologic changes may be detected by ultrasonography. There appears to be a continuum of fetal syphilis as it progresses *in utero* (Fig. 48.1). Newborns may also manifest rhinitis, pneumonia alba, myocarditis, or nephrosis.

If the neonate is clinically affected, the placenta may be involved, and characteristically is very large and "waxy" in appearance. Microscopic examination

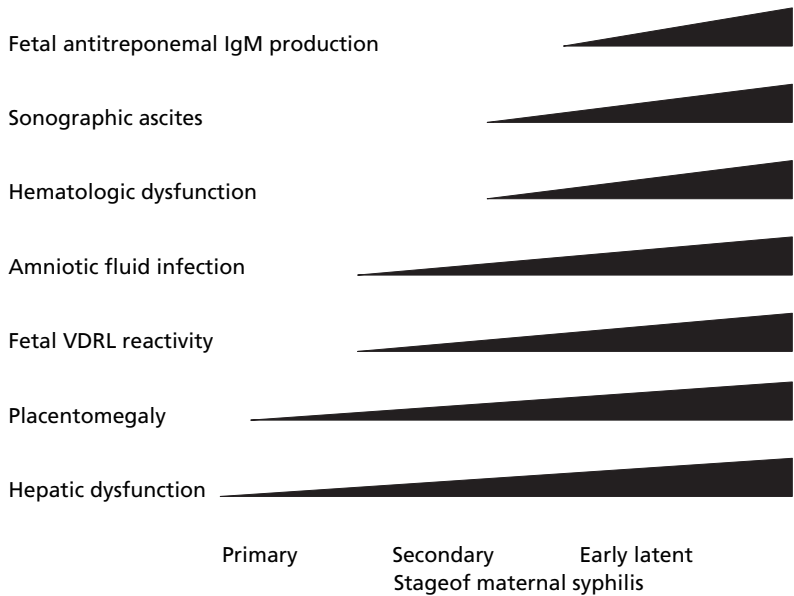


Fig. 48.1 Continuum of fetal syphilis *in utero* with stages of maternal syphilis. (Reprinted with permission from Hollier, *et al.* fetal syphilis: clinical and laboratory characteristics. *Obstet Gynecol* 2001;**97**:947–53.)

of the placenta frequently will reveal focal villitis, immature villi, and endarteritis. Spirochetes can be identified by special staining techniques.

DIAGNOSIS

The diagnosis of syphilis in the pregnant woman is essentially the same as for the non-pregnant patient. For pregnant women with primary syphilis, identification of *Treponema pallidum* spirochetes by dark-field examination of material taken from a chancre is confirmatory. However, the majority of pregnant women with syphilis are asymptomatic, and the diagnosis is frequently made by serologic testing which is recommended at the first prenatal care visit, during the third trimester, and at delivery. Currently available are non-treponemal tests such as the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) tests. These two serologic tests are reported quantitatively, and a change of two dilutions (i.e. fourfold change in titer) is considered a significant change. Specific treponemal tests include the microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP), the fluorescent treponemal antibody absorption test (FTA-ABS), and the *T. pallidum* passive particle agglutination (TP-PA) test. These specific antibody tests usually

remain positive for life. All pregnant women with syphilis should be carefully examined and tested for the presence of other sexually transmitted diseases, especially human immunodeficiency virus (HIV) infection.

The diagnosis of neonatal congenital syphilis is based primarily on clinical findings, maternal history, and positive serologic tests. For the asymptomatic newborn without clinical signs of syphilis, the diagnosis is much more difficult. Maternal immunoglobulin G (IgG) antibody readily crosses the placenta and may cause the newborn's serologic test to be positive. All newborns with suspected syphilis should have a lumbar puncture for cerebrospinal fluid analysis and radiographic studies of the long bones, which will reveal significant changes in metaphyseal bone in approximately 95% of affected infants.

Of infected fetuses, 40–50% will die *in utero*. The most common cause of fetal death is placental infection and overwhelming fetal infection. Confirmation of congenital syphilis in a stillborn infant may prove extremely difficult, especially in the severely macerated infant. Staining the fetal tissue to identify spirochetes, performing X-ray studies to look for osteochondritis, and histologically evaluating the placenta may prove helpful. Motile spirochetes can sometimes be identified in the amniotic fluid of women with syphilis and fetal death. *Treponema pallidum* can be identified in infected amniotic fluid, neonatal serum, and neonatal spinal fluid using polymerase chain reaction testing.

TREATMENT

Treatment is the same for pregnant and non-pregnant women, and consists primarily of long-acting benzathine penicillin G in doses appropriate for the stage of infection. According to the Centers for Disease Control and Prevention (CDC) 2002 guidelines, patients with early syphilis (primary, secondary, and early latent syphilis of less than 1 year's duration) should receive a single intramuscular dose of 2.4 million units of benzathine penicillin G. Some specialists also recommend additional therapy (e.g. a second dose of benzathine penicillin 2.4 million units intramuscularly) 1 week after the initial dose for pregnant women who have primary, secondary, or early latent syphilis. After treatment of early disease, more than 60% of women will have the Jarisch–Herxheimer reaction. Pregnant patients should be warned to watch for fever, decreases in fetal activity, and for signs of preterm labor.

For pregnant women with late latent syphilis of more than 1 year's duration or of unknown duration, or with cardiovascular syphilis, benzathine penicillin G, 2.4 million units intramuscularly, should be given weekly for 3 weeks (7.2 million units total). Pregnant women with neurosyphilis should receive aqueous crystalline penicillin G, 18–24 million units/day by an intravenous dosage of 3–4 million units every 4 h for 10–14 days. An outpatient program of intramuscular procaine penicillin, 2.4 million units/day, plus 500 mg oral probenecid four times daily for a total of 10–14 days, can also be utilized.

Serologic tests should then be repeated at the previously recommended times during the third trimester and at delivery. Monthly serologic testing may be used in high-risk patients in whom reinfection is likely. It is expected that there will be a fourfold drop in serologic test titers over a 6-month period in women treated for primary, secondary, or early latent syphilis. However, it should be noted that in one study 28% of those with primary syphilis and 44% with secondary syphilis had persistently positive non-treponemal test results 36 months after treatment, so it is not unusual for pregnant women to have insufficient time to be evaluated for serologic evidence of cure of their syphilis by delivery.

Treatment before 20 weeks' gestation is uniformly effective in preventing congenital syphilis, barring reinfection. Treatment failures occur in 1–2% of patients because of advanced, irreversible fetal infection. These failures are seen more frequently with maternal high-titer early latent syphilis, secondary syphilis, or treatment after 30 weeks' gestation. Little is known about the effect of syphilis and concomitant HIV infection in pregnancy. In adults, HIV infection may affect the clinical presentation of syphilis, the serologies, and the response to recommended therapy.

Treatment after 20 weeks' gestation should be preceded by an ultrasound to look for evidence of fetal infection. In the case of an abnormal sonogram (hydrops, ascites, skin edema, hepatomegaly), antepartum fetal heart rate testing is indicated prior to treatment. Spontaneous late decelerations and non-reactive fetal heart rate patterns have been associated with an infected fetus. When sonographic abnormalities are found and antepartum testing is abnormal, a neonatologist and maternal fetal medicine specialist should be consulted. In some fetuses, delivery with treatment of the newborn in the nursery may be the better management choice.

The pregnant woman with syphilis who is allergic to penicillin presents a therapeutic challenge. Tetracycline and doxycycline are not recommended for use in pregnancy. Although effective in non-pregnant patients, tetracyclines may discolor the deciduous teeth in the fetus. Erythromycin is not recommended, because it may not treat the fetus adequately. Azithromycin is a promising oral agent for treatment; however, there have been several reported treatment failures and evidence of resistance. Because of reported treatment failures, resistance concerns and the lack of clinical data in pregnancy, azithromycin is not recommended for use in pregnant patients. Skin testing and referral for penicillin desensitization for the pregnant patient who has been proved to be allergic to penicillin is recommended. Desensitization can be accomplished either orally or intravenously (Table 48.1). Patients who undergo successful desensitization and treatment with penicillin will again require desensitization if penicillin is used in the future.

Treatment of the newborn with congenital syphilis should consist of 100,000–150,000 units/kg/day of aqueous crystalline penicillin G, given daily

Table 48.1 Oral desensitization protocol for patients with a positive skin test.*†
 (Reprinted by permission of the *New England Journal of Medicine*, from Wendel GD, Stark RJ, Jamison RR, *et al.* Penicillin infections during pregnancy. *N Engl J Med* 1985;312:1229.)

Penicillin V suspension dose‡	Amount (units/mL)	mL	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

*Observation period, 30 min before parenteral administration of penicillin.

†Interval between doses, 15 min; elapsed time, 3 h 45 min; cumulative dose, 1.3 million units.

‡The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

at 50,000 units/kg/dose every 12 h, or 50,000 units/kg of procaine penicillin, given intramuscularly once daily for 10 days.

PREVENTION

The mainstays of prevention for congenital syphilis are early detection, appropriate treatment, and follow-up. All pregnant women should have serologic testing for syphilis at their first prenatal visit and, for women in high-risk areas, again in the third trimester of pregnancy. Many states also require maternal serologic screening at delivery. The CDC currently recommends that all seropositive pregnant women should be considered to be infected and treated unless a history of adequate treatment is obtained and confirmed with serologic antibody titers. Finally, all patients with syphilis should be counseled about the risks of HIV infection and be encouraged to be tested for the HIV antibody.

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Rubella

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INTRODUCTION

Rubella virus infection is acquired via the upper respiratory tract through inhalation of aerosol. The virus replicates first in the lymphoid tissue of the nasopharynx and respiratory tract. Infection is then disseminated through the blood circulation involving multiple organs, including the skin and the placenta. Infection with rubella during the first 5 months of pregnancy can result in severe fetal damage or death. The mother with rubella may have no symptoms at all (30%) or a mild 3-day rash with posterior auricular adenopathy. However, the child may have severe congenital heart damage, cataracts, deafness, damage to major blood vessels, microcephaly, mental retardation, or other abnormalities, as well as severe disease during the newborn period, including thrombocytopenia, bleeding, hepatosplenomegaly, pneumonitis, or myocarditis. The risk of major fetal damage varies with the time of maternal infection: 80–90% if infection occurs in the first 3 months of pregnancy; 10% in the fourth month; and 6% in the fifth month, often as isolated hearing impairment. There is probably no risk after the fifth month.

DIAGNOSIS

Exposure

If a susceptible woman is exposed to rubella, she is expected to develop the infection in 2–3 weeks, and antibody shortly thereafter. To document the infection, collect paired sera and test for antibody. The first specimen should have no antibody; the second specimen, taken approximately 4 weeks after exposure, would have significant antibody.

The tests for IgM or rubella antibody can also be used to document recent rubella following exposure or subclinical rubella when only a late serum specimen is available. This test becomes positive shortly after the onset of rash and remains positive for approximately 4 weeks.

Clinical or subclinical rubella

In the event a woman has a rash similar to rubella and might be pregnant, serologic testing is important. The serum taken at that time may already have a significant level of antibody, and it may be impossible to demonstrate a significant increase in antibody compared with a serum taken 2 weeks later. However, it is possible to test the latter serum for IgM antibody to rubella. This antibody appears just at the end of the rash and is present for approximately 4 weeks. The presence of IgM rubella antibody documents recent rubella. If clinical or subclinical rubella is diagnosed, the woman can be counseled on the basis of the risk of severe damage to the fetus.

Infected persons excrete high concentrations of the virus with their nasopharyngeal secretions for approximately 10 days before the onset of the rash and for approximately 2 weeks after its onset.

Congenital rubella infection

Infants with congenital rubella commonly shed high concentrations of rubella virus from body secretions for several months. To make a serologic diagnosis of congenital rubella in the infant, antibody titers in serum from both infant and mother need to be tested. In the infant, sequential rubella antibody titers are necessary to exclude passively acquired maternal antibody.

Diagnostic procedures and tests for prenatal diagnosis include placental biopsy at 3 months, rubella antigen immunohistochemistry, cordocentesis, and rubella detection by fluorescence *in situ* hybridization or polymerase chain reaction (PCR).

MANAGEMENT

Passive immunization

Routine use of immunoglobulin for rubella postexposure prophylaxis in pregnant susceptible women after exposure to rubella is not recommended. Immunoglobulin has been shown to suppress symptoms; however, it does not prevent viremia, and congenital rubella infections have occurred despite immediate postexposure use of immunoglobulin. It should be considered for exposed women when termination of the pregnancy is not an option.

Active immunization

The primary approach to the prevention of rubella infection is immunization (in the USA the RA 27/3 vaccine). This should protect the individual from rubella infection. Vaccine for measles, mumps, and rubella should be given to all children between 12 and 15 months of age and repeated at school age. Also, all women of childbearing age should be tested for antibody to rubella. If the woman does not have a significant level of antibody and is not pregnant, the vaccine should be given. If the woman is pregnant, she should not receive

the vaccine. If she is not pregnant and receives the vaccine, she should be instructed not to become pregnant for 3 months. These reservations are based on the remote possibility that the vaccine virus might damage the developing fetus if given to the mother early in pregnancy.

Data from the Centers for Disease Control (CDC) for over 800 susceptible pregnant women who inadvertently received the rubella vaccine during early pregnancy showed no evidence of rubella-related fetal damage. However, two children had immunoglobulin M (IgM) rubella antibody, indicating that fetal infection had occurred. The maximum theoretical risk for fetal damage could be approximately 2%; the currently observed risk is reported as zero.

Women who are to be immunized should be informed that they may experience transient rash and arthralgia after receiving the vaccine. Other members of the household who have received rubella vaccine may have vaccine virus isolated from their pharynx, but do not transmit to others, likely because of the low quantity of rubella virus shedding.

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Group B streptococcus

Mara J. Dinsmoor

INTRODUCTION

Between 10 and 30% of pregnant women are colonized with group B streptococcus (GBS), formally known as *Streptococcus agalactiae*. Colonization may result in symptomatic infection in some women, most commonly manifested as chorioamnionitis, postpartum endometritis, or urinary tract infections. Intrapartum and postpartum bacteremia may also occur in the face of maternal infection. Neonates may be colonized and develop symptomatic infections via transmission from the mother or by contact transmission in the nursery. These neonatal infections, including localized infections, meningitis, or septicemia, carry a high risk of sequelae and are potentially fatal.

PATHOPHYSIOLOGY

Carriage of GBS may be intermittent, and risk factors for maternal GBS colonization have been inconsistent in prior reports, although African-American women and non-smokers appear to be at higher risk. However, risk factors for transmission to, and subsequent infection of, the neonate are well characterized. They include prematurity (less than 37 weeks' gestation), prolonged membrane rupture (more than 18 h), and fever in labor (over 100.5°F). The increased risk with prematurity is thought to be a result of incomplete GBS antibody transfer across the immature placenta. The latter two risk factors are probably related to prolonged contact with the organism and increased colony counts in the presence of infection. Having a prior infected neonate is also a risk factor for having subsequent infected babies. Overall, the risk of neonatal colonization following delivery to a colonized mother, in the absence of treatment, is approximately 50%. Up to 2% of these infants will develop symptomatic disease, so that the overall risk of neonatal disease following delivery to a colonized mother is less than 10 in 1000 exposed births, and is as low as 1–2 in 1000 in term neonates (Table 50.1).

There are five major serotypes of GBS (Ia, Ib, II, III, and V), and all appear capable of causing both maternal and neonatal disease. Serotype III is found in

Table 50.1 Rate of early onset neonatal group b streptococcus (GBS) sepsis in the presence of maternal colonization and/or risk factors (prematurity, prolonged membrane rupture, fever in labor). (Adapted from Boyer and Gotoff, 1985.)

Maternal colonization	Risk factor(s)	Attack rate per 1000 births
Present	Present	40.8
Present	Absent	5.1
Absent	Present	0.9
Absent	Absent	0.3

most cases of late onset disease. Babies born to mothers who do not have antibodies to types II and III appear to be at increased risk for developing GBS disease. Because of its predominance in neonatal infections, efforts at creating an effective vaccine have focused on serotype III.

DIAGNOSIS

The most accurate mode of diagnosis of GBS is by means of a culture. Although GBS will grow on ordinary blood agar, use of selective media will increase the detection of GBS by approximately 50%. For this reason, it is currently recommended that all GBS cultures be performed on sheep blood agar following incubation in selective broth medium. Examples include Todd–Hewitt broth supplemented with antibiotics and the commercially available media, Trans-Vag broth supplemented with 5% defibrinated sheep blood or LIM broth.

Most GBS cultures are performed in the setting of late pregnancy (35–37 weeks' gestation), in an attempt to identify colonized women, so that they may be offered intrapartum antibiotic prophylaxis. The highest yield is obtained when the culture is obtained from the distal vagina and the rectum. Swabbing only the cervix or vaginal fornix will fail to detect approximately 50% of colonized women. GBS is also frequently isolated from amniotic fluid cultures obtained during the evaluation of patients with suspected subclinical or clinical intra-amniotic infection.

In the postpartum period, GBS is commonly found in endometrial cultures from patients with postpartum endometritis. Some patients with uterine infections with GBS will also have bacteremia with the same organism. GBS rarely causes endocarditis in immunocompetent patients, but there have been case reports of endocarditis resulting from GBS.

Although a number of rapid tests for the detection of GBS have been evaluated, none have proven adequately sensitive for clinical use. A new polymerase chain reaction (PCR) based test is currently under review, but is not widely available and is prohibitively expensive even in those institutions with PCR technology available.

TREATMENT

The recommended treatment regimens for intrapartum GBS prophylaxis are outlined in Table 50.2.

The treatment of clinically evident GBS infection depends somewhat on the clinical context in which it is identified. Appropriate antibiotic choices include penicillin, ampicillin, and first-generation cephalosporins. Because there has been increasing resistance of GBS strains to clindamycin and erythromycin, treatment of the penicillin-allergic patient should be based, if at all possible, on the results of sensitivity testing of the isolate. Up to 20% of GBS strains may be resistant to either clindamycin or erythromycin. The practitioner should also be mindful of the poor placental transfer of erythromycin when choosing this drug to treat any maternal infection that may potentially be transmitted to the fetus *in utero*. Vancomycin is another appropriate antibiotic choice for the penicillin-allergic patient, although concerns regarding the selection of vancomycin-resistant enterococcus should temper its use.

The Centers for Disease Control and Prevention currently recommend obtaining vaginal or rectal cultures in pregnant women between 35 and 37 weeks' gestation. Mothers who are colonized should be offered intrapartum antibiotic prophylaxis (IPAP), with penicillin being the preferred agent (Table

Table 50.2 Recommended regimens for intrapartum antibiotic prophylaxis.* (Adapted from the Centers for Disease Control, *MWWR*, 2002.)

Recommended	<i>Penicillin G</i> : 5 million units i.v. followed by 2.5 million units i.v. every 4h
Alternative	<i>Ampicillin</i> : 2g i.v. followed by 1g i.v. every 4h
<i>PCN allergy</i>	
Not high risk for anaphylaxis	<i>Cefazolin</i> : 2g i.v. followed by 1g i.v. every 8h
High risk for anaphylaxis (history of immediate hypersensitivity or history of anaphylaxis; underlying medical problems such as asthma that would make anaphylaxis potentially more dangerous or difficult to treat)	<i>Clindamycin</i> : 900 mg i.v. every 8h or <i>Erythromycin</i> : 500 mg i.v. every 6h
GBS resistant to clindamycin or erythromycin, or sensitivities unknown	<i>Vancomycin</i> : 1g i.v. every 12 h

*All antibiotics to be discontinued following delivery, in the absence of the clinical diagnosis of maternal infection.

50.2). Patients with unknown GBS colonization status who are less than 37 weeks' gestation should also be offered IPAP. All mothers who have previously delivered a baby infected with invasive GBS disease or had an antepartum urinary tract infection with GBS, should be offered IPAP, and the antepartum GBS culture may be eliminated. GBS cultures are also unnecessary in patients who are planning a scheduled repeat cesarean section, and IPAP is not indicated in the absence of labor and/or rupture of the membranes in these patients.

In laboring patients for whom antepartum GBS culture results are not available, patients should be offered IPAP in the presence of risk factors for invasive GBS disease (i.e. prolonged membrane rupture or fever in labor). Ideally, women with fever in labor should be treated for clinical chorioamnionitis, with a broad-spectrum antibiotic regimen that includes coverage for GBS, such as ampicillin and gentamicin.

PREVENTION

Although the CDC algorithm outlined above has reduced the incidence of early onset neonatal GBS sepsis by 50–80%, there are persistent cases that still occur. Some are a result of a false-negative maternal antepartum culture, while others are a result of “protocol violations” (i.e. the failure to administer appropriate or adequate antibiotic prophylaxis). Some babies will develop GBS sepsis despite appropriate and timely intrapartum antibiotic treatment. Although prevention of GBS sepsis appears to be effective, whether or not the overall incidence of early

Table 50.3 Suggested treatment of the asymptomatic colonized mother.

Site of GBS isolation	Treatment	Rationale
Urine	Ampicillin 500 mg t.i.d. × 7 days	Reduction in PTB
<i>Vaginal/rectum</i>		
Antepartum	None	No benefit of treatment
Intrapartum	IPAP	Reduces neonatal colonization and infection
PPROM		
antepartum	Intravenous broad-spectrum antibiotics with Gram-positive coverage	Prolongs latency period
intrapartum	IPAP	Reduces neonatal colonization and infection

GBS, group B streptococcus; IPAP, intrapartum antibiotic prophylaxis; PPRM, premature preterm rupture of the membranes; PTB, preterm birth (<37 weeks).

onset neonatal sepsis is decreasing is somewhat controversial. Some institutions are reporting increases in neonatal infections with Gram-negative organisms, particularly *Escherichia coli*, particularly in low birth weight babies.

CONCLUSIONS

GBS is commonly isolated in maternal and neonatal infections, and can potentially lead to mortality and serious morbidity. However, since 1994, when the initial draft of the CDC guidelines for the prevention of GBS disease was released, the incidence of neonatal early onset GBS sepsis has been declining. Although not well studied, maternal GBS disease may also be reduced by prenatal screening and intrapartum treatment. However, the long-term effects of such widespread antibiotic use remain unclear.

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Toxoplasmosis

Shad Deering

INTRODUCTION AND PATHOPHYSIOLOGY

The incidence of acute infection with *Toxoplasma gondii*, a protozoan parasite, during pregnancy in the USA has been estimated to be 0.2–1.0%. The majority of these cases go undiagnosed because as many as 90% are either asymptomatic or presumed to be from a viral illness.¹ It is contracted by ingesting raw or undercooked meat that contains *T. gondii* tissue cysts or other foods contaminated with viable organisms in either tachyzoite or bradyzoite form. These mechanisms account for nearly 50% of acute toxoplasma infections in pregnancy.² The parasite may also be transmitted by the inhalation of dust contaminated with *T. gondii* oocysts, which may occur during gardening or when changing a cat's litter box. The sequelae of congenital toxoplasmosis may be severe and include fetal death, blindness, deafness, and mental retardation. In addition, at birth, infected children may have a maculopapular rash, hepatosplenomegaly, seizures, or hydrocephalus.

Patients who are infected prior to conception are not at risk for fetal infection, and transmission to the fetus is generally limited to cases in which women acquire a primary infection during pregnancy. The risk of transmission to the fetus is dependent on the trimester during pregnancy that infection occurs. In a French study that tested seronegative women on a monthly basis, it was demonstrated that the risk of congenital infection increases as the pregnancy progresses.³ The risk at 13 weeks' gestation was only 6% and then increased rapidly to 40% at 26 weeks, 72% at 36 weeks, and 81% when an active infection occurred just before delivery at term. However, the risk of the child developing clinical signs of toxoplasmosis, such as hydrocephalus or retinochoroiditis, before the age of 3 years is inversely correlated with the gestational age when maternal seroconversion occurs. This risk is highest when infection occurs in the first trimester, estimated in one study to be nearly 61% at 13 weeks, and declines to only a 9% risk at term.³ If the risk of congenital infection at a specific gestational age is multiplied by the risk of clinical signs

of congenital infection occurring, the overall risk for having a child with clinical evidence of toxoplasmosis may be calculated. This risk is approximately 2% in the first trimester, increases to a maximum of nearly 10% around 28 weeks, and then declines to around 4% at term.⁴

At this time, issues concerning which women to screen, optimal methods for prenatal diagnosis of congenital toxoplasmosis, and treatment remain controversial.

DIAGNOSIS

Maternal infection

Approximately 90% of cases of toxoplasmosis are unrecognized either because of the mildness of symptoms or because they are mistaken for a viral infection. The most common clinical sign is bilateral non-tender lymphadenopathy which often involves the posterior cervical nodes. Additional symptoms that may be confused with a viral illness include generalized fatigue, myalgias, fevers, and headaches. In immunocompetent patients, the illness is almost always self-limited.

Infection with *T. gondii* should be suspected whenever a pregnant woman has non-specific viral symptoms in association with any of the risk factors mentioned previously. A relatively high index of suspicion is required in order to make the diagnosis.

Laboratory diagnosis

Infection with *T. gondii* can be diagnosed by culture, direct antigen detection in infected tissue, or serologic tests. Direct specimen culture and direct antigen detection methods are not widely available, are difficult to perform, and may be inaccurate. Although serologic testing has its drawbacks, including difficulty with reliability in the assay and interpretation, this is currently the preferred method for diagnosis.

Serologic tests for immunoglobulin (Ig) G and M antibodies should be obtained in patients who have symptoms suggestive of toxoplasmosis. IgG antibodies generally appear within 1–2 weeks of infection, and will peak at 6–8 weeks, and then decline over a period of approximately 2 years, but remain detectable for life. IgM antibodies appear within the first week of infection and then will usually decline over several months. It is important to note, however, that IgM antibodies may persist for years, and their presence is not necessarily indicative of an active or recent infection.

A positive IgG titer is evidence of either a recently acquired or a past infection. If a patient was known to be seronegative before pregnancy, the presence of a positive IgG antibody against *T. gondii* is evidence of a current or recent infection. Seroprevalence studies indicate that as many as 45% of healthy adults in the USA have been infected with *T. gondii*.

Immunoglobulin M antibodies may help to diagnose acute infection. However, IgM antibody titers may remain detectable for years. Thus, a single positive IgM result does not establish acute infection. In most cases, it is necessary to demonstrate a rise in antibody titer in serial serum specimens, preferably obtained at least 3 weeks apart, which are tested in parallel. The reliability of commercially available kits for IgM *T. gondii* antibodies varies considerably, thus, ideally, the serum samples should be tested and evaluated by an experienced reference laboratory. At these laboratories, a combination of tests, including the Sabin–Feldman dye test and IgM, IgA, and IgE ELISA results may be helpful in determining a recent or distant infection. One such laboratory is the Palo Alto Medical Foundation Research Institute’s Toxoplasma Serology Laboratory (650-326-8120).

A study by Liesenfeld *et al.*⁵ demonstrated that when a reference laboratory was used for over 800 serum samples submitted for evaluation, only 39% were considered likely to have had a recent infection. This study also showed that significantly fewer (0.4% vs 17.2%; $P < 0.001$) women had an abortion when notified that their infection was probably in the more distant past than a recent event. Table 51.1 illustrates the potential antibody test results and their interpretation and management.

Fetal infection

After maternal infection is documented, an attempt is made to determine if the fetus has been infected. The incidence of congenital infection is greatest when maternal infection occurs in the third trimester, but the risk of the child developing clinical symptoms after birth is higher the earlier in pregnancy the infection occurs.

Table 51.1 Maternal serum antibody results and interpretation.

Maternal serum antibodies	Interpretation/action
IgG ⁻ /IgM ⁻	No evidence of infection
IgG ⁻ /IgM ⁺	Possible current/recent infection (within 2 weeks) Send serum for confirmation to reference laboratory
IgG ⁺ /IgM ⁻	Probable past infection (unless known to be IgG ⁻ previously)
IgG ⁺ /IgM ⁺	Possible current/recent infection Send serum for confirmation to reference laboratory and/or recheck titers in approximately 3 weeks. If titers increasing, this is evidence of current/recent infection

Laboratory diagnosis

Prenatal diagnosis of congenital toxoplasmosis is possible. Amniocentesis, percutaneous umbilical blood sampling, or cordocentesis, mouse inoculation, and ultrasound examination have all been used for prenatal diagnosis.

Amniocentesis

Polymerase chain reaction (PCR) testing of the amniotic fluid is the most accurate, and recommended, method available for diagnosing fetal infection. This is generally performed in the second trimester or 4 weeks after an acute maternal infection. In a study of 122 women with seroconversion during pregnancy, the sensitivity and specificity of PCR on the amniotic fluid was 81% and 96%, respectively.⁶ Another study of more than 250 women, with serologic follow-up of the newborns, reported a positive predictive value of 100%, but a negative predictive value of only 88%, which indicates that a negative PCR cannot completely exclude the diagnosis of congenital toxoplasmosis.⁷ When counseling a patient regarding amniocentesis, it is important to discuss the potential procedure-related fetal loss rate of approximately 1% versus the risk of fetal infection, which is dependent on the gestational age.

Cordocentesis

The detection of *T. gondii* in fetal blood also offers evidence of fetal infection. Fetal blood obtained by cordocentesis may be analyzed for the presence of specific IgM and IgA antibodies. This method has drawbacks, however, in that the fetal loss rate is higher than with amniocentesis and specific fetal antibodies are not likely to be detected before 20–22 weeks' gestation. In addition, the fetal immune response may be weak and no antibodies detected even when an infection is present.

Mouse inoculation

Mouse inoculation can be used to isolate the parasite, using either amniotic fluid or fetal blood. However, this route of diagnosis may take 3–6 weeks and is not felt to be sensitive enough for routine use.

Sonographic examination

There are multiple sonographic abnormalities that may be seen with congenital toxoplasmosis; however, these are only suggestive of fetal infection and not diagnostic. These abnormalities include the following:

- Ventricular dilation
- Intracranial calcifications
- Increased placental thickness
- Hepatomegaly and/or intrahepatic calcifications

- Fetal ascites
- Pericardial or pleural effusions

In a study by Hohlfeld *et al.*,⁸ 36% of 89 patients with congenital toxoplasmosis showed abnormal morphologic signs on prenatal ultrasound examination. The most common abnormality was ventricular dilation, usually bilateral and symmetric. It was noted to evolve rapidly over a period of a few days. Thus, serial ultrasound examinations of an infected fetus may be helpful.

TREATMENT

The rationale for treatment of women with *Toxoplasma* infection during pregnancy is that it has been shown to reduce the incidence of severe sequelae (odds ratio 0.14, 95% confidence interval 0.036–0.584) and that the shorter the interval between diagnosis and treatment, the lower the incidence of sequelae.⁹ Neither the time between diagnosis and treatment with antibiotics nor the actual administration of maternal antibiotics appears to affect the rate of transmission to the fetus. This finding may be a result of transmission of the infection to the fetus during the time of parasitemia, which may be over by the time seroconversion occurs. Randomized trials in this area are currently lacking.

Once maternal infection is confirmed, treatment is started with spiramycin (1 g p.o. every 8 h without food). This antibiotic is similar to erythromycin and concentrates in the placenta. This drug is not available commercially in the USA; however, it can be obtained with the permission of the US Food and Drug Administration. Because it does not cross the placenta, if there is evidence of fetal infection, as diagnosed by amniocentesis and PCR, additional treatment is given. If the PCR is negative for fetal infection, spiramycin is generally continued until delivery.

When fetal infection is confirmed, treatment is changed in favor of medications that cross the placenta and penetrate the fetal brain and cerebrospinal fluid. This includes both pyrimethamine and sulfadiazine.

Pyrimethamine and sulfadiazine are both folic acid antagonists that work synergistically against the *T. gondii* parasite. Because these medications have been shown to be teratogenic in rats at doses similar to those given to humans, these are only administered from the second trimester onwards and supplementation with folic acid (10–25 mg/day) is given. Complications of these medications may include anemia, reversible acute renal failure, bone marrow suppression, and thrombocytopenia. Because of these potential side-effects, weekly monitoring of maternal complete blood and platelet counts should be carried out, with discontinuation of treatment if any of these events occur. Some common regimens are as follow:

- 1 Pyrimethamine (50 mg/day p.o.) + sulfadiazine (1 g p.o. t.i.d.) + folic acid (10–25 mg/day p.o.) for 3 weeks alternating with 3 weeks of spiramycin (1 g p.o. t.i.d.). This regimen is continued until term.

2 Pyrimethamine (25 mg/day p.o.) + sulfadiazine (2 g p.o. b.i.d. or 1 g p.o. q.i.d.) + folic acid (10–25 mg/day p.o.) given until delivery.

Alternative treatments that have been reported include azithromycin or clarithromycin in place of spiramycin or trimethoprim–sulfamethoxazole for women intolerant of pyrimethamine. To date, there are no significant clinical trials to demonstrate the efficacy of these treatments. Of note, when a woman becomes infected after 32 weeks' gestation, some hospitals will begin treatment with pyrimethamine and sulfadiazine immediately rather than spiramycin because of the increased risk for fetal transmission.

When maternal and/or fetal infection is confirmed, the patient may be offered counseling regarding the risk of serious congenital infection in light of the information presented and some patients will choose pregnancy termination. Because the risk of fetal transmission is low in the first trimester, it is prudent to perform amniocentesis with analysis of the amniocytes by PCR and send maternal serum to a reference laboratory before making any recommendations for pregnancy termination.

COMPLICATIONS

Complications from *Toxoplasma* infection are all related to the fetus if the mother is not immunocompromised. These may include fetal death, blindness, deafness, hydrocephalus with mental retardation, hepatosplenomegaly, and seizures.

FOLLOW-UP

After maternal infection is diagnosed, an amniocentesis is planned for the second trimester, at least 4 weeks after the acute infection, and spiramycin is started. Additional follow-up with ultrasound to monitor for the appearance of any sonographic markers of intrauterine infection should also be scheduled.

PREVENTION

- 1** Pregnant women should avoid eating raw or undercooked meat (it should be cooked up to 152°F or frozen for a day in a home freezer) and to wash hands thoroughly after handling raw meat.
- 2** Avoid eating unpasteurized milk or raw eggs.
- 3** Wash all fruits and vegetables prior to eating.
- 4** Have a non-pregnant person change the cat's litter box every day.
- 5** Avoid or wear gloves when gardening in dirt that might contain cat feces. Wash hands after contact with soil.

CONCLUSIONS

Toxoplasmosis is a relatively common infection that is often overlooked in healthy pregnant women. Appropriate follow-up testing to confirm both mater-

nal and/or fetal infection is key, and early antibiotic treatment may decrease the incidence of severe sequelae for those fetuses that do have congenital toxoplasmosis.

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Varicella

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EPIDEMIOLOGY

In temperate climates varicella is a childhood disease, while in tropical climates the primary infection with varicella commonly occurs later in life on average. In the USA, approximately 95% of adults are immune to varicella and fewer than 2% of reported cases occur in persons 20 years of age or older.

Primary infection with varicella-zoster virus (VZV) manifests as varicella (chickenpox). Herpes zoster (shingles) is an eruption that results from reactivation of latent VZV infection of dorsal root ganglia. Humans are the only source of infection with VZV. The virus is highly contagious and transmission occurs primarily through airborne spread from respiratory tract secretions and very rarely through contact with zoster lesions.

Asymptomatic primary varicella infection is unusual, but VZV symptoms can be discrete and are not recognized. Patients are most contagious from 1–2 days before to shortly after onset of the rash. The incubation period usually is 14–16 days, occasionally as short as 10 days or as long as 21 days after contact. It may be prolonged for as long as 28 days after use of varicella-zoster immunoglobulin (VZIG).

Clinical diagnosis

Clinical findings alone usually permit a diagnosis of varicella. On average 14 days (range 10–21 days) after exposure to varicella, susceptible individuals develop fever, malaise, and a pruritic rash. The rash, mostly truncal, includes crops of maculopapules that rapidly form vesicles, which eventually crust. New lesions continue to appear for 3–5 days. Lesions at various stages of development can be seen in the same anatomic area at the same time.

Herpes zoster

Painful skin lesions over the areas of distribution of one or more sensory nerve roots are characteristic. The eruption is usually unilateral but may sometimes cross the midline. Lesions evolve similarly to those of varicella.

Maternal complications of VZV infection during pregnancy

The estimated incidence of gestational varicella is 1–7 cases per 10,000 pregnancies. For shingles, the estimated incidence is only 0.5 cases per 10,000 pregnancies. In addition to the higher incidence of VZV complications during primary infection in adults, there is no further increased risk resulting from pregnancy.

VZV pneumonitis

VZV pneumonitis can develop in as many as 14% of pregnant women with varicella infection, most commonly 2–6 days after the rash appears. The pneumonitis can be mild or patients can present with severe dyspnea, hemoptysis, pleuritic chest pain, and cyanosis, requiring mechanical ventilation. Mortality ranges between 3% and 40%, depending on time of initiation of early antiviral therapy.

Neurologic complications

VZV encephalitis is characterized by depressed consciousness, progressive headaches, vomiting, and seizures. Maternal mortality is 5–20%, and as many as 15% of survivors may present with long-term neurologic deficits. Other neurologic manifestations include aseptic meningitis, Guillain–Barré syndrome, Reye syndrome, stroke, and transverse myelitis.

Secondary infections

Bacterial superinfection can lead to cellulitis and progress to abscess formation or necrotizing fasciitis. Etiologic agents are usually *Streptococcus pyogenes* or *Staphylococcus aureus*.

Other complications

Less common complications are bleeding diathesis, arthritis, pericarditis, acute retinal necrosis, and glomerulonephritis in the course of VZV infection.

LABORATORY DIAGNOSIS

Culture

VZV can be isolated from vesicular fluid by inoculating freshly collected specimens onto human diploid cell lines, usually during the first 3–4 days of the eruption in immunocompetent patients or from blood 1–11 days before the appearance of the rash.

Antigen detection

VZV-specific antigens can be detected in vesicular fluid by immunofluorescence staining of smears of cell scrapings collected from the base of fresh vesicles.

Molecular techniques

VZV deoxyribonucleic acid (DNA) can be found by polymerase chain reaction (PCR) in vesicle samples, including most crusted lesions. PCR can also be used to detect VZV DNA in blood or other body fluids.

Serologic diagnosis

The most commonly employed techniques are the enzyme-linked immunosorbent assay (ELISA), the fluorescent antibody against membrane antigen (FAMA), the immune adherence hemagglutination test, and the indirect fluorescent antibody assay. At present, the ELISA test is the most commonly used method for VZV antibody detection. ELISA is sensitive and specific and the results correlate well with those obtained by the more labor-intensive FAMA assay. The complement fixation (CF) test is too insensitive and is unsuitable for susceptibility testing; approximately two-thirds of individuals have no detectable CF antibody titers within 1 year of infection. Collecting two serum samples 1–2 weeks apart can provide a diagnosis if seroconversion or a four-fold rise in antibody titer is demonstrated. Caution should be exercised in interpreting serologic data. Up to one-third of individuals who have had a previous VZV infection will show an antibody rise if they develop a primary herpes simplex virus (HSV) infection. Thus, it is important to document the lack of an antibody titer rise to HSV before making a final diagnosis.

Detection of VZV-specific immunoglobulin M (IgM) antibodies is useful for documenting a recent infection. VZV-specific IgM antibodies can persist in serum for several weeks after varicella and may be transiently found after herpes zoster.

PROPHYLAXIS AND TREATMENT

In immunocompetent patients, most virus replication has stopped 3 days after onset of the rash.

Administration within 24 hours of the onset of rash results in only a modest decrease in symptoms. Oral acyclovir should be considered for immunocompetent patients only when older than 12 years of age, with chronic cutaneous or pulmonary disorders, long-term salicylate therapy, or treatment with corticosteroids, because of the expected increased risk of moderate to severe varicella.

Oral acyclovir is not recommended routinely for pregnant women with uncomplicated varicella, because the risks and benefits to the fetus and mother are unknown. It can be considered for pregnant women with varicella, especially during the second and third trimesters. Intravenous acyclovir is recommended for pregnant women with serious complications of varicella and for immunocompromised patients.

Famcyclovir and valacyclovir have been licensed for adults with zoster. Famcyclovir is the pro-drug of pencyclovir, which has a longer intracellular half-

life than acyclovir. Valacyclovir is a pro-drug of acyclovir and achieves higher plasma levels. Acyclovir-resistant VZV can be treated with foscarnet.

Uncomplicated chickenpox

Wound cleansing and use of antipruritics is important. Aveeno® (Johnson & Johnson Consumer Companies Inc.) baths or by topical application of calamine or Sarna® (combination of 0.5% camphor and 0.5% menthol; Stiefel Laboratories, Inc.) lotions can be used to decrease pruritus.

Varicella pneumonia

Isolation and supportive care with supplemental oxygen, mechanical ventilation, and intravenous acyclovir at 10–15 mg/kg every 8 h for 7 days. No increase of birth defects among infants born to women exposed to acyclovir during pregnancy has been reported. VZIG is not beneficial.

Varicella encephalitis

Supportive care and anticonvulsant therapy as needed. Acyclovir has not been shown to be effective.

Herpes zoster (shingles)

Uncomplicated cases can be treated with local application of heat, wet compresses, topical Burow's solution (aluminium acetate solution), calamine lotion, or ethyl chloride spray and symptomatic pain relief. Acyclovir should be considered for women with ophthalmic or disseminated zoster. Famcyclovir has not been used in pregnant women and its efficacy in ophthalmic or disseminated zoster has not been studied. VZIG has no proven benefit.

Prophylaxis

Exposure of susceptible people

Give VZIG (1 dose up to 96 h after exposure) or varicella vaccine (1 dose up to 72 h after exposure). A 7-day course of acyclovir may be given to susceptible adults 7–9 days after varicella exposure if vaccination is contraindicated or more than 72 h has elapsed from the time of exposure.

Hospital exposure

Discharge exposed susceptible patients as soon as possible. Place all other exposed patients in isolation from day 8 to day 21 after exposure, or 28 days when VZIG has been given.

Exposure during pregnancy

If a pregnant woman who has a negative or uncertain history of varicella has significant exposure, test her for susceptibility, provided sensitive assays are

available and results can be obtained quickly. Positive ELISA or FAMA results indicate past infection and immunity. For susceptible or exposed women without serology test results, administer VZIG to prevent or moderate maternal infection. It is not known whether maternal treatment with VZIG has a protective effect for the fetus. Infants born to mothers who develop varicella between 5 days before and 2 days after delivery should receive 125 IU VZIG to ameliorate a potentially serious infection.

Passive immunization

VZIG is given by intramuscular injection or intravenously when bleeding disorder is present. One vial (approximate volume, 1.25 mL, containing 125 IU) is given per 10 kg body weight. The suggested maximal dose of VZIG is 625 IU (i.e. 5 vials).

VZIG is most effective when given as soon as possible after exposure but no later than 96 h. Its effectiveness if given later has not been determined, but is believed to be reduced.

A thorough history of varicella should be used to establish immunity in immunocompromised patients. It is recommended to give VZIG to exposed immunocompromised patients with no history of varicella, regardless of serologic test results. The duration for which VZIG recipients are protected against varicella is unknown. If a second exposure occurs more than 3 weeks after administration of VZIG in a person who did not develop varicella, another dose of VZIG should be given. VZIG is not recommended for exposure to persons with varicella vaccine rash, because transmission is rare and disease, if it were to develop, would be expected to be mild.

VZIG can be obtained by contacting the local American Red Cross Blood Services or FFF Enterprises (41093 County Center, Temecula, CA 92591; telephone, 800-843-7477).

Varicella vaccination

A live attenuated varicella vaccine (Varivax®, Merck & Co., Inc., Whitehouse Station, NJ) is available in the USA (licensed in March 1995). Varicella vaccine within 72 h and possibly up to 120 h after varicella exposure can prevent or significantly modify disease. Pregnancy is a contraindication to varicella vaccination. Varicella vaccine is safe; reactions generally are mild (injection site reaction, mild rash, fever) and occur with an overall frequency of approximately 5–35%. Varicella vaccine is contraindicated in any patient with a history of anaphylactic-type reaction to a component of the vaccine, including gelatine and neomycin. However, allergy to neomycin most commonly results in contact dermatitis, which is not a contraindication to immunization. The varicella vaccine does not contain preservatives or egg protein.

Fetal complications of VZV infection during pregnancy

VZV infection during pregnancy does not increase the risk of spontaneous abortion but may lead to preterm delivery to a modest degree.

Congenital varicella syndrome

The incidence of congenital varicella syndrome among infants born to mothers with varicella is approximately 2% when infection occurs before 20 weeks' gestation. Children exposed to VZV *in utero* during the second 20 weeks of pregnancy can develop inapparent varicella and subsequent zoster early in life without having had extrauterine varicella. *In utero* infection occurs through transplacental passage of virus during maternal varicella infection. VZV can cause focal necrotic areas in the placenta facilitating fetal infection. Fetal infection after maternal varicella during the first or early second trimester of pregnancy occasionally results in varicella embryopathy, characterized by cutaneous scars, denuded skin, limb hypoplasia, muscle atrophy, and rudimentary digits. Other more frequent abnormalities are microcephaly, intracranial calcifications, cortical atrophy, cataracts, chorioretinitis, microphthalmia, and psychomotor retardation.

Prenatal diagnosis by ultrasound and laboratory tests

The most frequent finding on ultrasonography is polyhydramnios. Fetal hydrops, deformities of hands or feet, hyperechogenic foci within the liver, and hydrocephalus are less common. VZV was detected in amniotic fluid at 22 weeks gestation in one case, while VZV-specific IgM was negative. In another case, VZV-specific IgM was detected in fetal blood at 32 weeks gestation. Tissues obtained by chorionic villus sampling from women with varicella during pregnancy may be positive for VZV DNA by PCR, but this does not denote fetal involvement.

Management

It is not known whether the administration of acyclovir to the mother will prevent or modify fetal VZV infection. There is no treatment for fetal VZV infection. Infants with varicella embryopathy are not considered infectious and therefore do not require isolation in the nursery or at home.

Perinatal varicella infection

Varicella infection can be fatal in infants of mothers who develop varicella 5 days before, up to 2 days after delivery. When the gestational age of the infant is more than 28 weeks, the severity of VZV infection in the neonate will be modified by transplacental transfer of VZV-specific IgG, when varicella manifests more than 5 days prior to birth. For postnatal VZV exposure, the average interval from onset of rash in a mother to rash manifestation in the neonate is 9–15 days.

Management

If neonates with varicella require hospitalization, they need to be kept in strict isolation. Intravenous acyclovir is used for infants with severe disease. VZIG has no therapeutic value once clinical varicella has developed.

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Tuberculosis

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INTRODUCTION

Tuberculosis (TB) has re-emerged as a serious health problem throughout the world. After years of decline following the introduction of effective chemotherapy, the incidence of TB in the USA has increased significantly since 1985. From 1985 through 1992, reported cases of TB increased by 20%. Also during that time, the number of TB cases in women of childbearing age increased by 40%.¹ Currently, up to 10% of women of childbearing age are tuberculin skin test positive. The increase in TB can be attributed to a number of factors including the epidemic of human immunodeficiency virus infection (HIV), the increase in immigrants from endemic areas, and the lack of an adequate infrastructure to deal with the large increase in TB cases.

The primary strategy for preventing and controlling TB in the USA is to minimize the risk for transmission by the early identification and treatment of patients with active infectious TB. The second most important strategy is the identification of persons with latent tuberculous infection (LTI) and, if indicated, isoniazid chemoprophylaxis to prevent LTI from progressing to active infectious TB.

PATHOPHYSIOLOGY

Tuberculosis is a chronic bacterial infection caused by *Mycobacterium tuberculosis* or *M. bovis*, which is transmitted by respiratory droplet and spread from person to person via air. Transmission of TB is dependent on the number and/or viability of bacilli in expelled air, susceptible host factors, environment/shared air, and duration and/or frequency of exposure.² Tuberculosis infection is characterized by primary infection in the lungs with the development of cell-mediated hypersensitivity and formation of granulomas. Extrapulmonary infection can occur. One of the striking characteristics of TB infection is the occurrence of a latency period which is followed by reactivation.²

Primary TB infection can be asymptomatic, can produce a typical primary complex, or result in typical chronic pulmonary TB without a demonstrable

primary complex. Early pulmonary TB is usually asymptomatic, and does not produce symptoms until the bacillary population has reached a certain size. When symptoms occur they range from non-specific constitutional symptoms such as anorexia, fatigue, weight loss, chills, afternoon fever, and when this subsides, night sweats. A productive cough is usually present, and hemoptysis can occur.²

Given the prevalence and resurgence of TB, current recommendations state that all pregnant women who are at high risk for LTI or active TB be offered purified protein derivative (PPD) skin testing. The prevalence of PPD positivity among pregnant women varies depending on risk factors of the population. Up to 21% of HIV-infected pregnant women have been reported to have positive PPD skin tests, and up to 1% had active TB disease.³ However, pregnancy does not appear to increase the risk for developing active TB in those at risk.⁴

Children born to women with active TB have an increased risk of morbidity and mortality in the neonatal period, with an increase in prematurity, perinatal death, and low birth weight.^{5,6} However, when adequate therapy is initiated, TB appears to have no adverse effect on the pregnancy.^{7,8} Most perinatal infections occur when a mother with active TB handles her infant,⁹ and the risk of the child contracting TB from a mother with active disease during the first year of life may be as high as 50%.¹⁰ Transplacental passage of TB is extremely rare.

DIAGNOSIS

Screening for asymptomatic or symptomatic TB infection can be performed by administration of tuberculous antigens and observing for a delayed, cell-mediated hypersensitivity response (Fig. 53.1).¹¹ The delayed hypersensitivity response can take up to 10 weeks to develop after exposure.² Administration of 0.1 mL PPD to create a 6–10 mm subdermal wheal will result in varying degrees of induration in an individual 48–72 h after administration. Based on the sensitivity and specificity PPD tuberculin skin testing and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin skin reaction: ≥ 5 mm, ≥ 10 mm, and ≥ 15 mm of induration (Table 53.1).¹² Most pregnant women diagnosed with TB are asymptomatic and are only detected because of PPD screening (Fig. 53.2),¹³ emphasizing the importance of screening. Pregnancy does not increase the risk for anergy, and thus an anergy panel is unnecessary in the HIV-negative pregnant woman.¹⁴

False-positive reactions can occur in individuals not infected with *M. tuberculosis*. This may be caused by cross-reaction with other mycobacteria, prior vaccination with bacillus Calmette–Guérin (BCG), or incorrect interpretation of test.¹¹ However, because most persons who have received BCG are from high-prevalence areas, and BCG vaccination protection is inconsistent and wanes

Purified protein derivative (PPD) skin testing offered to all high-risk pregnant when they initiate prenatal care

<p><u>High-risk factors</u></p> <p>HIV positive</p> <p>Known recent contact with TB</p> <p>Organ transplant recipient or other immunocompromised patient (receiving equivalent of >15 mg/day prednisone for > 1 month)</p>	<p><u>Intermediate risk factors</u></p> <p>Intravenous drug use</p> <p>Immigration from high prevalence area (Asia, Africa, Latin America) within 5 years</p> <p>Underserved population</p> <p>Resident of long-term care facility, prison or shelter</p> <p>Certain medical conditions</p> <p>Healthcare worker for above populations</p>
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Administer 0.1 mL PPD to raise 6–10 mm intradermal wheal and interpret test at 48–72 h after placement by measuring induration

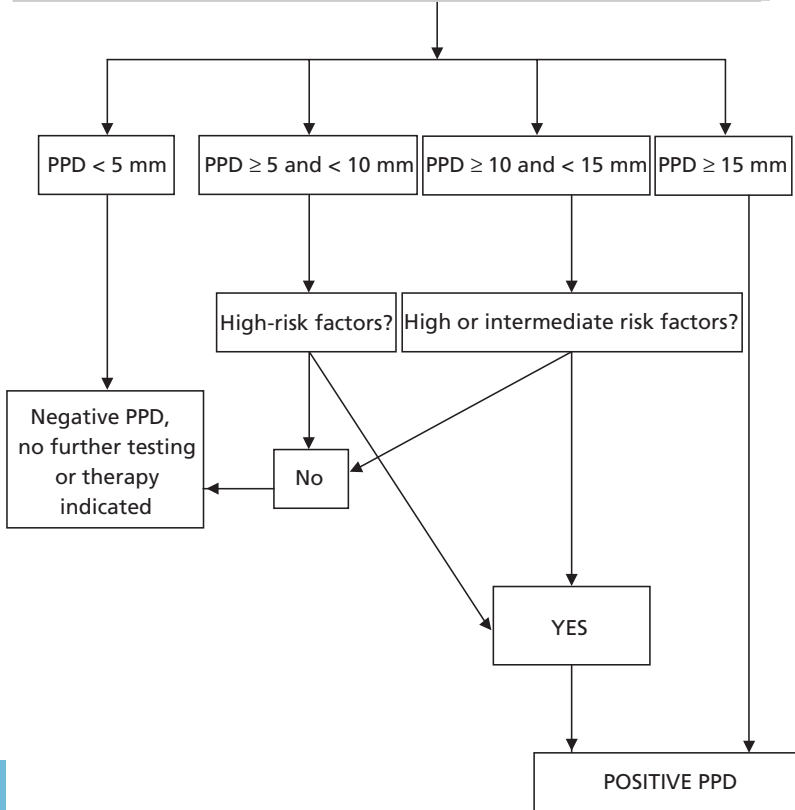


Fig. 53.1 Screening and diagnosis of tuberculosis during pregnancy.

Table 53.1 Interpretation of purified protein derivative (PPD) skin test.

Reaction \geq 5 mm induration	Reaction \geq 10 mm induration	Reaction \geq 15 mm induration
Human immunodeficiency virus (HIV) positive	Recent immigrants (i.e. within the last 5 years) from high-prevalence countries	Persons with no risk factors for TB
Recent contacts of TB case patients	Injecting drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees of high-risk settings: prisons, nursing homes and other long-term care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients	Mycobacteriology laboratory personnel and hospital workers Persons with: diabetes mellitus, silicosis, chronic renal failure, leukemia or lymphoma, lung or head and neck carcinoma, weight loss \geq 10% ideal body weight, gastrectomy, and jejunioileal bypass	

with time, persons who test positive by skin testing should be evaluated and managed accordingly, regardless of history of BCG vaccination.

The definitive diagnosis of TB is based on identifying *M. tuberculosis* by culture or acid-fast stain of the sputum. First morning sputum specimens obtained on 3 consecutive days are usually the best source for detecting TB and should be undertaken in those with symptoms of active TB and those with a positive PPD and abnormal chest X-ray.²

TUBERCULOUS INFECTION VERSUS TUBERCULOUS DISEASE

A positive PPD only means that the patient has been previously exposed to TB and that there are latent organisms present. Less than 10% of patients with a positive PPD and an intact immune system will progress to active disease.

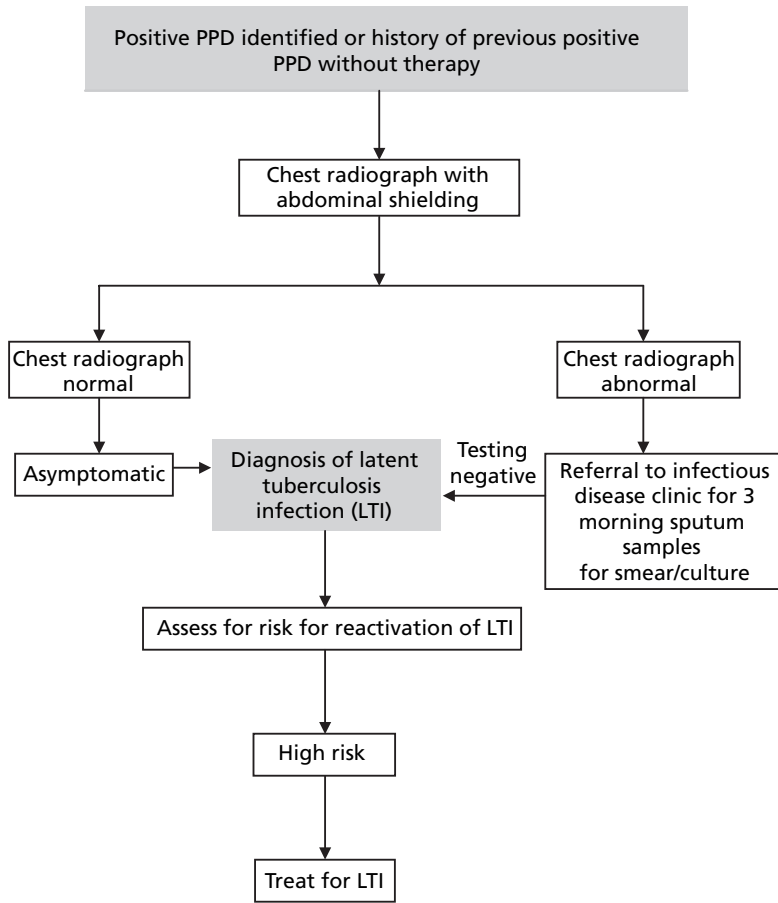


Fig. 53.2 Evaluation of positive purified protein derivative (PPD) skin test during pregnancy.

However, targeted tuberculin skin testing for LTI is a strategic component of TB control to identify persons at high risk for developing TB who would benefit by treatment of LTI, if detected. Persons with increased risk for developing active TB include those who have recent infection with *M. tuberculosis* and those who have clinical conditions that are associated with an increased risk for progression of LTI to active TB, such as HIV infection, injection drug use, chest radiograph evidence, or prior TB or chronic illness.^{15,16}

TREATMENT

Tuberculous disease

Untreated TB in pregnancy poses a significant threat to the mother, fetus, and family. Adherence to therapy during pregnancy is difficult because of concern regarding fetal toxicity and pregnancy-related nausea. The Advisory Council for the Elimination of Tuberculosis recommends initial treatment for non-pregnant patients with four drugs: isoniazid (INH), rifampin (RF), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin. Three of four first-line anti-TB drugs have an excellent safety record and are not believed to be associated with human fetal malformations. PZA is not recommended in pregnant women, as its effects on the fetus are unknown.^{12,17} Streptomycin should be avoided in pregnant women because it may cause congenital ototoxicity.^{12,17}

Latent tuberculous infection

Individuals with LTI who are at high risk for progression to TB disease should be given high priority for treatment of LTI regardless of age. Asymptomatic pregnant women with a negative chest X-ray should start INH preventive therapy as soon as possible if they have one of the following factors:

- HIV infection
- Close contact with infectious TB disease
- Recent (within 2 years) skin test conversion
- High-risk medical conditions

INH 300 mg/day for 6–9 months is the preferred regimen for treatment of LTI. Nine months of therapy offers the highest degree of protection against the progression of LTI to TB disease.¹⁸ Asymptomatic women with a negative chest X-ray and none of the risk factors listed above may elect to delay therapy until after delivery. The decision to administer INH prophylaxis during pregnancy or the postpartum period should be made after careful consideration of the risks and benefits of such therapy.

Toxicity to antituberculous medication is a concern. INH-induced hepatitis is a risk not limited to pregnancy but has been suggested as more prevalent among pregnant and immediately postpartum women.^{19,20} Maternal side-effects of commonly used antituberculous agents are shown in Table 53.2.² Pyridoxine (B6) 50–100 mg/day should be given with INH to those at increased risk for peripheral neuropathy (diabetes mellitus, malnutrition, HIV infection, seizure disorder, alcohol use more than three drinks per day, and pregnancy). INH is not contraindicated in breastfeeding women and breastfeeding infants whose mothers are taking INH should be offered pyridoxine (1 mg/kg/day) as a supplement.

INH for LTI is contraindicated for those with active hepatitis or end-stage liver disease. Prior to initiating INH prophylaxis, a baseline serum glutamic-oxaloacetic transaminase (SGOT) should be obtained for individuals at

Table 53.2 Side-effects of antituberculous agents.

Agent	Maternal side-effects
Isoniazid	Hepatitis, peripheral neuropathy (prevented with pyridoxine)
Ethambutol	Optic neuritis
Rifampin	Orange discoloration of body secretions, gastrointestinal upset, liver toxicity

higher risk for INH-induced hepatitis: those with average alcohol use of more than three drinks per day; those who are HIV-positive; those with underlying liver disease; pregnant women; and women within 3 months of delivery. If the baseline SGOT is ≥ 3 times the upper limit of normal, a risk-benefit analysis of LTI treatment should be carried out.¹² All patients should be assessed monthly for adverse reactions to INH, and SGOT should be followed monthly for all pregnant women taking INH. Therapy should be stopped if signs and symptoms of hepatotoxicity are present, or if SGOT is more than 5 times the upper limit of normal.¹²

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Urinary tract infections

F. Gary Cunningham

INTRODUCTION

Urinary infections are the most common bacterial infections encountered during pregnancy. Depending on the population studied, asymptomatic bacteriuria has a prevalence of 2–7% and up to 2% of all women are hospitalized during pregnancy for pyelonephritis.

PATHOPHYSIOLOGY

Under certain conditions, asymptomatic or covert bacteriuria can cause symptomatic cystitis or pyelonephritis. Normal pregnancy-induced urinary stasis and vesicoureteric reflux predispose to these infections. The invading organisms are those from the normal perineal flora, and approximately 10% of women have perineal colonization with strains of *Escherichia coli* that have adhesins or P-fimbriae that enhance their virulence so that they can cause pyelonephritis.

If bacteriuria is not treated, about one-quarter of these covertly infected women go on to develop acute symptomatic infection during pregnancy. Eradication of bacteriuria will prevent most of these.

DIAGNOSIS

Most recommend routine screening for bacteriuria at the first prenatal visit. When the prevalence is low, urine cultures may not be cost effective and other test systems can be used. Typically, cystitis is characterized by dysuria, urgency, and frequency with few systemic manifestations. Infection is confirmed by pyuria, hematuria, and bacteriuria. The upper urinary tract may also become involved by ascending infection, either with or without concomitant cystitis. Acute pyelonephritis occurs in 2–3% of all pregnant women and is a leading cause of sepsis syndrome. It is more common after mid-pregnancy and it is right-sided in approximately half of cases and bilateral in another one-quarter. The onset is usually abrupt with fever, shaking chills, and pain in one or both lumbar regions. There may be anorexia, nausea, and vomiting. Tenderness usually can be elicited by percussion in one or both cos-

tovertebral angles. The urinary sediment usually contains many leukocytes, frequently in clumps, and numerous bacteria. *E. coli* is isolated from urine cultures in 75–80% of infections, and bacteremia is documented in approximately 15% of women.

TREATMENT

Bacteriuria or cystitis is treated empirically with any of several antimicrobial regimens that include single-dose or 3-day treatment with an extended penicillin, a cephalosporin, a quinolone, trimethoprim-sulfamethoxane or nitrofurantoin. The recurrence rate for these is approximately 30%. For those women with recurrences, a 10-day course of one of these agents usually suffices to clear the infection. Also, nitrofurantoin 100mg at bedtime for 21 days is usually adequate. For women with persistent bacteriuria, or those with frequent recurrences, suppressive therapy for the remainder of pregnancy can be given with nitrofurantoin 100 mg at bedtime.

COMPLICATIONS

A number of complications can arise from antepartum pyelonephritis and the sepsis syndrome. Approximately 20% of women develop reversible renal dysfunction. Up to 2% develop varying degrees of the adult respiratory distress syndrome. After mid-pregnancy, uterine activity is common. Endotoxin-induced hemolysis causes anemia in approximately one-third of women, and mild to moderate thrombocytopenia is common.

MANAGEMENT

A scheme for management of the pregnant woman with acute pyelonephritis is shown in Table 54.1. Intravenous hydration is essential and antimicrobials

Table 54.1 Management of the pregnant woman with acute pyelonephritis.

1	Hospitalization
2	Urine culture
3	Hemogram, serum creatinine, and electrolytes
4	Monitor vital signs frequently, including urinary output—use indwelling bladder catheter
5	Intravenous crystalloid to establish urinary output to ≥ 30 mL/h
6	Intravenous antimicrobial therapy
7	Chest X-ray if there is dyspnea or tachypnea
8	Repeat hemogram and creatinine in 48 h
9	Switch to oral antimicrobials when afebrile
10	Discharge when afebrile 24 h, give antimicrobial therapy for 7–10 days
11	Urine culture 1–2 weeks after antimicrobial therapy completed
12	Consider suppression with nitrofurantoin, 100 mg at bedtime throughout pregnancy

are begun promptly at diagnosis. Therapy is empirical, and ampicillin plus gentamicin, cefazolin, or ceftriaxone have been found to be 95% effective in clinical trials. Careful surveillance for worsening of sepsis syndrome is provided, and vital signs and urinary output are monitored closely. Response will be relatively prompt and clinical symptoms usually resolve within 2 days. For women who do not respond promptly and appropriately, then a search for urinary tract obstruction, usually from stone disease, is undertaken with imaging studies. At discharge, oral antimicrobial therapy is given for 7–10 days.

FOLLOW-UP

Recurrent covert bacteriuria develops in approximately one-third of women following treatment for pyelonephritis. Because one-third of these will develop recurrent symptomatic infection, then retreatment is given as described above. Unless other measures are taken to ensure urine sterility, then nitrofurantoin, 100 mg at bedtime, is given for the remainder of the pregnancy.

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Acute abdominal pain resulting from non-obstetric causes

Sara Sukalich and Fred M. Howard

INTRODUCTION

Evaluation and treatment of the pregnant woman with acute abdominal pain represents a challenging clinical dilemma that demands great care and judgment. Common pregnancy symptoms such as nausea, vomiting, and urinary frequency are similar to those of many non-obstetric illnesses that cause acute abdominal pain. The etiology of acute abdominal pain in pregnancy can be separated into obstetric and non-obstetric causes; only non-obstetric will be discussed in this chapter. The most common etiologies for non-obstetric causes of acute abdominal pain in the pregnant patient are appendicitis, cholecystitis, pyelonephritis, hepatitis, pancreatitis, and degenerating uterine leiomyomas. Management is also more difficult, as interventions may adversely affect the pregnancy and concerns about harming the fetus may delay treatment. It is important to develop the clinical acumen to identify patients with problems that demand immediate intervention.

PATHOPHYSIOLOGY

Maternal physiologic and anatomic changes may modify symptoms and clinical responses from those normally seen in non-pregnant patients. The physical examination of the abdomen and pelvis are altered by the pregnant state. By 12 weeks' gestation the uterine fundus rises from the pelvis and becomes an abdominal organ, as do the adnexal structures. The intestines and omentum are displaced superiorly and laterally, with the appendix more likely to be closer to the gallbladder than to McBurney's point by late pregnancy (Fig. 55.1). Routine laboratory measurements may also be altered in the pregnant state. For instance, the leukocyte count varies considerably during normal pregnancy with elevations up to 12,000–16,000/mL, levels that overlap with intra-abdominal inflammatory conditions, such as appendicitis.

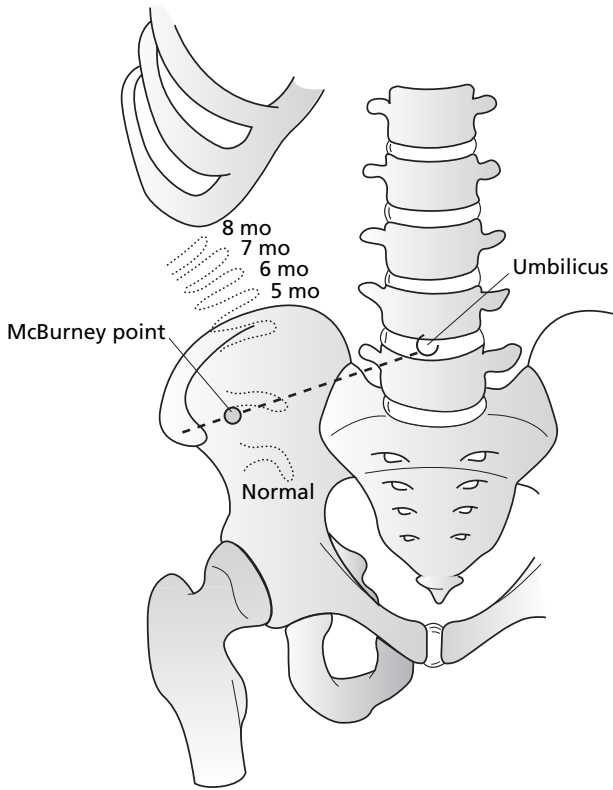


Fig. 55.1 Location and orientation of the appendix in pregnancy.

DIAGNOSIS

History and physical examination

A systematic and detailed history and physical examination are paramount. Having the most common diagnoses in mind during evaluation is essential to formulating a differential diagnosis, yet the clinician must remain sufficiently open-minded and unhurried to avoid missing important information. Acute abdominal crises should be recognized in an expedient manner. Pain may be the sole symptom but often there will also be vomiting, muscular rigidity, abdominal distention, or shock. In early pregnancy, excluding the possibility of ectopic pregnancy is often the first priority.

Location is crucial to potential diagnoses. Table 55.1 summarizes the location of pain associated with many of the causes of acute abdominal pain. Differentiating uterine from non-uterine pain can be difficult. One possible way to

Table 55.1 Differential diagnosis of acute non-obstetric abdominopelvic pain by location. More common causes are in italics.

Right upper quadrant

Cholecystitis/cholelithiasis
 Diaphragmatic pleuritis/abscess
Hepatitis
Pancreatitis
 Pneumonia/pneumonitis
Appendicitis (later gestation)

Epigastric

Cholecystitis/cholelithiasis
 Early acute *appendicitis*
 Early small bowel obstruction
Gastroenteritis/gastric ulcer
Gastroesophageal reflux
 Mesenteric thrombosis/ischemia
 Myocardial infarction
Pancreatitis
 Pericarditis
 Ruptured aortic aneurysm

Left upper quadrant

Gastroenteritis/gastric ulcer
 Myocardial infarction
Pancreatitis
 Pericarditis
 Pneumonia/pneumonitis
 Splenic rupture/abscess/infarction

Periumbilical

All early stage visceral diseases
 Abdominal trauma
 Abdominal wall hernias
 Bowel obstruction

Diffuse or generalized

All late stage visceral diseases
 Bowel obstruction
 Diabetic ketoacidosis

Continued on p. 362

Table 55.1 *Continued.*

Irritable bowel syndrome
 Mesenteric ischemia
 Metabolic disorders
 Peritonitis/perforated viscera
 Muscular strain/sprain

Lower quadrants

Adnexal torsion
Appendicitis (right lower quadrant)
Constipation
 Diverticulitis
 Endometriosis
 Inflammatory bowel disease
 Inguinal hernia
 Irritable bowel syndrome
Leiomyomas
Ovarian cyst/ruptured cyst
Pelvic inflammatory disease
Pyelonephritis
Urinary calculi

Suprapubic

Cystitis/urethritis
 Obstruction of the urinary bladder
Urinary calculi

do so is to have the patient lie supine and then roll to the left or the right. If the pain shifts when she lies on her side, it is more likely to be of uterine origin. If it remains in the same location, consider an intra-abdominal or retroperitoneal process.

Acute abdominal pain exacerbated by movement and coughing is generally consistent with peritoneal inflammation or irritation resulting from an infectious process or visceral rupture. Colicky pain refers to pain that is wavelike, with spasms that crescendo and decrescendo in a somewhat rhythmic pattern. This type of pain is characteristic of intestinal disorders, especially small bowel obstruction. It may also be consistent with adnexal torsion. Steady or constant pain is characteristic of a distended gallbladder or kidney.

The nature of the onset of the pain, chronologic sequence of events in the patient's history, and duration of the pain are important diagnostic elements. Associated symptoms may narrow the diagnosis. Fever and chills may suggest an infectious etiology. Pain followed by nausea and emesis is more characteristic of appendicitis, while patients with viral or bacterial enteritis may present with gastrointestinal complaints followed by pain.

Severity of pain does not necessarily correlate with the severity of disease and is not always useful in diagnosis. In most patients it is appropriate to give analgesia while the evaluation of acute pain is ongoing. A history of radiation of pain may also be helpful. For instance, acute obstruction of the intravesicular portion of the ureter is characterized by severe suprapubic and flank pain that radiates to the labia or inner aspect of the upper thigh. Pain referred to the abdomen from the thorax can be a difficult diagnostic problem and an intrathoracic etiology should be considered in every patient with acute abdominal pain.

Physical examination of the abdomen, pelvis, and rectum are critical components of evaluation of the pregnant woman with abdominal pain. The examination should be gentle but thorough. Examination begins with observation of the patient's appearance and activity. The patient with peritoneal inflammation may minimize motion and lie with hips flexed to reduce pain. Vital signs are essential. Hypovolemia and hyperpyrexia may point toward certain etiologies.

The fetal status should also be determined at this point in a manner appropriate for gestational age. The uterus should be monitored for contractions with a tocodynamometer because preterm labor may occur in this clinical setting. If viable, the fetus should be assessed by means of a non-stress test (NST) followed by a biophysical profile if the NST is not reactive. Fetal tachycardia resulting from a maternal fever may resolve with fever reduction measures.

Gentle examination of the abdomen may reveal tenderness, involuntary guarding, and rebound tenderness, which are characteristic of peritoneal inflammation of any etiology. Abdominal distention may occur with peritoneal inflammation or bowel obstruction. Palpation should be directed to the detection of possible abdominal masses as well as tenderness. Auscultation may reveal decreased or absent bowel sounds consistent with peritonitis or ileus. High-pitched bowel sounds and rushes may be heard if obstruction is present. Patients with findings consistent with generalized peritonitis, with guarding and rebound tenderness in all four quadrants of the abdomen, are commonly said to have a "surgical abdomen" and may require operative evaluation to arrive at a clear diagnosis.

Pelvic examination is often of limited value after the first trimester. Ultrasound is usually essential to rule out a pelvic mass in acute abdominal pain during pregnancy. The rectal examination may be helpful in further clarifying pelvic pathology, and testing for occult blood at the time of the examination may help recognize gastrointestinal bleeding.

Laboratory and imaging evaluation

Table 55.2 lists many of the laboratory and imaging studies generally useful in evaluating the gravid woman with acute abdominal pain. Laboratory examinations may be of great value, but rarely establish a definitive diagnosis. Not all are indicated in all women and their use should be predicated by the differential diagnosis determined from the history and physical examination. Studies that are usually indicated include complete blood count, urinalysis, urine culture, electrolytes, and pregnancy test (when gestational age is uncertain).

Imaging may be helpful. Magnetic resonance (MR) and ultrasound scans are considered safe in pregnancy and can be used without reservations. In general, examinations with ionizing radiation exposure are avoided, particularly in the first trimester. As a general rule, no single imaging study provides enough radiation exposure to the fetus to cause damage. Accumulative doses should not exceed 5 rad. Radioactive isotopes should also be avoided in pregnancy. It should be kept in mind that if the pregnant woman requires abdominal imaging

Table 55.2 Studies that may be useful in acute abdominal pain in the gravid patient.

Laboratory testing

Serum quantitative β -hCG

Urinalysis: assess for pyuria, hematuria, glucosuria, ketones

Urine culture and sensitivity: assess for urinary tract infection

Cervical cultures: assess for gonorrhea, *Chlamydia* infection

Complete blood count and differential: assess for leukocytosis, anemia

Glucose

Serum ketones: assess in patients who may have diabetic ketoacidosis

Liver function tests, total and direct bilirubin: assess for liver, gallbladder disease

Amylase, lipase: assess for pancreatic disease

Electrolytes, BUN, creatinine: assess metabolic state, renal function

Other specific tests when indicated (e.g. hemoglobin electrophoresis, ANA)

Imaging (scans with radiation exposure are generally second line)

Pelvic ultrasound: assess pregnancy, adnexa, uterus

Abdominal ultrasound: assess gallbladder, appendix, liver, free fluid

Renal ultrasound: assess kidneys for hydronephrosis, calculi

Chest radiograph: assess lungs, heart silhouette

Abdominal X-ray series: assess bowels if perforation, obstruction suspected

CT or MR scans as indicated

ANA, antinuclear antibody; β -hCG, β human chorionic gonadotropin; BUN, blood, urea, nitrogen; CT, computed tomography; MR, magnetic resonance.

such as a computed tomography (CT) scan, this might be an indication of severity of disease and need to proceed with operative exploration.

TREATMENT

Appropriate treatment of acute abdominal pain in the pregnant patient will be dictated by the differential diagnosis. In most cases, management will be unchanged from that employed in non-pregnant patients.

Acute appendicitis

Approximately 2% of women require a non-obstetric surgical procedure during pregnancy and acute appendicitis is the most common reason. Appendicitis occurs more often in the middle trimester and perforation of the appendix is skewed toward later pregnancy. This probably reflects both the difficulty and delay of diagnosis in later pregnancy. The clinical presentation of appendicitis during pregnancy is not greatly different from that in the non-pregnant woman. Most patients will complain of abdominal pain, nausea, or vomiting. Anorexia is not a consistent finding in pregnancy and diarrhea may be present. The presence of fever may be less common in pregnancy and white blood counts may be just mildly elevated, although the majority of women will have a left shift. Treatment is expedient appendectomy. Tolerance of a significant rate of normal appendixes is necessary to prevent the serious maternal and fetal morbidity associated with perforation. Antibiotics are generally administered prior to and after surgery. Tocolysis may be indicated.

Ovarian cysts and adnexal torsion

Ovarian cysts may cause acute abdominal pain because of rupture. Adnexal torsion may occur with normal adnexae, but more often occurs with adnexal cystic lesions, neoplastic lesions, or hyperstimulated ovaries. The majority of torsions occur in the first half of the pregnancy. Patients with ovarian torsion usually present with unilateral pelvic pain, possibly with vomiting. Ultrasound may demonstrate a pelvic mass and absent flow on Doppler evaluation. Adnexal torsion represents a surgical emergency because of the potential danger of permanent destruction of the organs involved, peritonitis, or even death. The traditional approach has been surgical removal of the adnexa. However, untwisting and preservation of the ovary is usually successful, even with an apparently necrotic ovary or tube.

Cholecystitis and cholelithiasis

Asymptomatic cholelithiasis occurs in 3–4% of pregnant women and is the cause of over 90% of cases of cholecystitis in pregnancy. Cholecystitis during pregnancy is uncommon, with 5–10 cases per 10,000 births. Steady and severe right upper quadrant pain is often the presenting symptom. Fever, leuko-

cytosis, nausea, vomiting, and anorexia may also be present. Ultrasound will show gallstones in almost all cases. Medical treatment is preferred in pregnancy. Initial treatment consists of no oral intake, intravenous hydration, bed rest, pain relief, and antibiotics if febrile. Most women respond to this approach and avoid surgical treatment during pregnancy. Surgery, if needed for failed medical management, is best performed in the second trimester.

Urinary tract infection

Acute cystitis is very common in gravid women. It may occur alone or in conjunction with pyelonephritis. Acute uncomplicated cystitis is manifested primarily by dysuria, with associated frequency, urgency, suprapubic pain, and/or hematuria. Fever, flank pain, costovertebral angle tenderness, and nausea or vomiting suggest pyelonephritis and warrant more aggressive diagnostic and therapeutic measures. Pyelonephritis is identified in 1–2% of all pregnancies. Treatment includes parenteral antibiotics and intravenous hydration. Close monitoring for complications such as renal impairment, hematologic abnormalities, septic shock, and pulmonary dysfunction is critical in the pregnant patient. Prophylactic antibiotics may be indicated for the remainder of the pregnancy.

Urinary calculi

Stones or calculi of the urinary tract usually cause severe abdominal pain associated with nausea, but sometimes patients present with milder symptoms during pregnancy. With ureteric obstruction, flank pain is present which may radiate to the ipsilateral groin and percussion may elicit tenderness over the costovertebral angle. Hematuria is usually present. Ultrasound examination may demonstrate hydroureter, hydronephrosis, or calculi. In most cases of renal or ureteric calculus, the stone eventually passes; thus, supportive treatment with intravenous hydration and pain control is usually sufficient. Lithotripsy is contraindicated in pregnancy.

Pancreatitis

Acute pancreatitis complicates 1 in 1000–10,000 pregnancies. Gallbladder disease is the most common cause; medications, infection, and hyperlipidemia are less frequent causes. Signs and symptoms are similar to those in the non-pregnant woman. Medical management includes bowel rest, pain relief, and correction of fluid and electrolyte imbalances. Patients with pancreatic abscess, ruptured pseudocyst, or hemorrhagic pancreatitis may require surgery while they are still pregnant.

Hepatitis

Viral hepatitis is the most common serious, non-obstetric liver disease in pregnant women. Although pregnancy has little influence on the presentation or

course of hepatitis, hepatitis carries significant implications to the pregnancy, fetus, and neonate, depending on the type and gestational age. Management is generally unchanged during pregnancy.

Uterine leiomyomas

Acute pain from myomas during pregnancy is usually caused by degeneration secondary to inadequacy of blood supply to the myoma. Pain and tenderness are generally localized and can be severe. Low-grade fever and leukocytosis can occur. Preterm labor may be initiated because of irritation of adjacent myometrium. Ultrasound is helpful in making the diagnosis. Management is non-surgical with use of analgesics and observation for preterm labor.

CONCLUSIONS

The ability to distinguish an acute process that requires surgical intervention or referral to a specialist is based on the clinical skills of the healthcare provider. This requires a complete history, careful physical examination, judicious use of laboratory and radiologic studies, and frequent re-evaluation until a firm diagnosis is reached. The primary care clinician should have a low threshold for seeking advice from a surgeon, obstetrician, or other specialist. The difficulties of diagnosing abdominal pain in pregnancy are well known. Prompt clinical diagnosis and surgical intervention when indicated are necessary to minimize maternal and fetal morbidity and mortality.

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Acute pancreatitis

Sarah H. Poggi

INTRODUCTION

Acute pancreatitis may complicate pregnancy and the puerperium with remarkable frequency. The incidence is estimated to be between 1 in 1000 and 1 in 10,000 deliveries. In the most recent series published in the USA, the incidence was 1 in 3333 pregnancies. Although acute pancreatitis may occur at any time in pregnancy, it is most common in the third trimester (over 50%). The disease has equally dangerous implications in pregnancy as it does in the non-pregnant state. Although in the most recent series there are no maternal deaths associated with acute pancreatitis in pregnancy, in the 20th century the mortality was 37%. The perinatal loss rate may be as high as 10–20%, although improvements in the care for preterm infants have improved these rates. Because the symptoms of acute pancreatitis can be confused with other pregnancy-related conditions, it may go unrecognized. This is particularly true early in pregnancy, when hyperemesis gravidarum is problematic. Later in pregnancy, severe pre-eclampsia and HELLP syndrome provide further confusion. Acute pancreatitis must always be considered in the pregnant patient with upper abdominal pain, nausea, and vomiting. Appropriate therapy can be instituted early and unnecessary obstetric interventions avoided.

ETIOLOGY

Cholelithiasis is the most common cause of acute pancreatitis in the obstetric patient (approximately 70%). Whereas ethanol plays a significant part in the general population, it is an unusual cause of acute pancreatitis in the pregnant patient. In general, conditions that may cause pancreatitis outside of pregnancy can have an exacerbated course in pregnancy (e.g. trauma, infection). Although drug reactions have a limited etiologic role in acute pancreatitis, many of these drugs are used in pregnancy. These include salicylates, acetaminophen (Tylenol®), sulindac, erythromycin, nitrofurantoin (Macrochantin®), methyldopa (Aldomet®), and metronidazole (Flagyl®). There are increasing reports of hyperlipidemia causing acute pancreatitis in

pregnancy, with the situation probably enhanced in susceptible women by the physiologic increase in plasma triglycerides during pregnancy. The morbidity associated with this subset of pancreatitis is especially high for both mother and fetus. An additional etiology of pancreatitis in pregnancy is hyperparathyroidism, which preferentially affects females during childbearing years. Specific pregnancy-related diseases that can rarely be associated with acute pancreatitis include pre-eclampsia/eclampsia and acute fatty liver of pregnancy.

CLINICAL DIAGNOSIS

Similar to the non-pregnant patient, the symptoms of acute pancreatitis include epigastric pain radiating to the back, referred pain to the left shoulder, retching, and severe vomiting. Upon examination the patient may exhibit tachycardia, fever, hypothermia, hypotension, and tachypnea. In addition, she may be jaundiced and exhibit Turner sign (ecchymoses along the flank) or Cullen sign (discoloration around the umbilicus), or both. Epigastric tenderness in the absence of muscle rigidity is found on palpation. Obviously the gravid uterus, particularly later in pregnancy, confounds the sensitivity of these abdominal examination findings.

The differential diagnosis of acute pancreatitis in pregnancy includes the following:

- 1 Cholecystitis
- 2 Cholelithiasis/choledocholithiasis
- 3 Acute appendicitis
- 4 Perforated peptic ulcer
- 5 Hepatitis
- 6 Occlusion of mesenteric vessels
- 7 Dissecting aortic aneurysm
- 8 Myocardial ischemia/infarction
- 9 Pulmonary embolus

Pregnancy-related conditions should also be part of the differential diagnosis, but are dependent on gestational age. These include ruptured ectopic pregnancy, hyperemesis gravidarum, severe pre-eclampsia (HELLP syndrome), and acute fatty liver of pregnancy.

LABORATORY DIAGNOSIS

The laboratory studies necessary to confirm the diagnosis of acute pancreatitis include serum amylase and lipase. Serum amylase levels are similar in healthy pregnant and non-pregnant women, regardless of trimester. Serum lipase activity is lower in the first trimester but normalizes later on in comparison with non-pregnant women. In the patient with pancreatitis, serum amylase levels may be falsely negative if the patient presents 24–48 h after initial symptoms. However, the serum lipase will be elevated for several days

after symptoms begin. Many conditions noted in the differential diagnosis may cause an elevated amylase. The degree of elevation of amylase does not correlate with the severity of the disease.

RADIOLOGIC DIAGNOSIS

Radiologic studies help to exclude secondary complications of acute pancreatitis and determine an etiology. Computed tomographic (CT) scan of the upper abdomen is the procedure of choice in the postpartum patient and may have a role in some pregnant patients, as care can be taken to minimize radiation. However, because X-ray exposure is relatively contraindicated in pregnancy, abdominal ultrasound or magnetic resonance imaging (MRI), or both, may be of benefit. These imaging techniques can detect complications such as peripancreatic fluid collections, pancreatic pseudocyst, and pancreatic abscess. The presence of peripancreatic fluid collections may identify those patients in whom septic necrosis of the pancreas will later develop. Such complications are rare in mild cases of acute pancreatitis in the obstetric literature.

PROGNOSIS

The maternal mortality risk can be estimated using Ranson criteria within 48 h of admission. With the exception of age, these include white blood cell count (WBC) $> 15,000/\mu\text{L}$, $Po_2 < 60\text{ mmHg}$, blood urea nitrogen (BUN) $> 45\text{ mg/dL}$, lactic acid dehydrogenase (LDH) $> 600\text{ units/L}$, glucose $> 180\text{ mg/dL}$, albumin $< 3.3\text{ g/dL}$, and calcium $< 8.8\text{ mg/dL}$. Because serum albumin and calcium tend to decrease in normal pregnancy, these criteria must be interpreted with caution. Non-obstetric patients with six or more of these criteria have close to 100% mortality. The most recent series in the obstetric literature have not had a single maternal mortality. The earlier series may have included cases of acute fatty liver of pregnancy before the availability of serum amylase assays.

TREATMENT

Acute pancreatitis therapy in the obstetric patient includes the following measures:

- 1 Nil-by-mouth, intravenous hydration, and/or hyperalimentation (limit intralipids if hypertriglyceridemia present).
- 2 Meperidine for pain control (this is preferential to morphine, which may cause a spasm of the sphincter of Oddi).
- 3 Nasogastric suction for ileus, severe vomiting.
- 4 Antibiotic therapy for clinical evidence of infection.
- 5 Intensive care unit (ICU) admission if respiratory failure (adult respiratory distress syndrome [ARDS]), disseminated intravascular coagulopathy, acute renal failure, or shock.

- 6 Surgical/gastroenterology consultation, particularly if septic necrosis is suspected; expanding pancreatic pseudocyst, pancreatic abscess, or biliary obstruction is present; or if condition is not improving with above therapy.
- 7 In the case of biliary obstruction, endoscopic retrograde cholangiopancreatography (ERCP) can be modified to minimize radiation exposure during common bile duct stone extraction. Cholecystectomy, once traditionally avoided during pregnancy, is considered relatively safe in the mid-trimester, and may be indicated for non-resolution of gallstone pancreatitis regardless of trimester. Laparoscopic entry is considered safe in appropriate patients (typically mid-trimester).
- 8 Plasmaphoresis may be needed for patients with hyperlipidemic pancreatitis. The suppression of pancreatic secretion with anticholinergic medication is no longer recommended. Likewise, the empiric use of nasogastric suction is not helpful in the absence of an ileus or severe vomiting.

OBSTETRIC CONCERNS

Fetal well being must be ascertained during the maternal evaluation because fetal loss rates are increased, particularly in severe cases of acute pancreatitis. Close monitoring of maternal electrolytes and acid–base disturbances may prevent fetal decompensation. Fetal surveillance is dependent on gestational age. At a previable gestational age, ultrasound is sufficient to assess fetal growth, anatomy, amniotic fluid amount, placental location, and cardiac activity. Beyond 24–25 weeks' gestation, biophysical profile and non-stress testing will be necessary in addition to a complete ultrasound evaluation. In general, termination of pregnancy in the first or second trimesters does not improve the course of acute pancreatitis. Obstetric intervention for non-reassuring fetal surveillance must be considered in light of the maternal condition. Intervention by cesarean section in an unstable patient may increase the risk of maternal mortality. The presence of acute pancreatitis does not contraindicate a vaginal delivery. Induction of labor in the third trimester in the presence of a mature fetus can be considered. Although delivery will not improve the course of acute pancreatitis, it may allow better management of its secondary complications if present. Maternal–fetal consultation can help to resolve these issues.

CONCLUSIONS

Acute pancreatitis can be recognized much earlier with the aid of clinical and modern laboratory confirmation. The obstetric patient provides many challenges in the diagnosis and management of this disease. Fortunately, most of the cases in pregnancy are mild and have minimal effect on maternal and fetal survival.

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Gallbladder

Monica Longo and Gary D.V. Hankins

INTRODUCTION

The gallbladder is a repository for bile and for cholesterol excreted from the body by the liver. The most common gallbladder disorder is cholelithiasis, seen four times more commonly in women than in men. Three to 4% of all pregnant women undergoing routine ultrasound screening of the gallbladder have cholelithiasis.

Ninety percent of gallstones removed at surgery are composed of cholesterol formed when the gallbladder becomes supersaturated with cholesterol. Ten percent of gallstones are formed from bilirubin pigments and may be found in patients with hemolytic disease such as the hemoglobinopathies or cirrhosis. Supersaturation and increased lithogenicity of cholesterol in bile are associated with increasing age, obesity, high-fat diets, diabetes mellitus, estrogen administration, and parity.

Pregnancy is associated with several physiologic changes that affect the function of the pancreas and gallbladder, leading to an increased risk of cholelithiasis and pancreatitis. Gallstone formation is enhanced by the increase in circulating levels of sex hormones. Progesterone has the highest potential for altering biliary motility and gallbladder contractility, delaying its emptying and increasing biliary sludge. Progesterone levels rise in the first 20 weeks' gestation, then remain stable until delivery, after which they immediately decrease.

Ultrasound findings confirm a pattern of change in gallbladder and biliary function that mimics the change in progesterone levels, with an increase in gallbladder volume and delayed emptying at the beginning of pregnancy and return to normal gallbladder function soon after delivery.

SYMPTOMS AND SIGNS OF CHOLELITHIASIS

It is estimated that 50% of patients with cholelithiasis remain asymptomatic. The frequency of symptomatic cholelithiasis and cholecystitis during pregnancy is 5–10 in 10,000 pregnancies. In addition, 2–4% of pregnant patients with cholelithiasis are diagnosed incidentally during obstetric ultrasound. In

some women, however, a stone enters the cystic duct and three major disorders may occur:

- 1 Biliary colic
- 2 Acute cholecystitis
- 3 Obstructive jaundice and pancreatitis

Biliary colic occurs whenever a stone attempts to traverse the cystic duct. The primary symptom is right upper quadrant abdominal pain of varying intensity and duration (1–3 h).

Acute cholecystitis occurs when a stone obstructs the cystic duct, resulting in chemical and/or bacterial inflammation of the gallbladder. Symptoms persist until the obstruction is relieved and include severe right upper quadrant pain, tenderness to palpation over the gallbladder (Murphy sign), and nausea and vomiting associated with low-grade fever. Significant laboratory findings include:

- 1 Elevated white blood cell count (WBC)
- 2 Elevated direct and indirect serum bilirubin levels
- 3 Elevated serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels
- 4 Positive urinary bilirubin

Obstructive jaundice occurs when a stone obstructs the common bile duct, resulting in a clinical picture of acute cholecystitis hallmarked by signs of obstructive jaundice, which include pale-colored stool and dark bilirubin-pigmented urine. Prolonged obstruction may lead to pancreatitis.

DIAGNOSIS

The diagnosis of cholelithiasis is made by ultrasound evaluation of the gallbladder, the cystic duct, and the common bile duct. A complete evaluation includes sonographic evaluation of the liver. The sensitivity and specificity of ultrasound in this disorder exceed 95% and render radiologic cholecystography obsolete. In over 95% of cases, the number, size, and location of gallstones can be determined along with the size of the gallbladder and the thickness of its wall, which is often indicative of chronic cholecystitis. Ultrasound examination in severe cases of suspected biliary empyema may demonstrate a pericystic fluid collection.

CLINICAL EVALUATION

Patients suspected of having gallbladder disease in pregnancy should be hospitalized for bed rest and the following procedures instituted as needed:

- 1 Nasogastric suctioning
- 2 Intravenous hydration
- 3 Analgesic administration

4 Broad-spectrum antibiotic coverage

Laboratory tests include:

- 1 Complete blood cell count (CBC)
- 2 Liver function tests: serial serum levels of total bilirubin, direct bilirubin, indirect bilirubin, SGOT, SGPT, alkaline phosphatase
- 3 Urinalysis, urine culture
- 4 Serum amylase levels to rule out pancreatitis
- 5 Blood cultures in febrile patients
- 6 Evaluation of stool color

MANAGEMENT

Medical management of biliary tract disease in pregnancy generally suffices. It consists of intensive supportive care with intravenous hydration, withholding oral intake, analgesics, and antipyretics. With mild disease, nasogastric suctioning may not be effective. If the biliary system is suspected to be infected or there is necrotizing pancreatitis, antibiotics are given. Monitoring of electrolytes, calcium, magnesium, and other levels with appropriate replacement is necessary.

Most patients are effectively managed with conservative, non-operative therapy. For some, however, surgery is required for refractory symptoms or complications. The clinician and patient must weigh the fact that cholecystectomy performed in the second or third trimester is associated with approximately 5% pregnancy loss, but if delayed until the woman's clinical condition is deteriorating the pregnancy loss rate is as high as 60%. A surgical approach should be considered if the attack is complicated by choledocholithiasis, pancreatitis, or both. Either open cholecystectomy (OC) or laparoscopic cholecystectomy (LC) are safe procedures during pregnancy. More than 20 studies have shown reassuring results with LC, while only one study reported a high risk of fetal loss.

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Mastitis

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INTRODUCTION

The last decade has seen a significant increase in the number of women choosing to breastfeed their infants. This has largely been the result of a growing body of evidence of the benefits of breastfeeding to an infant. Healthy People 2010, a national prevention initiative to improve the health of all Americans, has set the national goal for the percentage of women breastfeeding early postpartum to 75% (1998 baseline 64%).¹ In 1997, the American Academy of Pediatrics Work Group on Breastfeeding² strongly advocated human milk as the preferred feeding for all infants, including premature and sick newborns. They stated that exclusive breastfeeding for the first 6 months is ideal, and recommended that breastfeeding continue for at least 12 months, and thereafter for as long as mutually desired. Accompanying this increase in breastfeeding is a natural increase in the number of women presenting to healthcare providers with symptoms and signs of mastitis.

Although mastitis can occur at any time, the incidence of mastitis is highest in the first few weeks postpartum and gradually decreases thereafter. Historically, incidence rates were thought to be in the range 2–33% and this figure is widely quoted. However, recent data from two large prospective cohorts of breastfeeding women suggest that the incidence rates are in the range 9.5–20%. The first study followed 1075 breastfeeding women in New Zealand for 6 months and found a 20% incidence.³ The second study followed 946 women from Michigan and Nebraska until they stopped breastfeeding. Mastitis occurred in 9.5%.⁴ The twofold difference in incidence can be accounted for in part by differences in case definition.

Risk factors for mastitis have been more elusive. Both recent cohort studies found a history of mastitis with a previous child to be the most significant risk factor, challenging the long-held belief that primiparity and inexperience are actual risk factors. Other identified risk factors included: blocked duct, cracked nipples, use of creams on nipples (papaya cream in New Zealand and an anti-fungal nipple cream in the USA), and the use of a manual breast pump (women

with sore or cracked nipples would more likely use creams). Sociodemographic factors do not seem to play a significant part in the risk for mastitis. The role of mother–infant skin and nasal bacterial colonization in the development of mastitis has not been well studied.

DIAGNOSIS

Mastitis needs to be differentiated from other conditions. Simple breast engorgement usually presents gradually with bilateral generalized warmth, swelling, and very firm breasts. There is no erythema or fever. With a plugged duct, a breast segment is swollen, firm and tender, but there is no evidence of infection. These patients should continue nursing frequently.

Mastitis is an acute inflammation of the connective tissue of the mammary gland: a mammary cellulitis. Traditional teaching holds that nipple trauma allows the portal of entry for microorganisms and that inadequate emptying causes milk stasis, allowing a medium for bacterial growth. It is a clinical diagnosis and most commonly presents suddenly and unilaterally with fever (often 102°F or higher), chills, flu-like aching, myalgias and breast redness demarcated in a wedge-like pattern outlining the lobar anatomy involved in the infection.⁵ Although mastitis is a subcutaneous infection, cultured breast milk has been the gold standard for identifying the responsible organisms. The agents most frequently identified in milk culture include: *Staphylococcus aureus* and coagulase-negative staphylococci, followed by group A and B hemolytic streptococci, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella*, and *Bacteroides*.⁶ These organisms reflect common maternal skin and nasal bacteria, and can sometimes be cultured from the infant's throat.

TREATMENT

Treatment goals include resolution of infection, amelioration of symptoms, prevention of complications, and the continuation of breastfeeding. There is widespread agreement that breastfeeding should be continued, and that proper drainage of the breast is essential to prevent complications. Mastitic milk is associated with increased concentrations of immune components and inflammatory molecules which resolve within 1 week of proper treatment.⁷ Adverse effects on infants have not been reported. Mastitic milk poses no risk to the infant. First-line clinical treatment relies on an antibiotic with sensitivity to staphylococcal and streptococcal organisms along with continued emptying of the breast and supportive care. Culture of breast milk is not routinely performed in clinical practice. Penicillinase-resistant penicillins and cephalosporins are commonly used: dicloxacillin 125–250 mg every 6 h, or cephalexin (Keflex®) 500 mg p.o. every 6 h. In penicillin-allergic patients, erythromycin 250 mg every 6 h is another alternative. There are no data on duration but most prescribe for 7–10 days. Resolution of symptoms within 2 days was seen in 96% of women

when treated with antibiotics and breast emptying in a Danish study.⁸ Symptoms can be treated with analgesics such as non-steroidal anti-inflammatory drugs, fluids and rest. Follow-up is not necessary unless the mastitis persists longer than 48 h or worsens despite treatment. Weaning should be delayed until the infection has cleared. For severely cracked or damaged nipples, the use of a topical antibiotic ointment can aid healing and prevent mastitis (e.g. mupirocin, Bactroban® ointment).

When mastitis goes untreated or does not respond to the initial treatment, 5–11% of women will go on to develop a breast abscess. If mastitis signs and symptoms do not improve in 48 h, the woman should be re-examined. If an abscess is not suspected yet symptoms persist, a culture of the milk should be carried out and strong consideration should be given to starting an antibiotic for methicillin-resistant *Staphylococcus aureus* (MRSA). In general, MRSA infections are increasing in most communities and are no longer an infection of the immunocompromised.⁶ A case of toxic shock syndrome secondary to mastitis caused by MRSA was reported in Japan in 2001.⁹ In some hospitals and communities, an infectious disease specialist should be consulted. Outpatient intravenous therapy can often be achieved, thereby promoting the continuation of breastfeeding.

If the physical examination is suggestive of an abscess, an ultrasound of the breast can be performed for confirmation. Traditionally, incision and drainage has been the recommended treatment; however, more recently, successful ultrasound guidance with percutaneous catheter drainage has been described.¹⁰ Culture of the abscess material can potentially guide antibiotic treatment.

Episodes of recurrent mastitis warrant repeated therapy and continuation of nursing. A referral to a lactation consultant can be beneficial.

CONCLUSIONS

Mastitis is a common complication of breastfeeding and one that virtually all healthcare providers will encounter. The diagnosis is clinical and most will respond promptly to penicillinase-resistant penicillin or cephalosporin. If the clinical response is not prompt, re-examination is necessary with concern for MRSA or development of a breast abscess. Consultation should be strongly considered for complicated cases.

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PART 5

Obstetric problems

First trimester vaginal bleeding

Marsha Wheeler

INTRODUCTION

Two out of 10 pregnant women have vaginal bleeding in the first trimester; of these, 50% will go on to have normal pregnancies while the other 50% will have a pregnancy loss. The presence of heavy vaginal bleeding (defined as heavier than a menstrual period), abdominal pain, fever, or passage of tissue requires immediate evaluation. It is important to make the diagnosis, because ectopic pregnancy is a leading cause of maternal mortality. Vaginal bleeding in a viable pregnancy can be associated with subsequent adverse pregnancy outcomes.

EVALUATION OF THE PREGNANT PATIENT WITH VAGINAL BLEEDING

When a reproductive age female presents with vaginal bleeding, the following evaluation should be performed:

- 1 Obtain vital signs, both standing and recumbent.
- 2 Obtain a menstrual history, date and method used to confirm the pregnancy, gynecologic history, and history of coagulation disorder.
- 3 Perform a physical examination to assess uterine size, adnexal masses, and evaluate for peritoneal tenderness or peritoneal signs.
- 4 Perform a speculum examination to determine source or severity of bleeding. Determine whether the cervical os is open or closed. Identify presence of tissue.
- 5 If the patient has a history of amenorrhea or if pregnancy is a possibility, obtain a rapid urine pregnancy test. If the urine pregnancy test is negative but your suspicion for an ectopic pregnancy is high, obtain a quantitative serum human chorionic gonadotropin (hCG). Consider gynecologic causes of vaginal bleeding such as vaginal trauma, cervical cancer, cervical lesions, or pelvic inflammatory disease.
- 6 If the pregnancy test is positive and you are concerned about an ectopic pregnancy or pregnancy loss, obtain an ultrasound of the pelvis and quantitative serum hCG.

DIAGNOSIS

When a patient presents with vaginal bleeding, the physical examination and history, along with an ultrasound and hCG, are useful in differentiating between an intrauterine pregnancy, early pregnancy failure, ectopic pregnancy, and hydatidiform mole.

Viable intrauterine pregnancy

The most common diagnosis in a patient with a positive pregnancy test and vaginal bleeding is a threatened abortion. Once the positive pregnancy test is obtained, an ultrasound and serial hCG values can be used to make the diagnosis. If the ultrasound shows a viable intrauterine pregnancy over 7 weeks' gestation with a heart rate over 90 b/min, the likelihood of continuing pregnancy is 90–97%. The prognosis increases with increasing gestational age. Prognosis is worsened by advanced maternal age, heart rate less than 90 b/min and a subchorionic hematoma. Presence of first trimester bleeding can be associated with adverse perinatal complications (Table 59.1).¹ The presence of an intrauterine hematoma identified in the first trimester on ultrasound also identifies a population at risk for adverse pregnancy outcomes. The incidence of intrauterine hematomas in the first trimester is 3.1%. The rates of operative vaginal delivery (odds ratio [OR] 1.9, 95% confidence interval [CI] 1.1–3.2) and cesarean delivery (OR 1.4, 95% CI 1.1–1.8) were increased. The risk for pregnancy-induced hypertension and pre-eclampsia were significantly greater, as were placental abruption, premature delivery, growth restriction, fetal distress, and neonatal intensive care unit admissions. The frequency of intrauterine demise and perinatal mortality were increased in the hematoma group.²

Management should be conservative. Bed rest is usually recommended. Progestins and hCG therapy have been used in the past. A Cochrane review that evaluated progestogen for preventing miscarriage identified 14 trials. The

Table 59.1 Adverse pregnancy outcomes with first trimester vaginal bleeding.

Vaginal bleeding	Heavy (odds ratio)	Light (odds ratio)
Spontaneous loss before 24 weeks	4.2	2.5
Cesarean delivery	1.4	1.1
Pre-eclampsia	1.1	1.5
Preterm delivery	3.0	1.3
Placental abruption	3.6	1.6
Premature rupture of membranes	3.2	1.3
IUGR	2.6	1.4

IUGR, intrauterine growth restriction.

meta-analysis showed no improvement in threatened abortions. With a history of recurrent miscarriage, administration of progestins reduces the risk of miscarriage (OR 0.3, 95% CI 0.15–0.8).³ The safety of progestins in the first trimester is unknown because of lack of controlled studies. HCG administration has been shown to reduce the risk of miscarriage in patients with a history of recurrent abortion (OR 0.07, 95% CI 0.02–0.2).³ The efficacy of hCG in threatened abortions has only been seen in a small randomized study (OR 0.4, 95% CI 0.2–0.8).⁴ Again, safety has not been addressed in a controlled manner.

Ectopic pregnancy

The diagnosis of ectopic pregnancy is very important to decrease maternal mortality. Transvaginal ultrasound is very helpful in patients with a possible ectopic pregnancy. The failure to visualize an intrauterine gestational sac on transvaginal ultrasound with an hCG of more than 1000 mIU/mL has a positive predictive value of 86% and specificity of 93% for ectopic pregnancy.⁵ An intrauterine gestational sac should be visualized by transabdominal sonography at an hCG titer of 1800 mIU/mL. Other helpful ultrasound findings are abnormal complex adnexal masses, adnexal gestational sacs with and without embryos. False-negative diagnosis of ectopic pregnancy can result from intrauterine blood collections or thick decidual reactions (pseudogestational sac) that mimic an intrauterine pregnancy.

If the diagnosis is not made by the initial evaluation, then a repeat serum hCG in 48 h can be used. The hCG should double in 48 h. If it is less than 60% over 48 h, then the pregnancy would be either non-viable intrauterine pregnancy or an ectopic. If the serum hCG titer is rising and an intrauterine pregnancy cannot be identified, the diagnosis of an ectopic pregnancy is very likely. The combined use of uterine and adnexal sonography associated with an elevated hCG allows for a definitive diagnosis of ectopic pregnancy.

A dilatation and curettage (D&C) could aid in this diagnosis. If chorionic villi are identified on D&C, then the chance of a concurrent ectopic pregnancy is very rare, except in one circumstance. The diagnosis of an intrauterine and concurrent extrauterine pregnancy (heterotopic pregnancy) has been seen with artificial reproductive technology (ART). Patients with heterotopic pregnancies are at greater risk for hypovolemic shock and requiring blood transfusions, so this diagnosis should always be considered in patients who have had ART.⁶ Treatment of an ectopic pregnancy can be medical, with methotrexate, or surgical. Many ectopic pregnancies can be treated by laparoscopy.

Early pregnancy failure

The diagnosis of a pregnancy failure is made when a normal pregnancy cannot be demonstrated. There are several landmarks that can be used to diagnose when a pregnancy is not progressing normally:

- 1 A gestational sac should be visualized at 33.5 days with transvaginal ultrasound in 95% of cases.
- 2 Fetal cardiac activity should be seen at 44.5 days with transvaginal ultrasound in 95% of cases.
- 3 Fetal cardiac activity should be visualized when an embryo is 5 mm in length.
- 4 Fetal cardiac activity should be visualized when the gestation sac is 1.9 mm in 99% of cases.
- 5 A normal gestational sac grows 1 mm/day.⁷

These landmarks can be used along with serial hCG to determine if a pregnancy is non-viable. Once the diagnosis has been made, the management plan could be surgical, such as a D&C, or conservative management.

Molar pregnancy

The diagnosis of a complete mole can be made by ultrasonographic visualization. The typical pattern is echogenic mass in the uterine cavity without evidence of an embryo. In the first trimester, the pattern may be atypical and be similar to a non-viable pregnancy. Correlation of hCG titers is helpful. The diagnosis of a partial mole can be a challenge because a gestational sac and embryo are both present. The placenta is usually abnormal with multiple cystic spaces and the fetus is usually growth restricted. A karyotype may reveal a triploid conception. Management involves evacuation of the uterus after diagnosis of staging has been made.

CONCLUSIONS

Using the physical examination, history, hCG, and ultrasound, a physician can make a diagnosis of the etiology of first trimester vaginal bleeding. The appropriate management plan can be started and the patient's care can be tailored to her needs. The complications associated with first trimester bleeding that impact maternal mortality and morbidity can be minimized.

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Cervical incompetence

Wendy F. Hansen

BACKGROUND

Cervical incompetence, first described in the 1950s, is a diagnosis traditionally given to the classic clinical presentation of painless cervical dilation (without contractions) during the second trimester; most often ending in the loss of the fetus.

The cervix (*neck*) is composed mainly of connective tissue, predominantly collagen with a small portion of smooth muscle (10–15%). The vagina is attached around its mid-segment, dividing it into a supravaginal portion and a lower or vaginal portion. The lesion or defect of cervical insufficiency remains unknown, in part because of the ethical difficulty in obtaining tissue specimens. What is known is that one can remove a considerable amount of cervical tissue from the vaginal portion and not cause cervical insufficiency. This is frequently demonstrated with both the LEEP and cervical conization procedures and the low incidence of cervical incompetence afterwards.

Although a shortened cervix has been recognized as a risk factor for preterm birth for a decade, it is not known how much of the upper cervix needs to remain in order to ensure competence. Over the years, certain risk factors for cervical incompetence have been identified: multifetal gestation, mullerian anomalies, DES exposure, women with cervical lacerations from obstetric trauma, multiple cervical surgeries for dysplasia, or a congenital hypoplastic cervix.

With the advent of transvaginal ultrasound in the early 1990s and the ability to measure the entire length of the cervix from the internal to the external os, our model of preterm birth and cervical incompetence has evolved. Transvaginal ultrasound was able to image changes at the internal os of the cervix before the clinician could detect any change on digital examination. Cervical shortening occurred weeks before uterine contractions and subsequent preterm birth. The inverse relationship between the length of the cervix and the frequency of preterm birth was confirmed by several authors. Iams *et al.*¹ were the first to challenge the traditional (either/or) concept of competence

versus incompetence and proposed the model of “continuum of cervical performance.” They proposed that cervical length was a continuous and not a dichotomous variable.

Although a shortened cervix documented by ultrasound is well known to be a powerful predictor of preterm birth, the cause of the shortening is not known. Possible causes include: inflammation, infection, decidual hemorrhage, cervical incompetence, hormonal and receptor abnormalities in the setting of an individual’s genetic variation, and environmental exposures.

INCIDENCE

The incidence of cervical incompetence has remained elusive, in part because of the lack of clear diagnostic criteria and in part because of the lack of a true diagnostic test. Incidence ranges are crude and come from 1980s data and range from 1 in 182 to 1 in 222.² It is an uncommon diagnosis in its purest definition.

DIAGNOSIS

Modern day obstetrics continues to rely on history along with exclusion of other etiologies for preterm birth as the primary means of diagnosis. When the history is unclear, many women are followed throughout the next pregnancy with serial transvaginal ultrasounds for cervical length. Some investigators have advocated interpregnancy evaluation using a comprehensive approach including a thorough history, a review of the medical record, a hysterosalpingogram with particular emphasis on the length and diameter of the cervix and an estimation of cervical competence by passing a No 8 Hegar dilator through the non-pregnant cervix and recording the resistance.³ A scoring system was then designed to quantify the results. Although used in some areas, it has not gained widespread acceptance as it is neither completely sensitive nor specific.

ELECTIVE CERCLAGE

When the decision has been made to place a cerclage early in pregnancy, based on history or interpregnancy evaluation, it is most commonly performed between 13 and 15 weeks.

URGENT CERCLAGE

An urgent or therapeutic cerclage is placed when cervical change by either ultrasound or digital examination is detected in an otherwise asymptomatic woman. Several investigators have studied cerclage versus expectant management in women with a short cervical length on ultrasound. Early studies differed in design, in entry criteria, and in type of cerclage placed. Their findings were conflicting, with some showing no difference between expectant management and cerclage, and others favoring cerclage. The largest multicenter

study to date randomized 253 women with a cervix less than 15 mm, identified between 22 and 24 weeks' gestation, to Shirodkar cerclage or expectant management. The proportion of preterm births before 33 weeks was similar, with 22% in the cerclage group and 26% in the expectant management group. There were no significant differences between groups with respect to perinatal or maternal morbidity or mortality. Results of the recent literature are summarized in Table 60.1. A cerclage should only be considered when there is no evidence of chorioamnionitis, vaginal bleeding, or preterm contractions, and only following detailed counseling of the patient.

EMERGENT CERCLAGE

When a woman presents with a dilated cervix with or without prolapsing membranes, between 16 and 24 weeks, in the absence of contractions, bleeding or pain, consideration is often given to an emergent cerclage. This poses a therapeutic dilemma as there is a paucity of evidence to guide the practicing physician. The lack of evidence coupled with both the woman's and physician's desire to do something positive often results in an emergent therapeutic cerclage. Small observational and non-randomized comparative studies of emergency cerclage show variable results, ranging from prolongation of pregnancies from 1 to 19 weeks with reported perinatal mortalities up to 55%.¹⁰ The most common perinatal complications were chorioamnionitis and preterm premature rupture of membranes.

TECHNIQUE OF CERCLAGE

Prior to cerclage placement, a gestational age appropriate ultrasound evaluation of the fetus should be performed.

There are two widely recognized transvaginal procedures:

- 1 *McDonald*. The McDonald cerclage is commonly used because of its simplicity. A pursestring suture is placed circumferentially around the upper body of the cervix at the vesicocervical junction in four separate sutures. The knot can be tied anteriorly or posteriorly depending on the preference of the surgeon. A variety of permanent sutures are used including but not limited to: Ethibond, Mersilene, or Prolene.
- 2 *Shirodkar*. The Shirodkar cerclage, also widely used, is more complex. This technique requires dissection of the bladder anteriorly and the rectum posteriorly in an effort to place the cerclage closer to the internal os. A 2–3 cm transverse submucosal incision is made anteriorly at the level of the reflection. The bladder is then dissected superiorly 1–2 cm. A 2–3 cm transverse submucosal incision is then made posteriorly at the level of the reflection and the rectum is dissected superiorly. The edge of the anterior and posterior dissection is then grasped with an Alice clamp on both sides. A submucosal suture is then placed anterior to posterior and then posterior to

Table 60.1 Studies comparing management of women with incompetent cervix.

Study Place	Study criteria	Type of study, number of study subjects	Type of cerclage	results
Heath <i>et al.</i> 1998 ⁴ London, UK	Cervix < 15 mm at 23 weeks routine assessment asymptomatic, high risk and low risk	Comparative observational cohort non-randomized <i>n</i> = 43	22 Shirodkar No tocolysis 21 expectant	Cerclage 95% > 32 weeks bedrest 48% > 32 weeks 10-fold reductions in risk with cerclage Favored cerclage
Hibbard <i>et al.</i> 1999 ⁵ Chicago, USA	Cervix < 30 mm at 20 weeks asymptomatic high risk	comparative observational cohort non-randomized <i>n</i> = 85	43 cerclage 42 no cerclage bed rest, tocolytics Type of cerclage not stated	cerclage 34 + 5.4 bedrest 32 + 6.0 <i>P</i> = 0.04 Favored cerclage
Althusius <i>et al.</i> 2000 ⁶ CIPRACT, Netherlands	Cervix < 25 mm < 27 weeks high-risk patients only	Randomized controlled trial <i>n</i> = 35	McDonald 19 cerclage 16 bedrest	Delivery before 34 weeks 0/19 cerclage 7/16 bedrest Favored cerclage
Berghella <i>et al.</i> 1999 ⁷ Pennsylvania, USA	Cervix < 25 mm at 24 weeks high-risk patients	Comparative observational cohort non-randomized <i>n</i> = 63	39 cerclage 24 bedrest Did not specify type of cerclage	Cerclage 33 + 6.7 weeks Bedrest 35.0 + 5.4 weeks No difference
Rust <i>et al.</i> 2000 ⁸ Pennsylvania, USA	Cervix < 25 mm at 16–24 weeks high risk and low risk	Randomized controlled trial <i>n</i> = 61	31 McDonald 30 bedrest	Cerclage 33.5 + 6 weeks bedrest 34.7 + 4 weeks No difference
To <i>et al.</i> 2004 ⁹ Multicentre, international	Cervix ≤ 15 mm at 22–24 weeks high risk	Randomized controlled trial <i>n</i> = 253	Shirodkar 127 cerclage 126 no cerclage	Delivery before 33 weeks 22% cerclage 26% expectant No difference

anterior (or vice versa, depending on surgeon's preference). The suture is entirely submucosal. The knot is then tied and the tail classically secured to the band. Mersilene tape is the traditional suture of choice. The mucosa is then reapproximated.

EMERGENCY CERCLAGE

Several authors have described their techniques. All include antibiotics which continue for a variable period afterwards. Several techniques have been described to reduce the membranes from the vaginal vault back into the uterus. These include maternal Trendelenburg position, filling the bladder through a Foley catheter with 800–1000 mL, placement of a 30–50 mL Foley balloon up through the cervix, and a moistened sponge stick. Once the membranes are reduced, a McDonald or Shirodkar cerclage can be performed depending on the length of the cervix and the surgeon's preference.

Several modifications of both techniques have been described and adopted over the years. The Wurm procedure is an emergency cerclage technique that utilizes mattress sutures to close the cervix.

ABDOMINAL CERCLAGE

For those women who have a congenital or an acquired (multiple cervical surgeries) hypoplastic cervix and a transvaginal approach is not technically feasible, or for women who failed a transvaginal cerclage, an elective abdominal cerclage has been advocated. Traditionally, an abdominal cerclage required a laparotomy with adequate mobilization and visualization of the uterus between 13 and 15 weeks. After dissection of the bladder inferiorly, the uterus was removed from the abdomen and a Mersilene band was placed through the tissues of the lateral cervix at the level of the internal os. Various techniques have been described in order to minimize bleeding from the uterine arteries and their branches in this very vascular anastomotic network. The knot was then tied anteriorly and the laparotomy incision closed. A cesarean delivery was required. Abdominal cerclage is available in selected centers, is performed infrequently, and requires considerable skill and expertise. Recently, a laparoscopic approach to abdominal cerclage has been reported and holds promise.¹¹

CERCLAGE OUTCOMES

In the largest retrospective review to date of 482 cerclage placements, cervical dilation at time of cerclage, gestational age at placement, and number of previous pregnancy losses before 24 weeks' gestation were key determinants of pregnancy outcome.¹² Cervical dilation of more than 2 cm at cerclage was associated with a greater risk of preterm premature rupture of membranes and premature birth. No differences in obstetric outcomes were seen between Shirodkar and McDonald techniques, except for a higher incidence of cesarean

delivery with the Shirodkar technique. Two authors have addressed the effects of a retained cerclage in the setting of preterm premature rupture of membranes (PPROM). Ludmir *et al.*¹³ reported on 31 patients with prophylactic cerclage with PPRM between 24 and 32 weeks. Twenty had immediate removal and 10 were left in place. They compared outcomes with 33 women without cerclage and PPRM. They found a greatly increased risk of perinatal mortality in those women with a retained cerclage (70%), versus removed cerclage (10%), versus PPRM only (18%). More recently, McElrath *et al.*¹⁴ reported on 114 cases of PPRM and cerclage and matched with 288 controls. They found no differences between maternal or neonatal morbidities between groups and conclude that a cervical cerclage at the time of PPRM less than 34 weeks does not adversely affect pregnancy outcome.

FOLLOW-UP

There are neither standardized guidelines nor evidence on how best to proceed after cerclage placement. The traditional approach is to see a woman every 2–3 weeks after elective cerclage placement for cervical examinations. Activity level recommendations range from bed rest to full activity, with every modification in between being well represented. Several authors have described ultrasound follow-up of cervical lengths, although there is no evidence that such imaging changes outcome.

CONCLUSIONS

The clinical indications for cerclage have broadened over the past decade as has our understanding of the role of the cervix in preterm birth. However, there is little evidence to support this broader practice. In a recent Cochrane review to assess effectiveness and safety of elective and urgent cerclage, six trials for a total of 2175 women were analyzed.¹⁵ They concluded that the use of a cervical stitch should not be offered to women at low or medium risk of mid-trimester loss, regardless of cervical length by ultrasound. The recent randomized controlled study by To *et al.*⁹ supports their conclusions. Although it is clear that a short cervix is a powerful predictor of preterm birth, the etiology of a short cervix is unclear. Identifying those women with a short cervix resulting from cervical incompetence and in need of a cerclage remains a clinical challenge. The decision to place a cerclage should not be solely based on a finding of a short cervix but rather on a comprehensive assessment of obstetric and gynecologic history, the physical examination and imaging study of the cervix, and exclusion of other causes. Until further diagnostic studies are available to the clinician, the decision must rest on sound clinical judgment coupled with an understanding of the literature as it evolves.

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Nausea and vomiting

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INTRODUCTION

Approximately 75% of pregnant women may experience some degree of nausea and vomiting during a pregnancy. In addition, approximately 35% of gravidas with nausea and vomiting will consider their symptoms severe enough to limit activities of daily living. This disruption in quality of life further extends to loss of time at work, ineffectiveness at home or at work, and deterioration in relationships. The economic impact alone has been estimated in the \$3000–17,000 range for women with mild to severe symptoms of nausea and vomiting of pregnancy (NVP), respectively.¹ Hyperemesis gravidarum (HG), the most severe form of NVP, is seen in less than 2% of cases of nausea and vomiting, but the true incidence of HG is difficult to ascertain because of the varying diagnostic criteria that have been used over time. Unfortunately, because NVP is so common, symptoms and therefore treatment are often minimized by both patients and healthcare providers. When symptoms are minimized, treatment is also minimized and NVP will more often progress to more severe levels.²

The precise etiology of NVP is unknown. Various theories have been proposed which include a psychologic predisposition, evolutionary adaptation to pregnancy, hormonal stimulus, and gastric dysmotility.² Psychologic theories of stress or somatization disorder have not held up. Likewise, an adaptive mechanism that prevents a woman from eating foods that could harm the fetus would be difficult to verify. NVP as a response to increased estrogen and human chorionic gonadotropin (hCG) concentrations during pregnancy may have the most plausible association. Increased estrogen is associated with nausea and vomiting in a dose-dependent fashion, while increased hCG seen during molar gestation has a long-standing association with increased nausea and vomiting.² Gastrointestinal motility is diminished during pregnancy, and gastric emptying time is prolonged.

Risk factors for NVP include an increased placental mass as seen with molar gestation or multiple gestations, a family history or personal history of HG, and a history of motion sickness or migraines.

DIAGNOSIS

It is common for nausea to be most severe on rising; hence, the term *morning sickness* for this complaint. A number of pregnant women experience their most severe symptoms at other times of the day, and the failure of nausea to be restricted to the morning in no way invalidates the complaint.

Not all women who experience NVP have the condition strictly related to pregnancy alone. Other underlying conditions must always be excluded (Table 61.1), especially when symptoms of nausea and vomiting begin before 5 weeks' gestation, persist after 12 weeks, or are persistently severe. Findings not associated with simple NVP include abdominal pain upon palpation, fever, headache, goiter, and an abnormal neurologic examination.²

The disease along the entire spectrum of its presentation has been categorized according to severity, duration, and early manifestations. The condition may be considered mild when nausea and vomiting occurs for less than 1 h during the day and the amount of vomiting and retching occurs only up to twice daily. When the symptoms persist for 6 h or more with five or more

Table 61.1 Differential diagnosis of nausea and vomiting of pregnancy. (From ACOG 2004.²)

<i>Gastrointestinal conditions</i>
Gastroenteritis
Biliary tract disease
Hepatitis
Peptic ulcer disease
Pancreatitis
Appendicitis
<i>Genitourinary tract conditions</i>
Pyelonephritis
Ovarian torsion
Kidney stones
<i>Metabolic disease</i>
Diabetic ketoacidosis
Hyperthyroidism
<i>Neurologic disorders</i>
Pseudotumor cerebri
Vestibular lesions
Migraines
Tumors of the central nervous system
Drug toxicity or intolerance
Psychologic condition

episodes of vomiting and retching, NVP may be considered severe. Hyperemesis gravidarum is at the most severe end of this spectrum and in addition to nausea and vomiting, the diagnosis of HG is further characterized by weight loss ($\geq 5\%$), ketonuria, electrolyte disturbances, and dehydration. An appropriate evaluation for NVP through its spectrum to HG may include but not be limited to laboratory testing (Table 61.2). This battery of testing may identify medical conditions confused with NVP but in most cases no cause other than pregnancy will be found. Thyroid function testing has not been included in this battery of tests. The structural homology of hCG and thyroid-stimulating hormone (TSH) contribute to the appearance of transient hyperthyroidism in early pregnancy. This usually resolves by 18 weeks' gestation without further sequelae. Symptoms and/or laboratory testing suggestive of hyperthyroidism that predate the pregnancy are more likely to identify true thyroid disease; therefore, review of symptoms in these cases is most helpful in making the diagnosis.^{3,4} *Helicobacter pylori* have been suggested as an etiologic agent in NVP. Although no clear association has been established, the identification and treatment of *H. pylori* may resolve symptoms in some cases.⁵

Although rare, persistent vomiting over several weeks may result in a deficiency of vitamin B₁ (thiamine). Severe thiamine deficiency can further lead to Wernicke encephalopathy, characterized by the classic triad of ophthalmoplegia, gait ataxia, and mental confusion. Therefore, in the severest cases of NVP or HG, thiamine levels should be considered and treated as needed.⁶

TREATMENT

Treatment of NVP varies with the severity of the disease. The initial therapies are non-pharmacologic and include increased rest and avoidance of foods or odors that trigger symptoms (perfumes, smoke, petroleum products). Adjust eating habits to include small, frequent snacks to avoid having an empty stomach. Select bland and dry foods or foods high in protein and avoid spicy, fatty, or acidic foods. Meals high in protein have been shown to alleviate nausea and vomiting more successfully than carbohydrate or fatty meals.

Table 61.2 Laboratory evaluation.

Complete blood count
Urinalysis or urine culture, or both
Urine-specific gravity, acetone, ketones
Serology for hepatitis A, B, and C
Hepatic transaminases
Serum acetone
Serum electrolytes

Acupressure may be useful for the treatment of NVP by applying the pressure at the Neguian P6 acupoint. This point lies approximately 2 inches (5 cm) proximal to the wrist crease between the flexor carpi radialis and palmaris longus tendons.⁷

Pressure at this location may be simple pressure alone or combined with electrical stimulation. Studies conducted using P6 therapy show a preponderance

Table 61.3 Pharmacologic agents for use in nausea and vomiting in pregnancy. (From ACOG 2004² and Briggs *et al.* 2001.¹³)

Agent	Risk factor category
<i>H₁ blockers</i>	
Doxylamine (Unisom®)	Unlisted
Dimenhydrinate (Dramamine®)	B
Certirizine (Zyrtec®)	B
Meclizine (Antivert®)	B
Hydroxyzine (Vistaril®, Atarax®)	C
Diphenhydramine (Benadryl®)	B
Promethazine (Phenergan®)	C
<i>Anticholinergics</i>	
Scopolamine	C
<i>Dopamine antagonists</i>	
Trimethobenzamide (Tigan®, Benzacot®)	C
Metoclopramide (Reglan®)	B
<i>Butyrophenones</i>	
Droperidol (Inapsine®)	C
Haloperidol (Haldol®)	C
<i>Phenothiazines</i>	
Prochlorperazine (Compazine®)	C
Chlorpromazine (Thorazine®)	C
Perphenazine (Trilafon®)	C
<i>Benzodiazepines</i>	
Diazepam (Valium®)	D
<i>5-Hydroxytryptamine 3 receptor agonists</i>	
Ondansetron (Zofran®)	B
<i>Steroids</i>	
Methylprednisolone	C

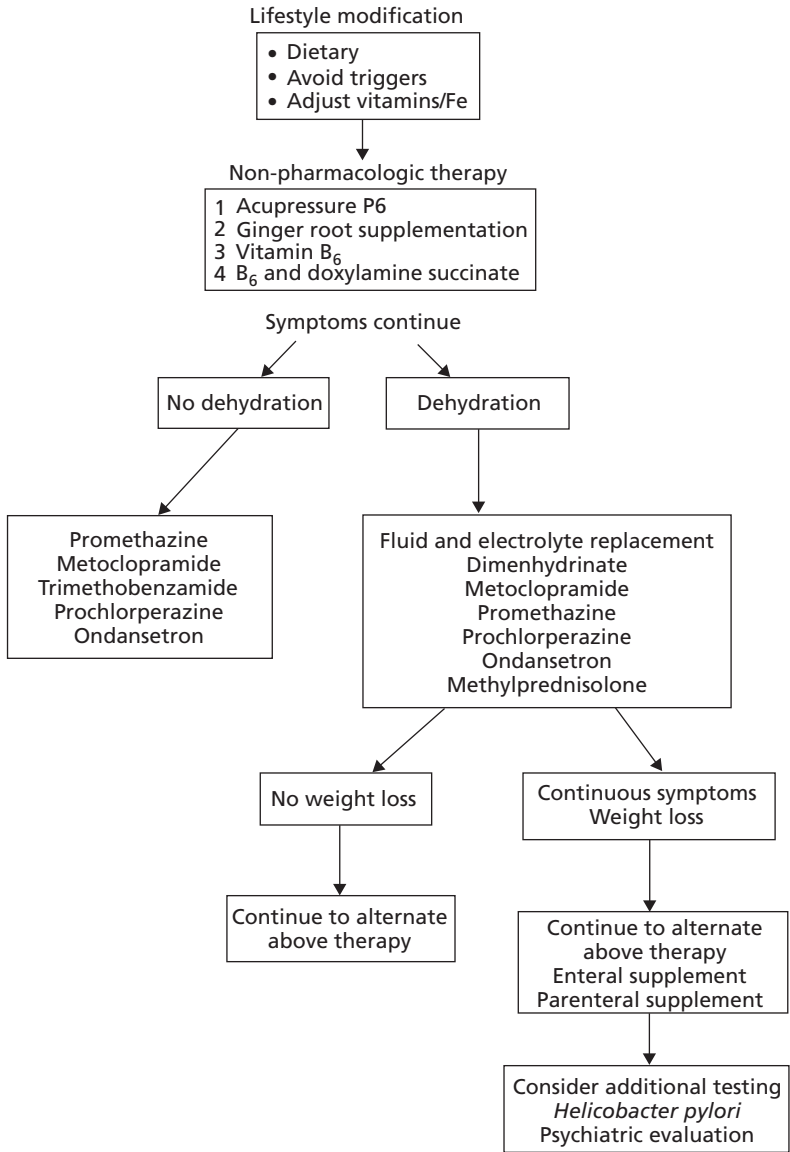


Fig. 61.1 Treatment algorithm for NVP.

of positive results in reducing nausea and vomiting.^{8,9} However, many of the trials are plagued by small sample size, inadequate blinding, and lack of appropriate controls. This being said, the modality is low cost, there are no known adverse effects, and, in general, is worth trying in the patient motivated to do so.

Ginger root, a common spice and flavorer, has been used for the treatment of NVP. Several randomized trials are now available suggesting benefit by the ingestion of ginger root for the reduction of nausea and vomiting.^{10,11}

Vitamin therapy, specifically vitamin B₆ (pyridoxine) has been demonstrated as effective in randomized controlled trials. A popular regimen would be 25 mg orally every 8 h for the reduction of severe nausea.¹² Historically, vitamin B₆ when combined with the antihistamine doxylamine succinate proved a successful antiemetic. A single pill combining both of these medicines is no longer available in the USA; however, the separate products can be obtained over the counter.

Many conventional antiemetics have also been used for treatment and include the classifications of agents seen in Table 61.3.

Treatment decisions for NVP must be based on numerous factors, including symptom severity, clinical consequences of treatment versus lack of treatment, and fetal safety. Treatment decisions must be individually based; however, treatment algorithms have been proposed to facilitate rational use of medicines (Fig. 61.1).

The most controversial of the agents are droperidol, and corticosteroids. Droperidol at doses greater than 25 mg maybe associated with Q-T intervals and therefore should be used with caution. Corticosteroids have shown some efficacy in cases of severe HG; however, they may be associated with oral clefts when used in the first trimester. Given this risk of teratogenesis, albeit weak, precaution should be used when considering steroids in the first trimester.

PREVENTION

Women with previous pregnancy-related NVP and/or hyperemesis may be at risk for similar occurrences in subsequent pregnancies. Studies have suggested that multivitamin use at the time of conception may be associated with a reduction of NVP. It is reasonable, therefore; to advise a woman with a history of this condition to take a multiple vitamin around the time of conception.

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Syncope

Gary D. Helmbrecht

INTRODUCTION

Syncope is derived from the Greek term *synkope*, meaning deliquium animi. Classically, it refers to the sudden loss of consciousness mediated by an autonomic nervous reflex, termed *neurocardiogenic syncope*. Except for the rare patient with frequently recurring “malignant” disease, most forms of neurocardiogenic syncope are benign in nature and require no special treatment. Syncope that occurs because of a non-reflexive mechanism, however, may be the only clinical sign of serious underlying pathology such as cardiac dysrhythmia or cerebrovascular accident. The clinician is then challenged to determine which patients can be reassured, and in whom an exhaustive work-up is required.

ETIOLOGY

Of the neurocardiogenic forms, vasovagal syncope occurs most commonly and is simply the result of enhanced antagonism of sympathetic and parasympathetic mechanisms that occur in response to pain, temperature, or other stimuli. The predominant pathophysiology may be cardiodepressive (i.e. bradycardia), vasodepressive (i.e. dilation of resistance arterioles), or mixed. Consequently, a fall in cardiac output or systemic blood pressure, or both, results in decreased cerebral perfusion and the observed loss of consciousness. The patient will recall a prodrome of flushing, lightheadedness, and perhaps loss of vision just before the event. Unconsciousness is usually quite brief and once cerebral perfusion is restored, the patient recovers rapidly. Generally, no serious sequelae result directly from vasovagal syncope. However, the patient may sustain injury from the fall, or worse if operating a motor vehicle at the time. Other forms of neurocardiogenic syncope are listed in Table 62.1.

Non-reflexive syncope may be a clinical sign of serious underlying pathology. The differential diagnosis includes seizure disorders, subarachnoid hemorrhage, amaurosis fugax, cerebrovascular accident, cardiac dysrhythmias, myocardial infarction, pulmonary embolus, hypoglycemia, hyponatremia,

Table 62.1 Causes of neurocardiogenic syncope.

Diagnosis	Description
Vasovagal syncope	Enhanced para and/or sympathetic antagonism in response to painful or other stimuli
Carotid syncope	Vagal reflex resulting from pressure applied to the carotid sinus
Hysterical syncope	Fainting brought about by, or to avoid, emotional stress
Laryngeal syncope	A paroxysmal neurosis characterized by attacks of coughing followed by fainting (Charcot vertigo)
Micturition syncope	Fainting caused by the increased parasympathetic tone associated with detrusor muscle contraction
Postural syncope	Fainting induced by assuming an upright position

hypomagnesemia, intoxication, superior vena cava syndrome, and supine hypotension syndrome. Various medications may also cause syncope by virtue of arrhythmogenic or psychogenic properties or effects on vasomotor tone. Paradoxical embolization is a rare cause of syncope. Following pulmonary embolus, right heart pressures may increase sufficiently to open an anatomically patent, but previously physiologically closed, foramen ovale, allowing embolization, via the left heart, to the cerebral circulation.

DIAGNOSIS AND MANAGEMENT

A careful history and physical examination are essential in the evaluation of syncope. Any persons who may have witnessed the episode should be involved. They may be able to comment on whether the patient exhibited seizure activity or had postictal weakness or confusion. A history of urinary or fecal incontinence also supports seizure as the cause. The patient may relate seeing “the shades pulled down over my eyes,” which is suspicious for amaurosis or other cerebral embolic phenomena. This should be highly suspected in a patient with a cardiac valve prosthesis or a history of atherosclerotic vascular disease. A history of palpitations, a garlic taste, and lightheadedness preceding the episode supports cardiac dysrhythmias, including ventricular tachycardia, torsade de pointes, Wolff–Parkinson–White syndrome, or supraventricular tachyarrhythmias. Hypoglycemia is suspected in the diabetic patient who is receiving insulin. Other metabolic derangements may be responsible in a patient on cancer chemotherapy or total parental nutrition. Syncope or near syncope is commonly seen in conditions in which venous return to the heart is compromised by transient obstruction. The presence of a neck or mediastinal mass may lead one to suspect superior vena cava syndrome, as seen in Hodgkin lymphoma, small cell lung cancer, or tuberculosis. As the gravid uterus is dextrorotated, inferior vena caval compression can occur when the

patient is supine, sitting, or standing. Rapid recovery in the left lateral position is diagnostic of supine hypotension syndrome. Syncope that occurs in a post-operative patient or a patient suspected of having an abruptio placentae or placenta previa should alert the clinician to circulatory failure on the basis of hypovolemia. A careful medication history will reveal the patient on digoxin who may be having hypokalemia-related dysrhythmias, or various antihypertensives that may cause postural hypotension.

The diagnostic evaluation is summarized in Table 62.2. Recently published

Table 62.2 Diagnostic evaluation and management of syncope.

Suspected diagnosis	Test: consulting service	Management
Neurocardiogenic syncope	Head-angle tilt table test Consultation: cardiology	Parasympatholytic agents, cardiac pacing
Seizure disorder	EEG, auditory evoked potentials, CT or MRI Consultation: neurology	Anticonvulsant
Embolic phenomenon	Cardiac echo, carotid Doppler, head CT or MRI, arterial blood gas, chest X-ray, ventilation– perfusion scan, cardiac catheterization Consultation: neurology, cardiology, pulmonary	Anticoagulation
Cardiac dysrhythmia	ECG, Holter monitor, cardiac echo, serum electrolytes Consultation: cardiology	Antiarrhythmic, cardiac pacing
Metabolic derangement	Serum electrolytes, glucose, calcium, magnesium, phosphorus Consultation: endocrinology	Glucagon, replace deficient electrolytes
Intoxication	Drug screen Consultation: psychiatry	Naloxone (Narcan®), detoxification
Hypovolemia	History, orthostatic vitals, complete blood count	Intravenous isotonic fluids, colloid, blood products
Superior vena cava syndrome	Chest X-ray, CT Consultation: pulmonary, oncology	Surgery, chemotherapy, radiation as appropriate

CT, computed tomography; ECG, electrocardiography; EEG, electroencephalography; MRI, magnetic resonance imaging.

studies have confirmed the diagnostic accuracy of the head-upright tilt test in evaluation of neurocardiogenic syncope. Upright tilt testing is commonly used in the evaluation of patients with syncope to provoke hypotension and/or bradycardia in the laboratory. The American College of Cardiology Expert Consensus has proposed indications for tilt testing. The most common indication is recurrent syncope of unexplained cause. Upright tilt testing methods have not been standardized. The most common protocols in the USA use a tilt angle of 60–80° and use isoproterenol infusion after a period of drug-free tilt testing. The sensitivity of upright tilt testing is estimated to be 67–83%, and the specificity 75–100%. The reproducibility of the test has been somewhat variable.

The appropriate tests and consultations are directed by findings on history and physical examination. Therefore, a “shotgun approach” for every patient is costly and should be discouraged.

Acute management of a syncopal episode in a gravid patient should begin with the ABCs of resuscitation. First, ask for help. In most institutions, this means calling a code blue. Next, place the patient in a supine position with left lateral tilt using a hip roll and, assuming no cervical injury, turn the head to the left with the neck somewhat extended. This will maintain a patent airway and minimize the risk of aspiration. While vital signs are being recorded, place a large-calibre intravenous line. Glucagon, naloxone (Narcan®), atropine, or anticonvulsant can then be administered as necessary. Once the patient is on a cardiac monitor, antiarrhythmic therapy can be given in accordance with ACLS guidelines. Only after the mother’s condition is stabilized should fetal well being be considered. Keep in mind that, in most instances, the best place to resuscitate a fetus following a hypotensive episode in the mother is *in utero* and heroic measures such as emergent cesarean delivery will represent undue hazard to the mother.

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Fetal wastage: genetic evaluation

Joe Leigh Simpson

INTRODUCTION

At least 12–15% of clinically recognized pregnancies terminate in fetal loss. Before the time pregnancy is ordinarily appreciated by clinical criteria (approximately 6 weeks' gestation), the frequency of loss is even higher. The majority of all conceptuses are lost before a woman recognizes she is even pregnant. Given the high frequency of clinically recognized spontaneous abortions, it is not surprising that recurrent fetal wastage is a common phenomenon. At least 1% of women have experienced three or more pregnancy losses.

PATHOPHYSIOLOGY

The most common general cause of spontaneous abortion is abnormal embryologic development, as judged both by morphologic studies and by chromosomal analysis. Over 50% of first trimester abortuses show chromosomal abnormalities, and there is evidence that the frequency is even higher. If chorionic villus sampling is used to obtain tissue from an abortus that has not yet been expelled spontaneously (i.e. missed abortion), approximately 80% of samples are normal. Approximately 50% of the abnormalities show autosomal trisomy, 25% triploidy, 20% monosomy X, and 5% structural abnormalities such as translocations.

Although accounting for only a relatively small proportion of all first trimester abortuses, overall translocations play a disproportionately important part in recurrent abortions. In approximately 2–5% of couples who experience repetitive abortions, one parent will show a balanced translocation. If a couple's pregnancy history includes not only abortions but also stillborns or anomalous infants, the likelihood of a parental translocation is higher. The prevalence of translocations is higher in females than males.

Other genetic factors—Mendelian (single gene) or polygenic/multifactorial—are responsible for spontaneous abortion. In fact, mutant genes probably

underlie most so-called “non-genetic” factors. For example, luteal-phase defect doubtless has a genetic basis, perhaps progesterone receptor defects. Heritable thrombophilias are clearly genetically mediated.

Likewise, any alloimmune causes of pregnancy loss must by definition be genetically determined. Here the presumptive mechanism involves an embryo failing to differ from its mother at certain histocompatibility (HLA) loci. This phenomenon has traditionally been invoked when mother and father share a given HLA antigen. If the fetus inherits from its father an antigen identical to that its mother already has, an opportunity is lost for embryo and mother to differ at that locus. Paradoxically, this may prove not to be salutary. Sharing need not necessarily involve HLA, and could involve other related or undefined genes.

Immunologic and other traditionally “non-genetic” causes will not be considered in detail in this chapter. Some are plausible, others probably less so as a common cause. Hormonal deficiencies, specifically luteal-phase deficiency, are popular hypotheses. Yet data on the frequency of luteal-phase defects in the general population and in recurrent abortion are meager, and treatment is unproved (no randomized clinical trials). Another plausible explanation is infection. Many different agents have been proposed, with *Ureaplasma urealyticum* receiving the greatest attention. Certain toxins (cigarettes, alcohol) seem to increase the risk of spontaneous abortions. However, exposure to toxins is a less plausible explanation for *recurrent* first trimester losses, given low absolute risk secondary to exposure and given knowledge that few exposed women abort. Uterine abnormalities are capable of causing recurrent second trimester losses: incompetent cervix, müllerian fusion defects, submucous leiomyoma, and uterine synechiae. However, in the first trimester, uterine factors are probably only infrequent causes of pregnancy losses. Attributing first trimester losses to uterine factors is most logical when the embryo was known to have been viable at, for example, 8–9 weeks’ gestation and if fetal karyotype was normal.

DIAGNOSIS

There is no universally accepted definition of “recurrent” losses. Usually, the criterion of at least two losses is applied and in younger women the more typical definition is three losses. Precise timing of loss is also not precisely defined, save less than 20 weeks. Pregnancies manifesting as clinically recognized abortions were once not recognized until 8–13 weeks following the last menstrual period (6–11 embryonic weeks). However, it is now clear that most abortuses have been deceased weeks prior to clinical manifestation (bleeding, passage of products of conception). Such a deduction was made because only 3% of pregnancies proven viable (heart rate, fetal motion) by an 8–9 weeks ultrasound examination were lost thereafter. Because 10–12% of clinical pregnancies are

lost overall, fetal demise in many clinically evident pregnancies must have occurred weeks or months before clinical recognition. The consequence is that the precise time in the first trimester when a loss is thought to have occurred need not bear pivotally on work-up or management.

WORK-UP

Evaluation for repetitive abortions is indicated after two or three first or second trimester abortions, the number reflecting individual circumstances (especially parental ages). Genetic evaluation is not necessarily indicated if *second trimester* losses have occurred in the presence of incompetent cervix or incomplete müllerian duct fusion. Conversely, uterine abnormalities should not necessarily lead one to exclude other explanation for *first trimester* losses.

Occurrence of a stillborn or anomalous liveborn infant necessitates genetic evaluation irrespective of the number of prior abortions.

A couple being evaluated for repetitive abortions should be seen together. Allow sufficient time to elicit appropriate history, provide relevant information, and answer any questions. Hurried sessions are likely to exacerbate anxieties and impede comprehension of important information. Appreciate that a couple experiencing a pregnancy loss undergoes the same sequence of grief reaction as occurs following death of a loved one or of an anomalous liveborn infant: denial, anger, depression, bargaining (rationalization). A couple's failure to comprehend seemingly lucid instructions or their display of inappropriately directed anger is to be expected and should be seen as part of the normal grieving process.

Obtain histories of exposures to potential toxins:

- 1 Past exposures to potentially noxious agents (e.g. chemotherapeutic agents, therapeutic X-rays, therapeutic radionucleotides)
- 2 Drugs either partner is currently taking
- 3 Employment history, specifically exposure to toxins in the workplace
- 4 Exposure to alcohol and cigarette smoke

Ask about the health status and presence of anomalies in first-degree (siblings, parents, offspring), second-degree (aunts, uncles, nieces, nephews, grandparents), and third-degree (first cousins) relatives of both husband and wife. Ask the couple to recall specifically each sibling and his or her pregnancy outcome. Misleading information can be obtained by posing only general questions such as, "Did any relative have a birth defect?" Inquire not only about birth defects and pregnancy losses, but also about stillborn infants, infant or childhood deaths, childhood operations, mental retardation, early adult deaths, and infertility.

MANAGEMENT

Empiric risk statistics has an important role in counseling. If a couple has experienced one or more fetal losses, the likelihood that a similar event will occur is

increased to 25–30%, assuming the couple has at least one liveborn infant. This risk applies whether the number of prior abortions is one, two, three, or even four. If a couple has no liveborn infants, the risk rises to approximately 40–45%. No evidence supports the concept that recurrence risk is dramatically increased after only three spontaneous abortions. The key epidemiologic correlate is maternal age. This positive correlation holds for trisomic as well as for normal (euploid) embryos.

Arguably the most useful service one can offer a couple who has experienced fetal wastage is education. Recitation of salient medical and genetic facts, specifically those mentioned above, is an essential component of management. Many couples are convinced that fetal wastage has occurred as a result of preventable factor(s) for which they are responsible. To place genetic causes in their proper context, mention luteal-phase deficiency, infectious processes, immunologic causes, uterine anomalies, and potential toxins. However, state that these causes in aggregate fail to sum to that of cytogenetic causes, which are not only responsible for most pregnancy losses but can neither be prevented nor do they reflect lifestyle. Such statements will mitigate against the guilt and blame that couples invariably experience.

Appreciate that a couple experiencing a pregnancy loss is undergoing the sequence of grief reactions that occurs following death of a loved one or birth of an anomalous liveborn infant: denial, anger, depression, bargaining (rationalization). Failure to comprehend grief reactions may impede communication and leave the provider perplexed with a couple's seemingly inexplicable reactions (e.g. misdirected blame).

If a couple has indications (e.g. advanced maternal age) for formal genetic counseling other than that relevant for repetitive abortions, discuss this concurrently.

Jewish, and in particular Ashkenazi Jewish couples should be screened to determine whether they are heterozygous for the autosomal recessive disorders Tay–Sachs disease, Canavan disease, or cystic fibrosis. Screening for other disorders common in the Ashkenazim (e.g. Fanconi anemia) is currently optional. African-Americans should be screened for sickle cell anemia. Individuals of Mediterranean origin (Italian, Greek) should be assessed for β -thalassemia and South-East Asians for α -thalassemia. Cystic fibrosis (CF) screening, using the ACOG/ACMG panel of 23 mutations, should be offered to Caucasians of European or Ashkenazi Jewish background. CF screening should be made available to other ethnic groups (African-American, Hispanic, Asian).

Chromosomal studies of the couple are obligatory because 2–5% of couples experiencing repetitive losses will show a chromosomal rearrangement. The likelihood of detecting a parental translocation is higher if a couple has experienced not only repetitive abortions but also a stillborn infant, an anomalous liveborn infant, or an unexplained neonatal death. In this group, cytogenetic studies are indicated after only a single fetal loss. Irrespective, parental

chromosomal studies should be performed whenever evaluation is considered appropriate. Do not order one set of laboratory tests after, say, two losses, yet another set of tests (e.g. parental chromosomes) after, say, three losses. The likelihood of detecting a parental translocation increases only slightly as the number of abortions increases from one to four, and is probably lower in couples experiencing six or more losses.

Finding a translocation should, in general, not be assumed to increase the likelihood of pregnancy loss over the stated 25–40% risk. However, in a few couples, gametes and embryos seem to be abnormal in such proportions as to result in clinical infertility and repeated abortions. This could simply be stochastic or it could reflect predilection of a particular rearrangement to yield lethal gametes preferentially.

If a parental translocation or inversion is detected, referral to a geneticist is appropriate. Geneticists may apply pooled empiric risk figures or attempt to derive translocation specific risks. Empiric risk figures are available for only a few common translocations and not for any inversion. Discussions concerning structural arrangements should include an offer for prenatal cytogenetic diagnosis (amniocentesis, chorionic villus sampling, preimplantation genetic diagnosis).

If neither a translocation nor an inversion is detected, the couple should be informed about recurrent aneuploidy. Not all authorities agree, but the likelihood of an abortus being aneuploid seems to be similar whether a loss is sporadic or is one of recurrent losses. Multiple losses do not mean non-genetic causation. Numeric chromosomal abnormalities in successive pregnancies can be the cause of recurrent abortuses. That is, repetitive abortuses usually show either all to be chromosomally abnormal (e.g. trisomy) or all to be chromosomally normal. The fear is that the couple's next trisomic conception might be viable and liveborn (e.g. trisomy 21). Thus, a previous trisomic abortus constitutes grounds for offering prenatal cytogenetic studies. If cytogenetic information on a prior abortus is desired and is not available, fluorescence *in situ* hybridization (FISH) with chromosome-specific probes (chromosomes 13, 16, 18, 21, X, and others) can be performed on tissue derived from paraffined products of conception.

Couples experiencing repeated losses as a result of unbalanced translocation or recurrent aneuploidy may benefit from preimplantation genetic diagnosis with transfer of euploid embryos. This regimen decreases the frequency of clinical abortions, increases the implantation rate, and, in selected patients, increases the frequency of liveborns.

FOLLOW-UP

If a balanced translocation is found in either parent, prenatal cytogenetic diagnosis must be offered.

If autosomal trisomy is detected in an abortus, the risk for aneuploidy is increased in any subsequent pregnancy. Prenatal cytogenetic studies should be offered.

If a pregnancy loss occurs in subsequent pregnancies, tissue for chromosomal studies should be obtained to determine chromosomal studies and, hence, exclude recurrent aneuploidy. Specimens should be collected in sterile containers and transported immediately to a cytogenetic laboratory. Balanced salt solutions (e.g. Hank balanced salt solution) are preferable vehicles, but Ringer lactate will suffice. If cultures are unsuccessful, paraffin blocks can be analyzed using chromosome-specific probes (FISH).

In couples manifesting seemingly retractile infertility or repeated losses, preimplantation genetic diagnosis with transfer of euploid embryos can be beneficial.

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Recurrent pregnancy loss: non-genetic causes

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INTRODUCTION

Spontaneous abortion (SAB) or miscarriage is defined as pregnancy loss before 20 weeks' gestation or fetal weight ≤ 500 g. Although most causes of SAB are genetic (50–75%), non-genetic factors are also associated with pregnancy loss. Historically, recurrent pregnancy loss (RPL) was defined as three or more consecutive SABs. RPL is a common clinical problem, affecting 1% of reproductive age women. A definite cause is established in only approximately 50% of couples.

EPIDEMIOLOGY

RPL is currently defined as three or more pregnancy losses, not necessarily consecutive. Of clinically recognized pregnancies, 10–15% result in SAB. Most of these pregnancy losses are clinically evident by 12 weeks' gestation. Embryonic or pre-embryonic demise usually occurs at least 1 week prior to the clinical features of pregnancy loss being recognized. The risk of RPL was once thought to increase progressively with each spontaneous abortion and result in a woman having an 80% chance of a subsequent spontaneous abortion after three SABs. Currently, it is believed that the SAB risk increases with the number of pregnancy losses, but very gradually, and rarely exceeds 40–50%. For a woman who has had a live birth, even if she has had multiple SABs, her risk of SAB in future pregnancies is 30% per pregnancy.

DIAGNOSIS AND TREATMENT

There is no specific number of losses or firmly established criterion that justifies evaluation for RPL or defines the scope of testing. Decisions must be individualized and consider the woman's age, the timing and circumstances surrounding earlier pregnancy losses, elements of the personal and family medical history, and the couple's level of anxiety. Although RPL is defined as three or more losses, clinical investigation and treatment may be considered in couples with two consecutive spontaneous losses when any of the following are also present:

- Embryonic heart activity observed in any earlier pregnancy loss
- Normal karyotype on products of conception from an earlier loss
- Age \geq 35 years
- Infertility

Parental karyotype abnormalities, antiphospholipid syndrome, uterine malformations, and cervical incompetence are the only causes of RPL that are widely accepted. Alloimmunopathology, inherited thrombophilias, endocrinopathies, infections, and environmental exposures have been implicated but are not established causes of RPL. Even after a comprehensive evaluation, recurrent pregnancy loss remains unexplained in more than half of affected couples. Most couples welcome the evaluation to identify any predisposing factor. When a likely cause can be defined, specific counseling and treatment can improve the prognosis for a successful pregnancy. Even when no specific cause can be found, physician reassurance and encouragement are important.

Anatomic factors

Congenital and acquired uterine abnormalities account for 10–15% of women with RPL and are identified by sonohysterography or hysterosalpingography. Magnetic resonance imaging may be required to differentiate septate and bicornuate uteri accurately. The septate uterus is the most common müllerian anomaly, the one most closely correlated with pregnancy loss (65% SAB rate), and the malformation most easily and successfully corrected by hysteroscopic septoplasty. Unicornuate uterus is associated with a 50% SAB rate. Uterine didelphys and bicornuate uterus are associated with approximately 40% SAB rate. However, abdominal metroplasty procedures are rarely indicated for women with a uterus didelphys or a bicornuate uterus. Cervical cerclage may help to improve pregnancy outcomes in women with bicornuate uteri and in those with a unicornuate uterus or a uterus didelphys who have a history of preivable delivery or exhibit progressive cervical shortening during early pregnancy.

Uterine leiomyomas are often identified in women with RPL, but only submucous myomas and larger intramural myomas that encroach upon or distort the uterine cavity are significant. Intrauterine adhesions are an uncommon but established cause of RPL, with improved pregnancy outcomes after hysteroscopic lysis. Lastly, although diethylstilbesterol (DES) use was banned in 1971, affected women are still occasionally seen. Approximately 70% of women exposed to DES *in utero* have a developmental uterine abnormality and have a twofold increased risk of SAB (24%). Cerclage should be considered in women with history of DES exposure and second trimester loss or preterm delivery (Table 64.1).

Table 64.1 Anatomic disorders leading to spontaneous abortion.

Disorder	Available therapy
Uterine septum	Hysteroscopic resection
Bicornuate uterus	Metroplasty
Uterus didelphys	Metroplasty
Unicornuate uterus	Cerclage
Leiomyomas*	Myomectomy
Intrauterine synechia	Hysteroscopic lysis
Cervical incompetence	Cervical cerclage

*Not established as cause.

Immunologic factors

Both autoimmune and alloimmune mechanisms are implicated as causes of RPL. Autoimmune disorders involve an immune response directed against a specific part of the host or self. Alloimmune disorders involve an abnormal maternal immune response to fetal or placental antigens including maternal cytotoxic antibodies, absent maternal blocking antibodies, and disturbances in natural killer cell function and distribution.

Autoimmune diseases such as systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS) are identifiable and treatable disorders associated with RPL. APS is characterized by significant levels of antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies; medium or high positive immunoglobulin G [IgG] levels on at least two occasions more than 8 weeks apart) and one or more clinical features, including RPL, fetal death, and thrombosis. APS is the cause of RPL in 5–10% of affected women. APS may occur as a primary condition in women or as a secondary condition in patients with an underlying autoimmune disease (e.g. SLE). Antiphospholipid antibodies predispose to placental thrombosis or interfere with normal development of the uteroplacental circulation to cause both early and late pregnancy losses. Lupus anticoagulant and anticardiolipin are the two best characterized antiphospholipid antibodies and the only validated immunologic tests in the work-up for RPL. These antibodies cause anticoagulation *in vitro* and thrombosis *in vivo*. The increased risk for pregnancy loss is dependent on both the titer of the antibody and the obstetric history. Low-positive results are of questionable significance, as patients with APS almost always have medium or high-positive titer results. Testing for additional antiphospholipid antibodies and antinuclear antibody (ANA) is of no proven benefit. Combined aspirin and heparin therapy is the most effective and safest treatment and is the preferred treatment for women with RPL associated with APS.

Alloimmune disorders involving maternal immune system recognition and response are suspected causes of RPL. HLA sharing between husband and wife was theorized to result in the absence of a pregnancy-specific antibody that protected the half-foreign fetus from maternal rejection. However, all current methods for the evaluation of suspected alloimmunopathology, including HLA testing, immune cell evaluation (mixed lymphocyte culture, natural killer cell assays), and cytokine testing are investigational. Neither of the two principal immunotherapies advocated for the treatment of alloimmune disorders in women with RPL, paternal leukocyte immunization and intravenous immunoglobulin, have been proven to be effective.

Inherited thrombophilias

Inherited thrombophilias resulting from genetic mutations in clotting factors leading to placental thrombosis have emerged as a potentially important cause of RPL. However, the majority of women with these mutations have completely normal reproductive outcomes. Women with more than one type of mutation or whose fetus inherits the mutation may be at greater risk for SAB.

The indications for screening women with RPL for the growing number of recognized thrombophilias are not yet established. Currently, screening seems appropriate for women with otherwise unexplained RPL with a suspicious loss (after 8 weeks' gestation or detection of embryonic heart activity) or history of other pregnancy complications that may have resulted from thrombosis or placental insufficiency (pre-eclampsia, intrauterine growth restriction, placental abruption). In addition to lupus anticoagulant and anticardiolipin for diagnosis of APS (acquired thrombophilia), screening includes tests for Factor V Leiden and prothrombin gene mutation G20210A. They are the two most common inherited causes of venous thromboembolism and the thrombophilias most highly associated with adverse pregnancy outcomes. The prevalence of these mutations is relatively high among those of European descent (up to 15%) but very low in Asians, Africans, and Native Americans. Measurement of activated protein C resistance is a more global test for detection of both inherited and acquired forms of activated protein C resistance. Screening for the methylene tetrahydrofolate reductase mutation (serum homocysteine) and antithrombin III, protein S, and protein C deficiencies may also warrant consideration, based on past and family medical history.

Given the available data, there is insufficient evidence to support screening for thrombophilia as part of the initial evaluation of RPL. In addition, it is unknown whether treatment will improve pregnancy outcome in these women. Preliminary data suggest that combined treatment with aspirin and heparin may improve pregnancy outcomes in women with RPL and thrombophilia but prospective, controlled trials are required.

Endocrinologic factors

Endocrinologic disorders are a relatively uncommon cause of RPL but include:

- 1 Diabetes mellitus
- 2 Subclinical thyroid disease
- 3 Polycystic ovary syndrome
- 4 Luteal-phase defect

Evaluation of blood glucose and hemoglobin A1C levels is indicated for women with known or suspected diabetes mellitus, but otherwise is unwarranted. It is established that well-controlled diabetes mellitus does not increase the risk of SAB. If a woman who has known diabetes conceives, euglycemic control is important in reducing the risk for SAB. Consistent hyperglycemia increases the risk of SAB.

Thyroid disorders are easy to identify and treat and should be excluded by thyroid-stimulating hormone (TSH) measurement; even subtle abnormalities may affect pregnancy outcome although there is controversy if there is a true relationship to RPL.

The risk of SAB is increased in women with polycystic ovary syndrome and may be reduced by treatment with metformin, an insulin sensitizer.

Luteal-phase defect (LPD) is a controversial cause of RPL. The success of early pregnancy is dependent on progesterational support from the corpus luteum until 7 weeks' gestation. LPD cannot be diagnosed during pregnancy; a consistently short luteal-phase duration is the most reliable diagnostic criterion. Diagnosis should be documented with two late-luteal endometrial biopsies, both histologically lagging at least 2 days behind the actual postovulatory date. LPD diagnosis based on serum progesterone levels is controversial because of natural variation in levels. LPD is treated with either luteal progesterone or clomiphene citrate (Table 64.2), but treatment efficacy has not been proven.

Table 64.2 Treatment of luteal-phase defect.

Progesterone vaginal suppositories	25 mg b.i.d. beginning 3 days after the luteinizing hormone (LH) surge and continuing until 8 weeks' gestation
Progesterone in oil i.m.	12.5 mg/day i.m. beginning 3 days after the LH surge and continuing until 8 weeks' gestation
Micronized progesterone	200 mg/day beginning 3 days after the LH surge and continuing until 8 weeks' gestation
Clomiphene citrate	50 mg/day \times 5 beginning on days 3–5 of the menstrual cycle (no pregnancy supplementation necessary)

Infection

Routine serologic testing, cervical cultures, and endometrial biopsy to detect genital infections in women with recurrent pregnancy loss are not justified. Evaluation for infection should be limited to women with cervicitis, chronic or recurrent bacterial vaginosis, or other symptoms of pelvic infection.

Environmental and other associations

Smoking increases the risk of spontaneous abortion and should be discouraged. Alcohol consumption exceeding 2 drinks per day and high caffeine consumption (more than 300 mg/day) may increase risk for pregnancy loss and are best avoided.

Environmental toxins such as heavy metals (mercury, lead), organic solvents (e.g. perchlorethylene or dry-cleaning solvent), ionizing radiation, and anesthetic gases have been implicated as causative agents of SAB. Exposure to video terminals, use of electric blankets or heated waterbeds is not associated with an increased risk of SAB. Exercise programs do not increase risk, and bed rest will not decrease the risk of RPL (Table 64.3).

FOLLOW-UP

After complete evaluation and successful treatment, couples who have experienced SAB are often afraid to become pregnant again. These patients need intensive physician support during their first trimester. It is useful to inform couples that the risk for SAB decreases as the duration of pregnancy increases: observation of a gestational sac (12%), yolk sac (8%), embryonic crown-rump length increases (greater than 5 mm, 7%; 6–10 mm, 3%; greater than 10 mm, less than 1%). The observation of embryonic cardiac activity by 6 weeks' gestation reduces the risk of SAB to 3–5%. However, the incidence of subsequent SAB is higher when there are other abnormal sonographic findings: slow or late appearing heart activity, size and/or date discrepancies, or subchorionic hematoma. Finally, the prognostic value of embryonic heart activity decreases with increasing maternal age from SAB rate of less than 5% in women under age 35 to 29% in women aged 40 and over.

CONCLUSIONS

RPL is a frustrating problem for both the patient and the physician. Despite a thorough and systematic evaluation, more than half of all women with RPL will have no identifiable etiology. Of the many possible causes of RPL, only parental karyotype abnormalities, APS, uterine malformations, and cervical incompetence are widely accepted. The most important aspects of managing the patient with RPL are frequent communication, education, and emotional support. Cautious reassurance should be offered as the large majority (70%) will ultimately achieve a successful pregnancy. Careful monitoring is warranted

Table 64.3 Summary of evaluation and treatment for recurrent pregnancy loss. The following table summarizes recommended evaluation and treatments for factors known to predispose to recurrent pregnancy loss. Established tests and treatments are shown in bold type. Tests and treatments that must be applied selectively and those not yet firmly established are shown in standard type. (Modified from Speroff L & Fritz M. *Clinical Gynecologic Endocrinology and Infertility*, 7th edn. Lippincott Williams & Wilkins, 2005; p.1093.)

Category	Evaluation	Treatment
Genetic	Karyotype, both parents Ovarian reserve test	Counseling Donor gametes where appropriate Preimplantation genetic diagnosis
Anatomic	Sonohysterography or HSG Magnetic resonance imaging IVP or renal ultrasound	Hysteroscopic septoplasty Hysteroscopic myomectomy Hysteroscopic adhesiolysis Abdominal metroplasty Abdominal myomectomy Cervical cerclage
Immunologic	Lupus anticoagulant Anticardiolipin antibody	Aspirin and heparin
Thrombophilias	Factor V Leiden Prothrombin gene mutation Activated protein C resistance Homocysteine Protein C Protein S Antithrombin III	Aspirin and heparin
Endocrine	TSH Luteal-phase duration Blood glucose, HgbA1C Prolactin	Thyroxine Clomiphene citrate Metformin Dopamine agonists
Infectious	As indicated by symptoms	Antibiotics
Environmental	History	Behavior modifications

HSG, hysterosalpingography; IVP, intravenous pyelogram; TSH, thyroid-stimulating hormone.

because women with RPL are also at increased risk for other complications of pregnancy such as preterm birth and ectopic pregnancy.

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Missed abortion and antepartum fetal death

Robert M. Silver

INTRODUCTION

The death of an advanced pregnancy is an extremely difficult medical and emotional challenge for clinicians and families. The problem is common, as pregnancy loss occurs in approximately 12% of clinically recognized pregnancies. Most of these are spontaneous abortions that happen early in gestation. However, approximately 3% of pregnancies result in fetal death. Thus, obstetric healthcare providers will care for many women with the condition. Nomenclature regarding pregnancy loss can be confusing and is based on historical terms that may no longer be clinically relevant. Missed abortion is a general term that refers to the presence of a non-viable pregnancy *in utero* prior to 20 weeks' gestation. Non-viable pregnancies after 20 weeks' gestation are traditionally referred to as stillbirths. It is more useful to distinguish between anembryonic pregnancy loss (gestational sac without an embryo—previously referred to as “blighted ovum”), embryonic demise (embryo without cardiac activity at less than 10 weeks' gestation), and fetal demise (fetus without cardiac activity after 10 weeks' gestation). These terms refer to fetal loss that occurs prior to the onset of labor. Fetal death or stillbirth that occurs during the labor process is referred to as intrapartum fetal death.

PATHOPHYSIOLOGY AND ETIOLOGY

There is no single pathophysiologic mechanism that explains all cases of missed abortion and fetal death. There are a myriad of causes and in many cases an etiology is never determined. Relatively common causes of fetal loss include genetic problems including chromosomal abnormalities, syndromes, and single gene mutations, birth defects, bacterial infections, viral infections, syphilis, fetomaternal hemorrhage, red cell alloimmunization, hypertension, diabetes, renal disease, thyroid disease, antiphospholipid syndrome, substance abuse, disorders unique to multiple gestation, and, possibly, heritable thrombophilias. Umbilical cord accidents are often attributed as the cause of fetal death, but this is difficult to prove. Common features of some of these conditions include

placental insufficiency, fetal anemia, cardiac insufficiency, and hypoxia. The frequency of these disorders varies among populations and also gestational ages. For example, chromosomal abnormalities are more common in pregnancy loss during the first trimester, while antiphospholipid syndrome is more strongly associated with second or third trimester losses. A majority of women in the USA with fetal deaths have incomplete or inadequate evaluations for possible causes.

DIAGNOSIS

Women may note the cessation of signs and symptoms associated with pregnancy or absence of previously perceived fetal movements. On physical examination, the uterus may be smaller than expected, and fetal heart tones are inaudible. After 10 weeks' gestation, the use of the Doppler apparatus to detect fetal heart tones may further assist in the diagnosis. Real-time ultrasonography confirms the absence of fetal movements and/or absence of fetal heart or aortic pulsations. In cases of anembryonic loss, there are specific sonographic criteria that can be used to confirm that the pregnancy is not viable. In cases of very early anembryonic loss, serial sonograms may be required to make a definitive diagnosis. Vaginal bleeding or uterine cramping will only occur in a subset of women with pregnancy loss. It is unclear why some, but not all women with pregnancy loss will present with bleeding or labor. Also, fetal death may precede bleeding or cramping by an extended and variable period of time.

TREATMENT

A significant part of the treatment of families with pregnancy loss is dealing with their (almost universal) feelings of failure and personal guilt. It is crucial to provide reassurance that there was nothing they did to cause the loss, nor anything they could have done to prevent it. They should be offered bereavement services, counseling, and support groups. Making every effort to determine an etiology is also very important for most couples. If a cause of pregnancy loss is determined it facilitates grieving and helps to bring "emotional closure" for the couple. It is also critical for counseling regarding subsequent pregnancies.

In all cases of pregnancy loss, the couple should be offered the options of uterine evacuation (either surgical or medical) or expectant management. Both of these options are medically safe for most women, and the decision may be made on an emotional basis. Many women have strong feelings about wanting to proceed immediately, while others desire as natural a process as possible. Most women will eventually miscarry or labor after a period of expectant management. In general, the later in gestation the less likely patients are to elect expectant management.

Expectant management

There are some theoretical risks of expectant management including intrauterine infection and maternal coagulopathy. These risks have prompted some authorities to advise delivery within 2 weeks of the demise and to institute surveillance for infection and coagulopathy. Examples of such surveillance include weekly visits for counseling and support, and examination for evidence of rupture of membranes, infection, cervical dilation, and/or bleeding. Determination of weekly complete blood count (CBC), platelet count, and fibrinogen level after 3 weeks of expectant therapy has also been advised. This latter recommendation is based on a reported 25% chance of consumptive coagulopathy if a dead fetus remains *in utero* for longer than 4 weeks. However, the risk appears to be less than originally reported and is limited to stillbirths. The vast majority of women with fetal deaths after 20 weeks' gestation do not choose prolonged expectant management. Although the aforementioned surveillance is not medically harmful, it is of unproven efficacy and is not required in the absence of symptoms, especially in cases less than 20 weeks' gestation. Patients should be advised to report symptoms associated with infection or bleeding.

Dilation and curettage (uterus 12 weeks' size or less)

- 1 Admit to the hospital, day operating room, office, or clinic.
- 2 Obtain baseline hematocrit if there is concern for baseline anemia. Obtain blood type if unavailable.
- 3 Administer misoprostol 4 h prior to the procedure in order to facilitate cervical instrumentation. A typical dose is 200 µg placed in the posterior fornix (may be placed by patient) or taken orally as a lozenge.
- 4 Perform dilation and evacuation.
- 5 Discharge to home after conscious sedation or anesthesia has worn off and the patient exhibits minimal vaginal bleeding.
- 6 Administer RhD immunoglobulin if the patient is RhD negative.
- 7 Schedule a follow-up visit in 2 weeks.
- 8 Prescribe non-steroidal anti-inflammatory drugs (NSAIDs) or mild narcotics.

Dilation and evacuation (uterus between 13 and 22 weeks' size)

- 1 Admit to the hospital, day operating room, office, or clinic.
- 2 Obtain baseline hematocrit and blood type and screen.
- 3 Administer misoprostol 4 h prior to the procedure in order to facilitate cervical instrumentation. A typical dose is 200 µg placed in the posterior fornix (may be placed by patient) or taken orally as a lozenge.
- 4 Perform dilation and evacuation.
- 5 Discharge to home after conscious sedation or anesthesia has worn off and the patient exhibits minimal vaginal bleeding.

- 6 Administer RhD immunoglobulin if the patient is RhD negative.
- 7 Schedule a follow-up visit in 2 weeks.
- 8 Prescribe NSAIDs or mild narcotics.

Dilation and evacuation at gestations beyond 22 weeks may be safely performed by a small number of experienced practitioners. Modifications to this protocol may be required for gestations beyond 22 weeks.

Induction of labor

Many patients wish to proceed with induction of labor rather than dilation and evacuation. This may be because of late gestational age or a desire to deliver an intact fetus. The availability of prostaglandins has greatly improved our ability to induce labor successfully at early gestational ages. The appropriate dosing of prostaglandins is determined by:

- 1 whether the fetus is viable; and
- 2 the size of the uterus

Even in the presence of a non-viable fetus, lower dosing is required when the uterus is greater than 28 weeks' size because of the potential for uterine rupture. Prostaglandin $E_{2\alpha}$ has been the most commonly used drug for the induction of labor during the past 30 years. However, misoprostil has become the prostaglandin of choice for induction of labor in cases of fetal demise because of similar efficacy (compared with prostaglandin $E_{2\alpha}$) with fewer side-effects. Misoprostol may be placed in the vaginal fornix or taken orally as a lozenge. The interval to delivery is shorter on average when the drug is administered vaginally. Adverse effects of prostaglandins include nausea, vomiting, diarrhea, and pyrexia. There may be only minimal changes in cervical dilation with strong uterine contractions. Delivery often occurs suddenly, after only minimal cervical dilation. Contraindications to the use of misoprostol include active cardiac, pulmonary or renal disease, and glaucoma. Also, the drug (or any prostaglandin product) should not be used for labor induction in cases of prior uterine scar if the uterus is greater than 26 weeks' size.

Fetal demise

Uterus smaller than 28 weeks' size

- 1 Admit the patient to the hospital.
- 2 Obtain baseline laboratory values of CBC and type and screen. Consider assessment of platelet count and fibrinogen level if the fetus has been dead for more than 4 weeks' duration.
- 3 Misoprostol is administered at a dose of 200mg placed in the posterior fornix. This is repeated every 4 h until delivery of the fetus and placenta. Up to 400 mg given every 2 h may be safely used at this gestation. However, it does not shorten the interval to delivery compared with 200 mg given every 4 h. Misoprostol may also be given orally (taken as a lozenge) at a

dosage of 200–400 mg every 2–4 h. This route of administration requires (on average) a few hours longer to cause delivery compared with vaginal administration; however, it is preferred in some cases. There is substantial risk for retained placenta, especially prior to 20 weeks' gestation. This risk can be diminished by allowing the placenta to deliver spontaneously. Patience and the avoidance of pulling on the cord are essential. Additional doses of misoprostol can be administered (at appropriate intervals) to promote uterine contractility between delivery of the fetus and placenta.

- 4 Vital signs should be assessed per routine for labor and delivery.
- 5 Epidural anesthesia can be utilized.
- 6 Narcotics, antiemetics, and antipyretics should be used as needed.
- 7 If vital signs are stable and the patient is not bleeding excessively, she may be discharged from the hospital in 6–24 h. Many women wish to leave the hospital as soon as it is medically safe so as to avoid emotional duress. If possible, patients suffering fetal demise should receive postpartum care on a non-maternity ward.
- 8 The parents should be encouraged to spend time with their infant and offered pictures, hand and foot prints, casts, etc.
- 9 Administer RhD immunoglobulin to RhD negative mothers.
- 10 A follow-up visit (2–6 weeks) and bereavement services should be offered.

Uterus larger than 28 weeks' size

- 1 Admit the patient to the hospital.
- 2 Obtain baseline laboratory values of CBC and type and screen. Consider assessment of platelet count and fibrinogen level if the fetus has been dead for more than 4 weeks' duration.
- 3 Misoprostol is administered at a dose of 25 mg placed in the posterior fornix. This is repeated (at a dose of 25–50 mg) every 4 h until delivery of the fetus and placenta. The misoprostol may also be given orally (taken as a lozenge) at a dosage of 25 mg every 4 h. This route of administration requires (on average) a few hours longer to cause delivery compared with vaginal administration. There is substantial risk for retained placenta, especially prior to 20 weeks' gestation. This risk can be diminished by allowing the placenta to spontaneously deliver. Patience and the avoidance of pulling on the cord are essential. Additional doses of misoprostol can be administered (at appropriate intervals) to promote uterine contractility between delivery of the fetus and placenta.
- 4 In the presence of a favorable cervix (Bishop score of 6 or more), either before or after the administration of one or more doses of misoprostol, oxytocin may be infused per usual protocol for induction of labor.
- 5 Vital signs should be assessed per routine for labor and delivery.
- 6 Epidural anesthesia can be utilized.

- 7 Narcotics, antiemetics, and antipyretics should be used as needed.
- 8 If vital signs are stable and the patient is not bleeding excessively, she may be discharged from the hospital in 12–24 h. Many women wish to leave the hospital as soon as it is medically safe so as to avoid emotional duress. If possible, patients suffering fetal demise should receive postpartum care on a non-maternity ward.
- 9 The parents should be encouraged to spend time with their infant and offered pictures, hand and foot prints, casts, etc.
- 10 Administer RhD immunoglobulin to RhD negative mothers.
- 11 A follow-up visit (2–6 weeks) and bereavement services should be offered.

If the duration of fetal death is more than 4 weeks or is unknown, obtain blood fibrinogen levels and CBC and platelet counts. Because fibrinogen levels are elevated up to 450 mg/dL in pregnancy, normal blood fibrinogen level (300 mg/dL) may be an early sign of consumptive coagulopathy. A significant coagulopathy does not occur until fibrinogen levels fall to less than 100 mg/dL. Subsequent tests showing elevated prothrombin time and thromboplastin time, decreased fibrinogen and platelet count, and the presence of fibrin degradation products confirm the diagnosis of a consumptive coagulopathy. Manifestations of the coagulopathy are variable and may include localized bleeding, petechiae or minor generalized bleeding, or no evidence of bleeding. Upon diagnosis of a clotting deficit, continue monitoring clotting mechanisms and deliver the patient by the most appropriate means. If the clotting defect is severe or there is evidence of bleeding, replenish blood volume and depleted clotting factors with blood component therapy before inducing labor and delivery. Again, this complication of fetal demise is rare. Thus, it is unnecessary to order extensive and serial laboratory studies in the absence of clinical bleeding and if an initial coagulation screen is normal.

Diagnostic evaluation

- 1 Perform a Kleihauer–Betke test to assess for fetomaternal hemorrhage. Ideally this should be carried out soon after the diagnosis of fetal demise. In addition to determining a potential cause for the demise, excessive fetomaternal hemorrhage may require additional dosing of RhD immunoglobulin in RhD negative individuals.
- 2 The placenta should undergo gross and microscopic evaluation.
- 3 Autopsy should be offered and encouraged. If the family does not consent to autopsy, consider magnetic resonance imaging (MRI), X-ray, and/or gross evaluation by a trained dysmorphologist (typically a pediatric geneticist). This can provide valuable information in lieu of autopsy.
- 4 Clinical data should be assessed for evidence of hypertension, renal disease, infection, occult rupture of membranes, cervical insufficiency, abruption.

- 5 Antibody screen should be obtained (if unavailable from the prenatal record).
- 6 Serologic screen for syphilis should be assessed.
- 7 Toxicology screen should be assessed.
- 8 Although cost may be an issue, fetal karyotype should be considered. This may be of greater emotional value in patients with recurrent pregnancy loss, or with second or third trimester losses. Although abnormal karyotypes are common in first trimester losses (relative to losses later in gestation), they are usually a result of *de novo* non-dysjunctional events that do not tend to recur. Tissues that remain alive despite *in utero* death (either placental tissue or tissues that remain alive at low oxygen tension) are most likely to provide cells for chromosome analysis. Examples include chorionic plate (near the insertion of the umbilical cord), fascia lata, and the nape of the neck. Techniques such as comparative genomic hybridization (CGH) may allow for the assessment of chromosomal abnormalities, even in cases where cells will not grow in culture.
- 9 Consider testing for antiphospholipid syndrome with lupus anticoagulant screen, and testing for anticardiolipin antibodies if there is evidence of placental insufficiency or the patient has recurrent pregnancy loss, thromboembolism, or autoimmune disease.
- 10 TORCH titers are recommended by some authorities. However, clinical utility is uncertain. Careful autopsy and placental evaluation may be more valuable in the diagnosis of fetal infection.
- 11 Clinically overt diabetes and thyroid disease are associated with fetal death. However, the utility of screening for asymptomatic disease with glycosylated hemoglobin and/or thyroid-stimulating hormone (TSH) is uncertain and is not routinely advised.
- 12 Several investigators report an association between heritable thrombophilias such as the factor V Leiden mutation, the 2010A prothrombin gene mutation, hyperhomocysteinemia, protein C deficiency, protein S deficiency, antithrombin III deficiency, and fetal death. However, the association is controversial and routine screening is not currently advised for isolated cases of fetal demise. Consider testing in cases of recurrent fetal death or thromboembolism.
- 13 Consideration should be given to assessment of the uterine cavity after the patient fully recovers (3 months postpartum). Clinical evidence of cervical insufficiency, second trimester losses, and evidence of placental insufficiency increase the likelihood of finding a uterine abnormality.

FOLLOW-UP

The patient should be offered a postpartum visit at 1–2 weeks to assess emotional well being and to offer support. Another visit should be scheduled at 6

weeks' postpartum. At this time, data should be available from diagnostic testing so that counseling may be accomplished.

The American College of Obstetricians and Gynecologists' technical bulletin, *Diagnosis and Management of Fetal Death*, clearly and systematically outlines the medical psychosocial roles for various healthcare providers involved in the patient's treatment. Most importantly, the process emphasizes the need for collation and presentation of all the data in a counseling session 2–3 months postpartum.

The application of sound obstetric judgment and standard practice, even in the presence of a non-viable fetus, will ensure maternal health and safety.

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Oligohydramnios

Maryam Tarsa and Thomas R. Moore

INTRODUCTION

Adequate amniotic fluid volume is necessary for proper fetal growth and development. Severe and long-standing oligohydramnios, especially prior to 22 weeks' gestation, inhibits lung growth and promotes limb positional defects such as club foot and arm contractures. Thick meconium, deep variable fetal heart rate decelerations, and low birth weight centile are common findings in the term or post-term gestation complicated by low amniotic fluid. Perinatal mortality has been reported to be increased 13- to 47-fold in the presence of marginal to severe oligohydramnios, respectively.¹ Presence of oligohydramnios in the second trimester carries a 43% perinatal mortality rate. When amniotic fluid is essentially absent (anhydramnios), lethal outcomes are as high as 88% (Table 66.1).²

PHYSIOLOGY OF NORMAL AMNIOTIC FLUID VOLUME

Amniotic fluid volume is normally regulated within a surprisingly narrow range. Studies of normal human pregnancies have shown that the amniotic fluid volume rises linearly from early gestation up to 32 weeks, whereupon it remains constant in the range 700–800 mL until term. After 40 weeks' gestation, the volume declines at a rate of 8% per week. By 42 weeks, this volume decreases to approximately 400 mL.³

DIAGNOSIS OF OLIGOHYDRAMNIOS

Effective management of oligohydramnios begins with accurate diagnosis. Unfortunately, sonographic methods for determining amniotic fluid volume such as amniotic fluid index (AFI) and single deepest pocket perform best for identifying normal amniotic fluid volumes. However, identification of oligohydramnios or hydramnios by the above methods is poor.⁴

The AFI is calculated by summing the vertical amniotic fluid pocket depth in each of four quadrants of the uterus. General guidelines for interpreting the AFI are given in Table 66.2. Mild oligohydramnios should be suspected with an

Table 66.1 Correlation of amniotic fluid index (AFI) and perinatal morbidity. (Modified from Chauhan *et al.* Perinatal outcome and amniotic fluid index in the antepartum and intrapartum periods. A meta-analysis. *Am J Obstet Gynecol* 1999;**181**:1473–8.)

Antepartum AFI < 5.0 cm	Relative risk*	95% Confidence interval
Risk of cesarean delivery for fetal distress	2.22	1.47–3.37
Risk of Apgar score < 7 at 5 min	5.16	2.36–11.29

*Pooled relative risks from meta-analysis.

Table 66.2 Diagnostic categories of the amniotic fluid index (AFI) at term. (From Moore TR, Cayle JE. The amniotic fluid index in normal human pregnancy. *Am J Obstet Gynecol* 1990;**162**:1168–73.)

Amniotic fluid volume	Patients (%)	AFI value (cm)
Severe oligohydramnios	2	≤5
Decreased amniotic fluid	20	5.1–8.0
Normal	76	8.1–24.0
Polyhydramnios	2	> 24

AFI of less than 8 cm. AFI values less than 5 cm are distinctly abnormal (less than 2% of normal patients). However, it should be noted that the lower 5th centile boundary for the AFI varies significantly with gestational age. At term, an AFI of less than 5 cm has been used as a convenient cut-off.

Particular care should be taken in validating the AFI when amniotic fluid volume is low. Intraobserver and interobserver errors have been shown to average 5–10 mm, respectively, or approximately 3–7%.⁵ However, the margin of error is higher for an AFI of less than 7 cm. To minimize this error in patients with decreased amniotic fluid, the AFI measurements should be performed in triplicate and averaged.

Rule out ruptured membranes

The work-up of oligohydramnios is generally initiated by careful sonography and physical examination. Near term, ruptured membranes as the cause of oligohydramnios can reliably be confirmed by examination of the fluid in the vaginal fornix. However, chronic leakage of amniotic fluid may be difficult to detect especially in the second trimester. If a normal-sized fetal bladder is observed in the presence of oligohydramnios, the most likely cause is preterm premature rupture of membranes (PPROM). Prior to 20 weeks' gestation, sterile speculum tests may be negative or equivocal, and the patient may not be

sure whether vaginal moisture represents amniotic fluid or cervical mucus. Although instillation of a dye such as indigo carmine may provide unequivocal proof of PPRM, such invasive procedures rarely affect management except in cases of previable PPRM (less than 23 weeks).

Assess fetal urinary tract anatomy and function

If there is no evidence of PPRM, detailed assessment of fetal urinary tract anatomy should be made. Renal and ureteral anomalies are the most common cause of severe oligohydramnios. Sonographic evaluation should include the renal parenchyma, dimensions of the renal pelvis, and morphology of the urinary bladder. Bilateral renal agenesis is typically associated with severe oligohydramnios and is usually detectable after 16 weeks' gestation. However, unilateral or bilateral ureteropelvic junction obstruction or polycystic kidney disease may not be detectable until late in the second trimester and is usually associated with less severe oligohydramnios. Unilateral urinary obstruction rarely causes measurable decrement in amniotic fluid volume. Because prenatal studies have established that urinary tract defects are commonly found in many chromosomal defects, amniocentesis should be offered if these findings are present.⁶

Consider intrauterine growth restriction

In the absence of PPRM and urinary tract anomalies, uteroplacental insufficiency should be considered. Oligohydramnios may result from poor placental function associated with maternal hypertension, chronic placental abruption, and autoimmune states such as systemic lupus and antiphospholipid syndrome. In such cases, fetal abdominal circumference growth typically lags behind that of the head. High placental vascular resistance evident on umbilical artery Doppler studies may help corroborate the diagnosis of oligohydramnios resulting from placental insufficiency.⁷ The risk of fetal asphyxia and demise is high when severe oligohydramnios accompanies intrauterine growth restriction (IUGR). Intensive fetal testing and hospitalization should be considered in cases diagnosed after 23 weeks' gestation. After 32 weeks, severe oligohydramnios and fetal growth restriction should generally lead to evaluation for delivery.

Assess likelihood of pulmonary hypoplasia

Long-standing oligohydramnios predisposes to pulmonary hypoplasia. Although the mechanism of this potentially lethal complication is not clear, inhibition of fetal breathing, loss of lung liquid because of reduction in amniotic pressure, and simple mechanical compression of the chest have been proposed.⁸ The end result is restricted lung growth leading to an alveolar volume inadequate to support postnatal respiration. It appears that the risk of pul-

monary hypoplasia is greatest when severe oligohydramnios is present from 16 to 24 weeks' gestation, the period of alveolar proliferation.

Although several methods have been proposed to predict the subsequent occurrence of pulmonary hypoplasia, no single criterion has adequately confirmed sensitivity and specificity for clinical decision-making. Thus far, measurement of chest circumference, use of thoracic : head circumference ratio, calculating the lung area ratio [(chest area : cardiac area)/chest area] and thin-slice three-dimensional fetal lung volume : fetal body weight ratios have been proposed to assess the presence of pulmonary hypoplasia.⁹ Recently, magnetic resonance imaging (MRI) and Doppler assessment of fetal pulmonary tissues have also been utilized for prediction of pulmonary hypoplasia. In a recent small study, use of MRI-based abnormal lung volume : fetal weight ratio gave a sensitivity of 88% with a false-positive diagnosis of pulmonary hypoplasia of 12%.¹⁰ When chest development appears markedly compromised in a previable fetus using one or more of these measurements, the option of termination of pregnancy should be discussed with the patient.

TREATMENT

Although the outcome of severe long-standing oligohydramnios is grave, lesser degrees of fluid restriction may be amenable to intervention. The issues related to late-pregnancy oligohydramnios are of particular concern. Data suggest that most of the perinatal morbidity associated with postdate pregnancy is confined to cases with an AFI of less than 5 cm and, particularly, those that lack a vertical fluid pocket of at least 2 cm. In such cases, continued antepartum testing is likely to result in higher rates of meconium staining, fetal distress, low Apgar scores, and cesarean section.¹¹

Intrapartum amnioinfusion

Induction of labor in patients with severe oligohydramnios at term is recommended to decrease perinatal morbidity but carries a significant risk of prolonged labor and failed induction. Recent meta-analysis data suggest that prophylactic intrauterine saline infusion significantly improves neonatal outcome and lessens the rate of cesarean delivery, without increasing the rate of postpartum endometritis.¹² Potential complications associated with amnioinfusion include inadvertent overdistention of the uterus, increased uterine contractions during the infusion, and the theoretical possibility of amniotic fluid embolus.

Maternal hydration

The interrelationship between amniotic fluid volume and maternal intravascular volume has been recognized. In hypertensive patients with decreased maternal intravascular volume, amniotic fluid volumes are lower than those

with normal intravascular volume.¹³ In a randomized trial, women assigned to oral hydration with 2 L tap water increased their mean AFI by 3.0 ± 2.4 cm ($P \leq 0.0001$), whereas those in the control group had a significant decline in AFI by 1.5 ± 2.7 cm ($P \leq 0.02$).¹⁴ These results suggest that augmenting maternal fluid volume or decreasing maternal osmolality may be effective in ameliorating oligohydramnios by increasing fetal urinary flow rate.¹⁵

CONCLUSIONS

Mild oligohydramnios (AFI 5–8 cm) can be managed conservatively with frequent fetal surveillance and appropriately timed delivery. With severe oligohydramnios, fetal structural and chromosomal anomalies should be ruled out. If intrauterine growth restriction is present with oligohydramnios, the risk of fetal asphyxia and death is high. Such pregnancies should be managed aggressively with early delivery unless lethal anomalies are present.

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Polyhydramnios

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INTRODUCTION

Polyhydramnios is the pathologic accumulation of excessive quantities of amniotic fluid. When polyhydramnios is diagnosed, a thorough examination for underlying abnormalities is indicated and the risk of adverse pregnancy outcome is increased.

CLINICAL IMPORTANCE

While the presence of polyhydramnios may be idiopathic, it should alert the physician that congenital or chromosomal anomalies may be present. In addition, there are several potentially treatable causes that may be identified and corrected. Because pregnancies complicated by polyhydramnios are at significantly increased risk for perinatal mortality and other complications, heightened surveillance and monitoring, as well as possible interventions must be considered.¹

FREQUENCY

Polyhydramnios complicates approximately 1% of pregnancies.² The reported incidence varies slightly depending on the threshold used for the diagnosis and the gestational age that is studied.

PATHOPHYSIOLOGY

The amniotic fluid volume (AFV) increases from early in pregnancy until term. The AFV is kept in balance by fetal micturation, pulmonary secretions, and fluid passing through membranes. As pregnancy progresses, AFV constitutes a decreasing portion of the total uterine volume. For example, it may represent 50% at 16 weeks' gestation but only 17% at term. Normal AFVs generally increase from early pregnancy until approximately 36–38 weeks' gestation, at which time the maximum volume may be 1.0–1.5 L.³ As the pregnancy approaches term, the volume may decrease, which continues as the pregnancy goes past term.

More recent para-amino-hippurate (PAH) studies reported AFV in 144 normal singletons. Using a non-linear regression model they found wide variations in the AFV and noted that the AFV increased up to 40 weeks' gestation. They also noted that the AFV doubles after 30 weeks' gestation.⁴

Fetal swallowing is a major mechanism for amniotic fluid removal. If something happens to upset this delicate balance then either olighydramnios (see Chapter 66) or polyhydramnios can develop. The pathologic accumulation of an ounce of excess fluid a day would amount to a liter in a little more than a month.

The pathophysiology of polyhydramnios is dependent on the underlying abnormality. In pregnancies complicated by diabetes, maternal hyperglycemia results in fetal hyperglycemia and increased fetal micturation. When there are anatomic abnormalities, such as esophageal atresia, fetal swallowing is impaired and may result in polyhydramnios. Multiple gestations are at increased risk for polyhydramnios resulting from twin–twin transfusion syndrome. Pregnancies complicated by abnormalities of the central nervous system (CNS), such as anencephaly, neural tube defects, or substance abuse, may have polyhydramnios from CNS depression.⁵ Neuromuscular disorders with impaired fetal swallowing may also result in polyhydramnios. Fetal anemia, caused by Rh-isoimmunization, parvovirus infection, or fetal–maternal hemorrhage, may cause polyhydramnios through increased cardiac output. There have also been reports of polyhydramnios as a result of lithium, presumably resulting from fetal diabetes insipidus.^{6,7}

Table 67.1 shows a breakdown of the underlying etiology in two large studies of patients with polyhydramnios.^{8,9} While the majority of cases are idiopathic, the degree of polyhydramnios affects the probability that an etiology will be identified prior to delivery (Table 67.1). When only mild polyhydramnios is present, one study reported that a cause was identified in only 17% of cases, while the underlying etiology was found in 91% of cases of moderate or severe polyhydramnios.⁸

Table 67.1 Etiology of polyhydramnios.

Cause	Hill <i>et al.</i> (1987) ⁸ (<i>n</i> = 107)	Many <i>et al.</i> (1995) ⁹ (<i>n</i> = 275)
Idiopathic	66%	69%
Diabetes mellitus	15%	18%
Congenital malformations	13%	15%
Rh incompatibility	1%	—
Multiple gestation	5%	Not available

DIAGNOSIS

The diagnosis of polyhydramnios is often suspected clinically by palpation of the abdomen and an increased fundal height and is confirmed by sonographic evaluation.

While the gold standard for determining AFV is the PAH dye dilution technique where a known quantity of PAH is injected into the amniotic cavity and, after thorough mixing, the amniotic fluid PAH concentration is sampled to determine the actual AFV, this method is invasive. This technique has been replaced by sonography to calculate the amniotic fluid index (AFI).¹⁰

The AFI is determined by dividing the uterus into four equal quadrants. The deepest pocket of amniotic fluid is then measured in each of the quadrants with care taken to not include any pockets that contain loops of umbilical cord. The sum of all pockets, in centimeters, is used to calculate the AFI.

While different levels have been reported for different degrees of polyhydramnios, in general, the following definitions apply:

Mild: 24.0–30.0 cm

Moderate: 30.1–34.9 cm

Severe: ≥ 35.0

Another commonly used definition for polyhydramnios is the finding of a single deepest pocket of fluid of 8 cm or more.

Even though neither measuring the AFI nor the single deepest pocket of amniotic fluid correlates well with the dye dilution technique, as demonstrated in a study of 31 patients with hydramnios,¹¹ these sonographic tests remain a non-invasive alternative and provide an objective measure that can be followed with serial examinations.

EVALUATION

When polyhydramnios is identified, a detailed sonogram for fetal anomalies or evidence of hydrops is performed (Fig. 67.1). Laboratory studies for gestational diabetes, a Kleihauer–Betke test, serologic studies for maternal infections such as parvovirus, cytomegalovirus, rubella, and syphilis, as well as a work-up for hemoglobinopathies are performed. Toxicology studies are also indicated to look for evidence of substance abuse. While amniocentesis has often been recommended in the past, there is some debate as to whether or not this is indicated in a fetus with no congenital anomalies and mild polyhydramnios demonstrated on sonogram.

A study of 672 pregnancies reported that the risk of aneuploidy was 10% when the fetus had sonographic anomalies and only 1% when no anomalies were found on sonogram.² Although the risk of aneuploidy is much lower when no anomalies are noted on sonogram, the risk of aneuploidy of 1% is still greater than the risk of fetal loss with an amniocentesis.

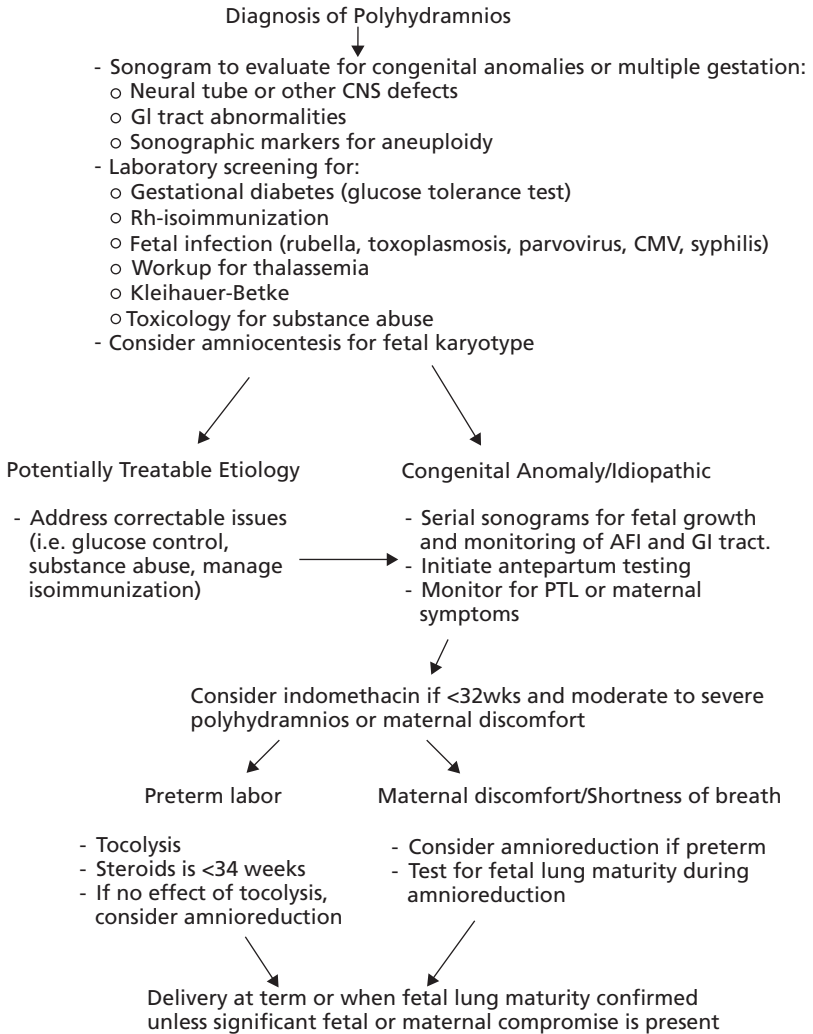


Fig. 67.1 Treatment algorithm for polyhydramnios.

TREATMENT

The treatment of polyhydramnios depends on the underlying etiology (Fig. 67.1). In those cases where there is a potentially reversible cause—poorly controlled diabetes, substance abuse, lithium use, or isoimmunization—it is necessary to address the underlying problems. When polyhydramnios is caused by a congenital anomaly or is idiopathic, treatment is expectant and focused on

closely monitoring the fetus and intervening for maternal complications. Importantly, a significant number of cases of mild polyhydramnios will resolve spontaneously.

Delivery should occur at term or when fetal lung maturity is documented. While a vaginal delivery is anticipated, care must be taken during labor to ensure that the presenting part remains vertex and a transabdominal amnioreduction may be required to allow for the fetal vertex to apply itself well to the cervix. Sudden decompression with rupture of membranes may result in placental abruption or umbilical cord prolapse.

If the patient experiences preterm labor as a result of polyhydramnios, steroids should be administered if the gestational age is less than 34 weeks and tocolytics given. If the patient continues to contract despite tocolytics, amnioreduction may be considered.

Amnioreduction refers to reducing the amount of amniotic fluid through an amniocentesis and is performed for either the relief of maternal symptoms of abdominal discomfort or respiratory complaints such as shortness of breath. It may also be considered when preterm labor is not responsive to tocolytics. While there are no trials to give guidance on exactly how much fluid to remove, there are data that demonstrate a linear relationship between the AFI and the volume of amniotic fluid drained.¹²

In general, an 18-gauge needle is inserted under ultrasound guidance into the uterus after the skin has been prepped with a surgical scrub. Tubing is either connected to wall suction or a three-way stopcock to permit removal with a large syringe, at least 50 mL in volume. Fluid should be removed no faster than 1000 mL over 20 min and the procedure is terminated when the AFI returns to a normal range. No more than 5 L is removed during a single procedure. One study of over 200 amnioreduction procedures reported a median of 1500 mL amniotic fluid removed during each procedure, but this series also included a large number of cases of twin–twin transfusion syndrome.¹³ While amnioreduction is considered safe, with an expected complication rate of approximately 3%, problems reported include chorioamnionitis, fetal bradycardia, placental abruption, and preterm rupture of membranes.¹⁴ Antibiotics are not generally given in the absence of infection, and tocolytics are administered only if preterm labor occurs. If the gestational age is ≥ 34 weeks, then amniotic fluid should be sent for determination of fetal lung maturity.

This procedure may need to be repeated if the fluid reaccumulates although this usually does not occur for at least several days to a week. If repeat procedures are necessary, then treatment with indomethacin may be considered.

Indomethacin is a prostaglandin synthetase inhibitor that decreases fetal urine output and may enhance reabsorption of lung liquid.¹⁵ It may be administered when the gestational age is less than 32 weeks, as treatment after this time may result in premature closure of the ductus arteriosus. The starting dosage for this treatment is 25 mg p.o. four times per day, but has been

increased up to 3 mg/kg/day total in some reports.¹⁶ Indomethacin should not be used in the trapped twin syndrome because of its adverse effect on the trapped twin. The AFI is monitored 2–3 times per week and treatment stopped when the AFI returns to the normal range.

COMPLICATIONS

- *Premature labor*: in one study of 275 singleton pregnancies, premature delivery occurred in 19% of patients and the degree of polyhydramnios did not change this risk.⁹
- *Preterm premature rupture of membranes*.
- *Fetal malposition*: secondary to the increased AFV, allowing fetal mobility, a breech or transverse position is much more likely.
- *Umbilical cord prolapse*: if the fetal vertex is not applied to the cervix, or the fetus is in a breech presentation, umbilical cord prolapse may occur when the membranes rupture.
- *Cesarean delivery*: patients with polyhydramnios have been reported to have a threefold increased risk of cesarean delivery.¹ This is likely related to fetal malposition at the time of labor.
- *Placental abruption*: when the amniotic sac ruptures, rapid decompression may lead to placental abruption and hemorrhage.
- *Postpartum hemorrhage*: caused by overdistention of the uterus.
- *Maternal respiratory compromise*: secondary to mechanical pressure on the maternal diaphragm.
- *Fetal mortality*: in a study of over 40,000 singleton pregnancies, the risk of fetal mortality was increased as compared with patients with a normal AFI (49 per 1000 births vs 14 per 1000 births; $P < 0.001$). This finding remained significant when controlled for the presence of diabetes.¹

FOLLOW-UP

Serial sonograms should be scheduled every 1–2 weeks for monitoring of the polyhydramnios and the development of maternal or fetal distress. In addition, antepartum testing is started to include either twice weekly fetal non-stress tests, or biophysical profiles. Delivery is usually accomplished at term unless fetal distress or maternal compromise necessitates earlier delivery.

PREVENTION

In most cases, no significant measures will prevent polyhydramnios. Exceptions to this include diabetes mellitus, Rh-immunization, and substance abuse. With control of maternal glucose levels, fetal hyperglycemia may be prevented leading to a decrease of fetal urination to a more normal level. In Rh-negative patients, appropriate use of Rh-immunoglobulin is used to prevent isoimmunization and resultant polyhydramnios. If substance abuse is confirmed, steps may be taken to correct this.

CONCLUSIONS

Polyhydramnios is a relatively common obstetric complication that requires a complete work-up and careful pregnancy monitoring in an attempt to reverse the process and decrease the risk of adverse pregnancy outcomes. In general, the more severe the polyhydramnios, the more likely a cause will be identified prior to delivery and the degree to which maternal and fetal risks are increased.

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Pre-eclampsia

Baha M. Sibai

INTRODUCTION

Hypertension complicates 7–10% of pregnancies, of which 70% are caused by gestational hypertension pre-eclampsia and 30% caused by chronic essential hypertension. Risk factors include the following:¹

- Nulliparity
- Obesity
- Multiple gestation
- Family history of pre-eclampsia or eclampsia
- Pre-existing hypertension or renal disease
- Previous pre-eclampsia or eclampsia
- Diabetes mellitus
- Non-immune hydrops
- Antiphospholipid antibody syndrome
- Molar pregnancy

Pre-eclampsia rarely develops before 20 weeks. In this early stage, rule out underlying renal disease or molar pregnancy.

PATHOPHYSIOLOGY

Pre-eclampsia is a disorder of unknown etiology that is peculiar to human pregnancy. The pathophysiologic abnormalities in pre-eclampsia include inadequate maternal vascular response to placentation, endothelial dysfunction, abnormal angiogenesis, and exaggerated inflammatory response with resultant generalized vasospasm, activation of platelets, and abnormal hemostasis. These abnormalities result in pathophysiologic vascular lesions in peripheral vessels and uteroplacental vascular beds, as well as in various organ systems, such as the kidneys, liver, lungs, and brain. Consequently, these pregnancies, particularly those with severe pre-eclampsia, are associated with increased maternal and perinatal mortality and morbidity resulting from reduced uteroplacental blood flow, abruptio placentae, and preterm delivery.² Recent evidence indicates that pre-eclampsia is an endothelial disorder. Thus, in some patients the disease

may manifest itself in the form of either a capillary leak, fetal growth retardation, or a spectrum of abnormal hemostasis with multiple organ dysfunction.²

DIAGNOSIS

Pre-eclampsia is now defined by the new onset of hypertension and proteinuria.

Gestational hypertension

- Systolic blood pressure (BP) of 140 mmHg or greater.
- Diastolic BP of 90 mmHg or greater.

The above pressures should be observed on at least two occasions 6 h apart; no more than 7 days apart.

Blood pressure readings can vary with the type of equipment used, cuff size, position of the arm, position of the patient, duration of rest period, obesity, smoking, anxiety, and the Korotkoff sound used to assess diastolic BP. Only Korotkoff V should be used to establish diastolic BP.

Severe hypertension is sustained elevations in systolic BP to at least 160 mmHg and/or in diastolic BP to at least 110 mmHg for at least 6 h.

Proteinuria

- Greater than 0.3 g in a 24-h urine collection or 0.1 g/L ($\geq 2+$ on the dipstick) in at least two random samples collected 6 h or more apart, but no more than 7 days apart.

Pre-eclampsia is characterized by intermittent vasospasm of the renal vessels, resulting in variable amounts of proteins in different spot urine samples. Protein excretion in the urine increases in normal pregnancy from approximately 5 mg/dL in the first and second trimesters to 15 mg/dL in the third trimester. These low levels are not detected by dipstick. The concentration of urinary protein is influenced by contamination with vaginal secretions, blood, bacteria, or amniotic fluid. It also varies with urine-specific gravity and pH, exercise, and posture.

Proteinuria usually appears after hypertension in the course of disease process.

Edema

Excessive weight gain greater than 4 lb/week in the third trimester may be the first sign of the potential development of pre-eclampsia. Thirty-nine percent of eclamptic patients do not have edema.

Severe pre-eclampsia

Pre-eclampsia is labeled as severe in the presence of any of the following abnormalities:

- Systolic BP of 160 mmHg or greater or diastolic BP 110 mmHg or greater on two occasions at least 6 h apart with the patient at bed rest.
- Proteinuria of 5 g or greater on 24-h urine collection. Urine dipsticks are not accurate for this purpose.
- Oliguria (≤ 400 mL in 24 h).
- Persistent cerebral or visual disturbances or cerebral edema.
- Persistent epigastric pain with nausea or vomiting, or both.
- Pulmonary edema.
- Thrombocytopenia.

Chronic hypertension with superimposed pre-eclampsia

Chronic hypertension is persistent elevation of BP to at least 140/90 mmHg on two occasions more than 24 h apart before 20 weeks' gestation, or more than 42 days postpartum.

Superimposed pre-eclampsia is exacerbation of hypertension and the development of proteinuria that was not previously apparent; 15–30% of chronic hypertensive patients will develop superimposed pre-eclampsia.

MANAGEMENT

Delivery is the only available cure for pre-eclampsia. The ultimate goals of any management plan must be the safety of the mother first and then delivery of a live mature newborn that will not require intensive and prolonged neonatal care. The decision between immediate delivery and expectant management will depend on one or more of the following: maternal and fetal conditions at the time of evaluation; fetal gestational age; presence of labor; severity of the disease process; Bishop cervical score; and maternal desire.^{1,2}

Mild hypertension

Pre-eclampsia beyond 37 weeks (Fig. 68.1)¹

In the patient with a favorable cervix (Bishop score of 6 or more), treatment is induction. Induce also for any signs of maternal–fetal distress. In the case of an unfavorable cervix, carry out expectant management in hospital or at home until the onset of labor or until completion of 40 weeks' gestation. Maternal and fetal evaluation should be performed twice weekly.^{1,3}

Pre-eclampsia less than 37 weeks

All patients should have evaluation of maternal and fetal condition. Outpatient management is possible if the patient's systolic BP ≤ 150 mmHg and/or diastolic BP ~ 100 mmHg, with no significant proteinuria (less than 1 g/24 h), a platelet count of greater than 100,000/ μ L, normal liver enzymes, and

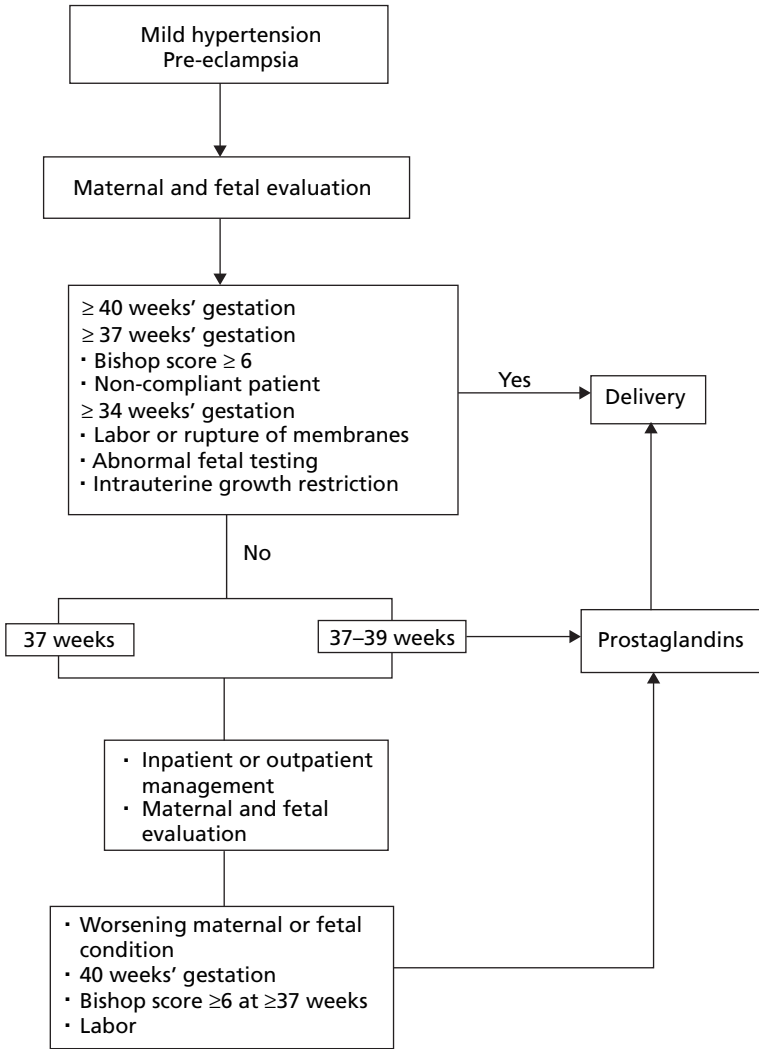


Fig. 68.1 Recommended management of mild gestational hypertension or pre-eclampsia. (From Sibai 2003.¹)

reassuring fetal testing. The patient should also have no subjective symptoms, and should be compliant and reliable.³

Whether the patient is in the hospital or being managed at home, the following should be observed:

- Salt restriction, diuretics, antihypertensive drugs, and sedatives are not used.

- The patient should have relative rest, daily dipstick measurement of protein, daily blood pressure monitoring, 1–2 times per week fetal testing, laboratory evaluation of hematocrit and platelets, and liver function tests 1–2 times a week. The patient should be educated about pre-eclampsia warning signs, such as headache, visual disturbances, epigastric pain, nausea and vomiting. She should be instructed about daily kick counts and labor signs or vaginal bleeding.
- Fetal testing should consist of at least weekly non-stress testing (NST), and measurement of amniotic fluid volume as needed, in addition to assessment of fetal growth by ultrasound every 3 weeks. Testing is considered non-reassuring if:
 - NST is non-reactive with abnormal fetal biophysical profile
 - NST shows late deceleration, moderate to severe variable decelerations, or prolonged deceleration
 - Oligohydramnios is present
 - Estimated fetal weight is less than 10th percentile for gestational age
 Prompt hospitalization is needed for disease progression, acute hypertension, development of significant proteinuria (2 g/24 h), outpatient management unsatisfactory for the specific patient, or abnormal fetal testing.^{1–3}

Severe pre-eclampsia (Fig. 68.2)

- *Beyond 34 weeks:* induction and delivery. No need for assessment of fetal lung maturity.
- *33–34 weeks:* amniocentesis is performed for lung maturity. Deliver if mature, steroids if immature and expectant management.
- *23–32 weeks:* expectant management and steroids.
- *Less than 23 weeks:* offer termination with prostaglandin E₂ (PGE₂) vaginal suppository, laminaria and oxytocin (Pitocin®, King Pharmaceuticals Inc., Bristol, TN), or dilation and evacuation. Overall perinatal survival without termination is 6.7%. If the patient does not elect to terminate, manage expectantly.

Conservative management of severe pre-eclampsia^{3,4}

In a tertiary care center:

- Initial intravenous magnesium sulfate for 24 h.
- Antihypertensives: intravenous boluses, then shift to oral administration, nifedipine, labetalol.

Hydralazine: 5–10 mg boluses every 20–30 min (maximum dose 20 mg)

Labetalol: 20–40 mg boluses (maximum dose 220 mg). Then 200 mg orally every 8 h (maximum 600 mg every 6 h).

Nifedipine: 10–20 mg orally every 30 min (maximum 50 mg). Then 10–20 mg every 4–6 h (maximum 120 mg/day)

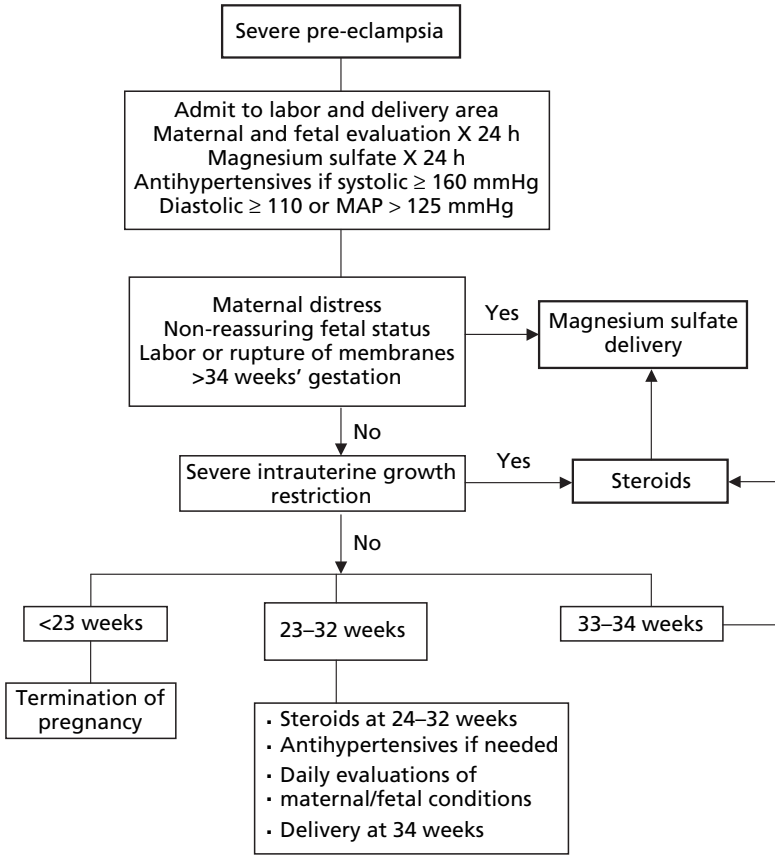


Fig. 68.2 Recommended management of severe pre-eclampsia. MAP, mean arterial pressure. Maternal distress: thrombocytopenia, imminent eclampsia, pulmonary edema, hemolysis plus elevated liver enzymes. (From Sibai 2003.¹)

The aim is for diastolic BP 90–100mmHg and systolic BP 140–150mmHg.

Avoid normal BP because of the risk of decreased uteroplacental perfusion.

Adequate therapeutic response is expected in 12 h.

- Give steroids for immature lungs and attempt to delay delivery at least for steroid benefit (48 h).
- Daily fetal–maternal testing.

The majority of patients with severe pre-eclampsia managed conservatively will require delivery within 2 weeks of admission. Indications for delivery of these patients include the following:

- *Maternal indications:* thrombocytopenia or HELLP (hemolysis, elevated liver enzymes, low platelets), disseminated intravascular coagulation (DIC), pulmonary edema, renal failure, eclampsia, uncontrolled severe hypertension, suspected abruptio placentae, labor or rupture of membranes, ascites; warning signs: persistent and severe headache, blurring of vision, epigastric pain.
- *Fetal indications:* fetal distress irrespective of gestational age or lung maturity, persistent severe oligohydramnios, severe intrauterine growth restriction (IUGR; less than 5th percentile), or gestational age greater than 34 weeks achieved.

HELLP syndrome

- *Hemolysis:*
 - Abnormal peripheral blood smear
 - Increased bilirubin ≥ 1.2 mg/dL
 - Increased lactic dehydrogenase greater than 600 IU/L
- *Elevated liver enzymes:* increased serum glutamic-oxaloacetic transaminase (SGOT) greater than 70 IU/L
- *Low platelets:* less than $100 \times 10^3/\mu\text{L}$

HELLP syndrome occurs in 2–12% of severe pre-eclamptic patients. It is more frequent in caucasians and multiparas. Patients complain of nausea and vomiting (50%), malaise of a few days' duration (90%), epigastric or right upper quadrant pain (65%), or swelling. Others will have vague abdominal pain, flank or shoulder pain, jaundice, hematuria, gastrointestinal bleeding, or gum bleeding. The onset is antepartum in 70% of cases and postpartum in 30% of cases. In the postpartum period, the time of onset of the clinical manifestations may range from a few hours to 1 week, with the majority developing within 48 h.⁵ Hypertension may be absent in 20% and mild in 30% of cases. Temporary management of HELLP for 48 h is only possible in the absence of DIC, particularly for benefit of corticosteroid administration.

Intrapartum management of pre-eclampsia and HELLP

The first priority is to assess and stabilize maternal condition and then to evaluate fetal well being. Finally, a decision must be made as to whether immediate delivery is indicated (Table 68.1).

Intravenous magnesium sulfate 6 g loading dose over 20 min (6 g in 150 mL 5% dextrose in water) is given followed by the maintenance dose of 2 g/h during labor and for 12–24 h postpartum (40 g in 1 L LR at 50 mL/h or 20 g in 1 L LR at 100 mL/h). This may be offered also to patients considered to have mild disease. Remember that the risk of eclamptic convulsion in those with mild disease is less than 1%. For HELLP patients type and cross-match with 2 units blood.

Table 68.1 Management outline of antepartum HELLP syndrome.

1	Assess and stabilize maternal condition <ul style="list-style-type: none"> • Antiepileptic prophylaxis with magnesium sulfate • Treatment of severe hypertension • Transfer to tertiary care center if appropriate • Computed tomography or ultrasound of the abdomen if subcapsular hematoma of the liver is suspected
2	Evaluate fetal well being <ul style="list-style-type: none"> • If fetal lung maturity or > 34 weeks' gestation → delivery • If immature fluid or ≤ 34 weeks' → steroids → delivery in 24–48 h

Deliver if abnormal fetal assessment
Deliver if progressive deterioration in maternal condition

Accurate measurement of input–output should be carried out using a Foley catheter. Restrict total intake to 100 mL/h to avoid pulmonary edema. If pulmonary edema is suspected, chest X-ray is performed and diuretics can be given. Monitoring of pulse, blood pressure, and respiration should be frequently carried out. Monitor for signs of magnesium toxicity and have a magnesium level drawn if needed; be ready to counteract magnesium toxicity with 10 mL 10% calcium gluconate intravenously. Be ready to deal with convulsions. Fetal monitoring should be carried out continuously. Oxytocin induction and allow normal vaginal delivery for favorable cervix or gestational age of 30 weeks or beyond. If the cervix is unripe and gestational age is less than 30 weeks, consider elective cesarean delivery or cervical ripening with PGE₂.

If anesthesia is needed, intermittent small doses of meperidine IVP (25–50 mg). Epidural anesthesia is preferred to general anesthesia in case of abdominal delivery if personnel skilled in obstetric anesthesia are available. Pudendal block and epidural are not advisable in HELLP patients as they might result in hematoma formation.⁶

If thrombocytopenia is present, it should be corrected before surgery. Transfuse with 10 units of platelets in all patients with a platelet count less than $40 \times 10^3/\mu\text{L}$.

In HELLP patients, to minimize the risk of hematoma formation, the bladder flap should be left open, a subfascial drain is used, and the wound is left open. The wounds can be successfully closed within 72 h after drain removal.⁶

Postpartum management

Adequate observation of the mother in the recovery room for 12–24 h under magnesium sulfate coverage. Remember that 25–30% of eclampsia cases and 30% of HELLP cases occur in the postpartum period. Most patients will show

evidence of resolution of the disease process within 24 h after delivery. Some, especially those with severe disease in the mid-trimester, HELLP, or eclampsia, require close monitoring for 2–3 days.

By the time of discharge, most patients will be normotensive. If hypertension persists, antihypertensive medications are prescribed for 1 week, after which the patient is re-evaluated.

COMPLICATIONS OF PRE-ECLAMPSIA/HELLP

Complications include abruptio placentae, pulmonary edema, acute renal failure, liver hematoma with possible rupture, postpartum hemorrhage, wound or intra-abdominal hematomas, DIC, and multiorgan failure, including liver, kidneys, and lungs (adult respiratory distress syndrome [ARDS]). Neurologic-like eclampsia, hypertensive encephalopathy, ischemia, infarcts, edema, and hemorrhage can also occur, as can cardiorespiratory arrest.

FOLLOW-UP AND MATERNAL COUNSELING

Women who develop pre-eclampsia in their first pregnancy are at increased risk (20%) for development of pre-eclampsia in subsequent pregnancies. The risk of pre-eclampsia in the sister of a patient with pre-eclampsia is 14%.

With severe disease in a first pregnancy, the risk of recurrence is approximately 30%. With severe disease in the second trimester, the risk of recurrent pre-eclampsia is 65%. In 21% of cases, the disease also occurs in the second trimester. HELLP recurs in approximately 5% of cases.⁶

There is increased risk of chronic hypertension and undiagnosed renal disease. This is especially true in patients with two episodes of severe pre-eclampsia in the second trimester. These patients should have adequate medical evaluation postpartum. There is also an increased risk of IUGR in subsequent pregnancies.

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Intrauterine growth restriction

Ursula F. Harkness and Ray O. Bahado-Singh

INTRODUCTION

Intrauterine growth restriction (IUGR) contributes disproportionately to fetal and neonatal morbidity and mortality. Clinical challenges include the detection of growth-restricted fetuses, determination of the etiology, antepartum surveillance and determination of the optimal time for delivery. Specific treatment and prevention of IUGR represent a more formidable challenge.

DEFINITIONS

The terms small for gestational age (SGA) and intrauterine growth restriction (IUGR) are often mistakenly used interchangeably. SGA refers to the fetus whose estimated fetal weight is less than the 10th percentile for gestational age and encompasses both growth-restricted and constitutionally small fetuses. Growth restriction implies a failure to reach growth potential for pathologic reasons with consequent increased risk for adverse outcomes. According to one report, 3–10% of all neonates are small for gestational age. Of these, 30% have pathologic growth impairment whereas the remaining 70% are constitutionally small.

PATHOPHYSIOLOGY

Fetal growth is determined by maternal, fetal, and placental factors. IUGR itself is not a single disease, but rather a common endpoint resulting from disparate etiologies. It is estimated that up to 20% of growth-restricted fetuses have a genetic disorder, most commonly aneuploidies. Other fetal risk factors for IUGR include congenital malformations, multiple gestation, and infection. The most common etiology of IUGR in the structurally normal fetus is maternal vascular disease. Such vascular disorders include chronic hypertension, pre-eclampsia, renal insufficiency, systemic lupus erythematosus, collagen vascular disease, antiphospholipid antibody syndrome, pregestational diabetes, or uncorrected cyanotic congenital heart disease. Other maternal risk factors include extreme malnutrition, tobacco smoking, recreational drugs such as

alcohol, cocaine, heroin and, less commonly, prescription medications such as anticonvulsants and warfarin. Placental factors that are associated with IUGR include circumvallate placenta, chorioangiomas, placenta previa, partial abruption, and placental mosaicism (i.e. with trisomy 16).

DATING THE PREGNANCY

Precise gestational dating is extremely important in the diagnosis of the IUGR fetus. Last menstrual period (LMP) dating is often imprecise, particularly if the patient has irregular menses or if she currently or recently used hormonal contraception around the time of conception. First trimester crown–rump length (CRL) measurement is highly accurate. When the discrepancy between dating by the LMP and CRL is more than 7 days, the pregnancy should be dated by ultrasonography. Fetal biometry can also be used in the second trimester to date a pregnancy accurately. Biometry should be used to estimate the date of delivery if there is more than a 7 to 10-day discrepancy between LMP and ultrasound dating until 20 weeks' gestation. With advancing gestational age, the accuracy of ultrasonography for the determination of gestational age decreases. In the third trimester, the margin of error is ± 3 weeks. Serial ultrasounds at 2–3 week intervals should be used to date the pregnancy during this gestational period.

CLINICAL DIAGNOSIS OF THE SMALL FETUS

Routine use of symphysis–fundal height measurements can detect 41–86% of SGA babies. Between 20 and 34 weeks' gestation, the fundal height in centimeters should equal the gestational age in weeks. A measurement 3–4 cm below the expected number suggests growth abnormality. There is no clear evidence that routine ultrasound is a better screening method for SGA than careful fundal height measurement when performed by the same observer in the general population. Differences in maternal habitus and fetal position, however, may have significant negative effects on the precision of both fundal height ascertainment and ultrasonographic estimation of fetal weight.

INITIAL ASSESSMENT

Patients at risk for or with clinical suspicion of reduced growth should undergo sonographic biometry. Estimated fetal weight is most commonly used to assess growth in the third trimester. Many different formulas have been used to estimate fetal weight. Two commonly used methods are the Hadlock formula which incorporates head circumference, abdominal circumference and femur length, and the Shepard formula which uses biparietal diameter and abdominal circumference. The estimate of random error for the Hadlock formula is $\pm 15\%$ (2 standard deviations). Most estimates of fetal weight using the Shepard formula are within 10% of actual weight. The diagnosis of SGA is made if the

fetal weight estimate is less than the 10th percentile for gestational age. The abdominal circumference indirectly reflects liver size. The latter is an important indication of fetal nutrition. Even if the fetal weight estimate is greater than the 10th percentile, a reduced abdominal circumference (less than 10th percentile) indicates the need for continued surveillance. Because genetic, racial, and environmental factors influence growth, population-specific growth curves are ideal.

A targeted ultrasound should be performed if the fetus is small, to look for evidence of fetal chromosomal or structural abnormalities. The amniotic fluid volume is a critical indicator of uteroplacental insufficiency and should be carefully estimated.

For the SGA fetus with normal amniotic fluid and without congenital anomalies, Doppler velocimetry helps to differentiate the IUGR fetus from the constitutionally small fetus. First, umbilical artery (UA) Doppler studies should be performed. In pregnancies complicated by IUGR, there is a chronologic process of deterioration characterized by an increased umbilical artery resistance (increased S : D ratio), absent end diastolic velocity and, finally, reversal of end diastolic velocity. Those fetuses with absent or reversed end diastolic flow in the umbilical artery are at significantly elevated risk of perinatal morbidity and mortality as well as adverse long-term outcome. Many authors have suggested, on the other hand, that small fetuses with normal umbilical artery flow represent a group not at risk for adverse perinatal outcome. Most of these babies are thought to be constitutionally small. Some authors suggest that antenatal surveillance is not necessary for the SGA fetus with normal amniotic fluid and umbilical artery Doppler studies, although this has not yet been studied in a sufficiently large prospective randomized trial.

Evaluation of the middle cerebral artery (MCA) of the fetus can also give useful information in the assessment of the small fetus. The fetal response to chronic hypoxia is redistribution of blood flow to the tissues most needed such as the brain, myocardium, and adrenal glands. This response is referred to as the “brain-sparing effect.” The cerebral : placental ratio (CPR) is the ratio between the MCA and umbilical artery pulsatility indices (PI), resistance indices (RI) or S : D ratios. Either this ratio or the MCA PI can be used to assess for “brain sparing,” although the former is a more sensitive predictor of perinatal complication. A decreased MCA PI reflects hypoxia-induced vasodilation. A CPR below 1.0–1.1 is considered abnormal.

Other diagnostic tests should be considered based on maternal history and ultrasound findings. Karyotype is indicated with early onset or severe growth restriction, particularly when associated with normal fluid volume or a structural abnormality. An infectious etiology occurs in 5–10% of IUGR pregnancies. Maternal serology for rubella, cytomegalovirus, varicella, syphilis, and *Toxoplasma gondii* should be considered if severe symmetric IUGR is present.

When ultrasonographic findings associated with intrauterine infection are noted, a work-up for such an etiology is also appropriate. Ultrasound features can include cerebral ventriculomegaly, non-immune hydrops, microcephaly, intracranial hemorrhage or calcifications, hepatosplenomegaly, echogenic hepatic foci, echogenic bowel, and placentomegaly. Finally, the presence of a thrombophilic disorder may be suspected in the patient with a history of vascular thrombosis, second or third trimester fetal demise, early onset IUGR, or severe early onset pre-eclampsia.

COMPLICATIONS

Perinatal morbidity and mortality increases considerably as birth weight decreases from the 10th to the 1st percentile for gestational age. There is a higher rate of neonatal death, neonatal asphyxia, sepsis, meconium aspiration, hypoglycemia, polycythemia, and necrotizing enterocolitis in growth-restricted infants. There is some controversy over whether respiratory distress syndrome and intraventricular hemorrhage are increased or decreased in SGA versus appropriate-for-gestational-age babies.

The problems of the small fetus continue well beyond the perinatal period into childhood and adulthood. These babies are at risk of impaired intellectual development. Recent data suggest an increased risk of hypertension, hypercholesterolemia, myocardial infarcts, obesity, and impaired glucose tolerance in adulthood.

TREATMENT

Various treatment options for IUGR have been studied. Thus far there is insufficient evidence to support or refute the use of continuous maternal oxygen administration, maternal nutrient supplementation, hospital bed rest, or medications such as betamimetics, calcium-channel blockers, or low-dose aspirin. Avoiding smoking does have a positive effect on birth weight.

FOLLOW-UP: ASSESSING THE FETUS

Non-stress test

There is no clear evidence from randomized trials that antepartum surveillance with non-stress tests (NSTs) improves outcomes for IUGR fetuses. In addition, an abnormal fetal heart rate tracing occurs relatively late in fetal deterioration. NST, however, is the most frequently used test for assessment of fetal well being and remains the standard of care.

Ultrasound

Fetal growth should be monitored by ultrasound at 2–3-week intervals. Ultrasounds for growth performed before waiting this time period may give confusing information because of the large margin of error in the third

trimester. Delivery should be considered if cessation of growth, defined as no increase over a 2-week interval, is noted, particularly in the term or near-term fetus.

A recent Cochrane review assessed the effects of biophysical profile (BPP) on perinatal outcome. The authors concluded that at the present time there is inconclusive evidence from randomized controlled trials to support or argue against the benefit of BPP in improving outcome in high-risk conditions that include IUGR. Thus, BPP or NST may be used for ongoing monitoring.

Monitoring amniotic fluid volume is important as a component of the BPP or as a component of the “modified BPP,” which includes the NST and fluid assessment. The likely explanation for the association of oligohydramnios and IUGR is decreased urine output as a result of blood volume redistribution leading to diminished renal blood flow.

Doppler velocimetry

A recent meta-analysis compared the use of Doppler velocimetry of the umbilical artery with no Doppler in high-risk pregnancies, many of which were complicated by IUGR. Findings included a trend in reduction of perinatal deaths along with significantly fewer inductions of labor and hospital admissions with the use of umbilical Doppler information.

There may be a benefit to inclusion of ductus venosus Doppler velocimetry into the antepartum surveillance of the IUGR fetus with abnormal UA and/or MCA Doppler waveforms. The ductus venosus is a vein that carries fetal blood from the umbilical vein to the inferior vena cava, bypassing the hepatic circulation. The oxygenated blood from the ductus venosus is preferentially shunted through the foramen ovale to the left atrium and left ventricle. Reduced oxygenation of the heart and myocardial stiffening occurs when significant hypoxia ensues. Forward flow during atrial contraction (nadir of the velocimetry waveform) is reduced because of decreased compliance and raised intracardiac pressures. In severe cases, reversal of flow occurs during the atrial contraction phase of the ductus venosus waveform.

Recent longitudinal studies have described a temporal sequence in the IUGR fetus prior to fetal distress; it appears that UA and MCA Doppler changes occur early and venous Doppler changes, such as those in the inferior vena cava and ductus venosus, occur late. The perinatal mortality once absent or reversed flow in the ductus venosus has developed ranges from 63 to 100%. The perinatal mortality rate for fetuses with significant UA and MCA Doppler changes are low in comparison at up to 10% of fetuses.

While there are currently insufficient data from randomized trials regarding the utility of ductus venosus Doppler studies, mounting evidence indicates that abnormal ductus velocimetry is an ominous finding and should prompt hospitalization, antenatal steroids, continuous monitoring, and possibly delivery.

Additional information regarding the use of Doppler studies can be found in Chapter 13.

Recommendations

In the case of an IUGR fetus with an elevated UA Doppler and/or evidence of brain sparing, the fetus should have UA, MCA, and possibly ductus venosus Doppler studies weekly. An NST and AFI or a BPP should be performed once or twice weekly.

In the case of an IUGR fetus with absent or reversed end diastolic flow in the umbilical artery, the patient should be promptly hospitalized until delivery with daily NST or BPP and weekly UA, MCA, and ductus venosus Doppler study. If the fetus is at or near term, delivery should be considered. Ductus venosus Doppler appears to be extremely promising for timing the delivery of the very preterm IUGR fetus.

In the case of a small fetus with normal anatomy, normal amniotic fluid, and normal UA and MCA Doppler studies, an ultrasound should be performed every 2 weeks for growth and Doppler studies.

For IUGR cases deemed appropriate for home management, reduced activity and daily fetal kick counts are recommended.

FOLLOW-UP: TIMING OF DELIVERY

Amniocentesis should be considered for the IUGR fetus beyond 34 weeks. If fetal lung maturity studies suggest pulmonary maturity, the fetus should be delivered.

If a diagnosis of severe pre-eclampsia is made in association with a severely IUGR fetus ("5th percentile), delivery should occur if the fetus is beyond 34 weeks' gestation. If the fetus is less than 34 weeks, a course of steroids should be initiated to reduce the risk of respiratory distress syndrome and intraventricular hemorrhage in the neonate. The fetus should be delivered after the steroid course is completed unless maternal or fetal status warrants earlier delivery.

Delivery should be considered for an IUGR fetus with significant oligohydramnios beyond 34 weeks.

Cessation of growth on serial ultrasounds is an indication for delivery. Other ominous findings that should prompt consideration of delivery are sustained non-reassuring fetal heart rate tracing or BPP of 4 or below.

Timing of delivery for the extremely premature IUGR fetus remains a major conundrum. The Growth Restriction Intervention Trial (GRIT) randomized women with IUGR fetuses between 24 and 36 weeks' gestation when the management course was uncertain. Most of the cases had severe umbilical artery Doppler abnormalities. Expectant management was compared with expeditious delivery. There was no overall difference in deaths before hospital discharge

associated with either approach with more stillbirths in the delayed delivery group and more neonatal deaths in the expeditious delivery group. There was a significantly increased cesarean section rate in the expeditious delivery group.

Strong consideration should be given to delivering even the very preterm viable fetus who has severe ductus venosus Doppler changes after a course of steroids has been administered.

Expectant management is recommended for the small fetus with normal amniotic fluid, antepartum surveillance, and UA and MCA Doppler velocimetry.

PREVENTION

Currently, we know little about how to prevent IUGR. Unfortunately, many of the placental and fetal risk factors are not modifiable. Maternal risk factors are similarly difficult to alter in many circumstances. Smoking cessation is known to moderately increase fetal weight and thus reduce IUGR risk. Identification of risk predictors does, however, permit heightened surveillance and expert perinatal management, which may improve outcome.

CONCLUSIONS

IUGR remains an important perinatal threat. While not preventable, recognition and proper management can improve outcomes. Currently, however, only umbilical artery Doppler velocimetry has been proven to improve the management of IUGR pregnancies in prospective randomized studies.

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Rh and other blood group alloimmunizations

Kenneth J. Moise, Jr

INTRODUCTION

Once a significant cause of perinatal loss, alloimmunization to red cell antigens is infrequently encountered today in obstetric practice. Sensitization to the RhD antigen remains the leading cause of hemolytic disease of the fetus/newborn (HDFN), accounting for over 50% of cases.¹ A recent review of the 2002 birth certificates in the USA by the Centers for Disease Control indicates an incidence of 6.7 in 1000 live births.² In a report of 37,506 female patients at two New York blood centers, 1.1% of samples contained an antibody associated with HDFN. After anti-D, Kell antibodies were next most frequent (29%) followed by Duffy (7%), MNS (6%), Kidd, and anti-U.¹ Despite the frequency of this disease, significant advances in diagnostic tools have occurred with the addition of genetic testing of the fetus and Doppler ultrasound for the detection of fetal anemia.

PATHOPHYSIOLOGY

The fetal–maternal interface was once thought to be an impervious barrier. However, more recent evidence suggests there is considerable trafficking of many types of cells between the fetus and its mother throughout gestation. In most cases, the antigenic load of incompatible antigen on the fetal erythrocytes and erythrocytic precursors is insufficient to stimulate the maternal immune system. However, in the case of a large antenatal fetomaternal hemorrhage (FMH) or a FMH at delivery, B lymphocyte clones that recognize the foreign red cell antigen are established. The initial maternal immunoglobulin M (IgM) antibody response is short-lived with a rapid change to immunoglobulin G (IgG) antibody.

Although the fetus of the sensitizing pregnancy often escapes the effects of the maternal antibody, subsequent fetuses are at risk for HDFN. Maternal IgG crosses the placenta and attaches to fetal erythrocytes that have expressed the paternal red cell antigen. These cells are then sequestered by macrophages in the fetal spleen where they undergo extravascular hemolysis producing fetal

anemia. In cases of HDFN related to the Kell (anti-K1) antibody, *in vitro* and *in vivo* evidence suggest an additional mechanism for the fetal anemia—suppression of erythropoiesis.^{3,4} Hydrops fetalis is the most significant manifestation of fetal anemia although its exact pathophysiology remains unknown. An elevated central venous pressure has been reported in these fetuses and may cause a functional blockage of the lymphatic system at the level of the thoracic duct as it empties into the left brachiocephalic vein. Reports of poor absorption of red cells transfused into the peritoneal cavity in cases of hydrops support this theory.

MANAGEMENT OF THE FIRST ALLOIMMUNIZED PREGNANCY

Obtain an antibody screen on all pregnant women at their first prenatal visit. If the antibody screen returns positive, the antibody should be identified to see if it has been associated with HDFN (Table 70.1). If this is the case, an anti-globulin titer should be undertaken. Obtain an early ultrasound for pregnancy dating and determine the paternal antigen status:

- If negative and paternity is assured, no further evaluation is necessary
- If positive, consult with a blood bank pathologist to determine the paternal zygosity (homozygous or heterozygous)

Repeat the titers every month until 24 weeks' gestation; then every 2 weeks for the remainder of the pregnancy. Perform titers with the older tube technology (gel methods have not been correlated with clinical outcome). Use an experienced blood bank; most commercial laboratories use enhancement techniques that will elevate titers. If the titer is 1 : 32 or greater (use a titer of 1 : 8 for the Kell antibody), there is a risk for fetal hydrops. Consult a maternal–fetal medicine specialist for further management.

In cases of a heterozygous partner, perform amniocentesis by 24 weeks' gestation to assess the fetal blood type through DNA analysis. Send maternal and paternal blood samples to the reference laboratory with the amniotic aliquot to minimize errors caused by gene rearrangements in the parents.

The fetus can be monitored for the development of anemia by one of two methods which are performed serially every 1–2 weeks:

- Peak middle cerebral artery (MCA) Doppler velocity: a value of greater than 1.5 multiples of the median (MoM) for gestational age is highly suggestive for fetal anemia (Fig. 70.1).⁵ MCA Dopplers can be obtained as early as 18 weeks but are not useful after 35 weeks because of the high false-positive rate.
- Perform serial amniocenteses for $\Delta OD450$ using the Queenan curve (Fig. 70.2). Avoid a transplacental approach to decrease the chance for enhanced maternal sensitization.

If the MCA Doppler velocity is more than 1.5 MoM or the $\Delta OD450$ value enters the Rh positive (affected) zone of the Queenan curve, perform cordocentesis with blood in readiness for intrauterine transfusion for a fetal hematocrit of less than 30%.

Table 70.1 Non-RhD antibodies and associated HDFN. (Reproduced with permission from: Moise, KJ. Hemolytic disease of the fetus and newborn. In: *Maternal-Fetal Medicine*, Creasy R, Resnik R, Iams J, eds. WB Saunders, Philadelphia Copyright © 2003.)

Antigen system	Specific antigen	Antigen system	Specific antigen	Antigen system	Specific antigen
<i>Frequently associated with severe disease</i>					
Kell	K (K1)				
Rhesus	c				
<i>Infrequently associated with severe disease</i>					
Colton	Co ^a	MNS	Mur	Scianna	Sc2
	Co3		M ^v		Rd
Diego	ELO		s	Other Ags	Bi
	Di ^a		s ^D		Good
	Di ^b		S		Heibel
	Wr ^a		U		HJK
	Wr ^b		Vw		Ht ^a
Duffy	Fy ^a	Rhesus	Be ^a		Jones
Kell	Js ^b		C		Joslin
	k (K2)		Ce		Kg
	Kp ^a		C ^w		Kuhn
	Kp ^b		ce		Li ^a
	K11		E		MAM
	K22		E ^w		Niemetz
	Ku		Evans		REIT
	Ul ^a		G		Reiter
Kidd	Jk ^a		Go ^a		Rd
MNS	En ^a		Hr		Sharp
	Far		Hr _o		Vel
	Hil		JAL		Zd
	Hut		Rh32		
	M		Rh42		
	Mi ^a		Rh46		
	Mt ^a		STEM		
	MUT		Tar		
<i>Associated with mild disease</i>					
Duffy	Fy ^b	Kidd	Jk ^b	Rhesus	Riv
	Fy ³		Jk ³		RH29
Gerbich	Ge ²	MNS	Mit	Other	At ^a
	Ge ³	Rhesus	C ^x		JFV
	Ge ⁴		D ^w		Jr ^a
	Ls ^a		e		Lan
Kell	Js ^a		HOFM		
			LOCR		

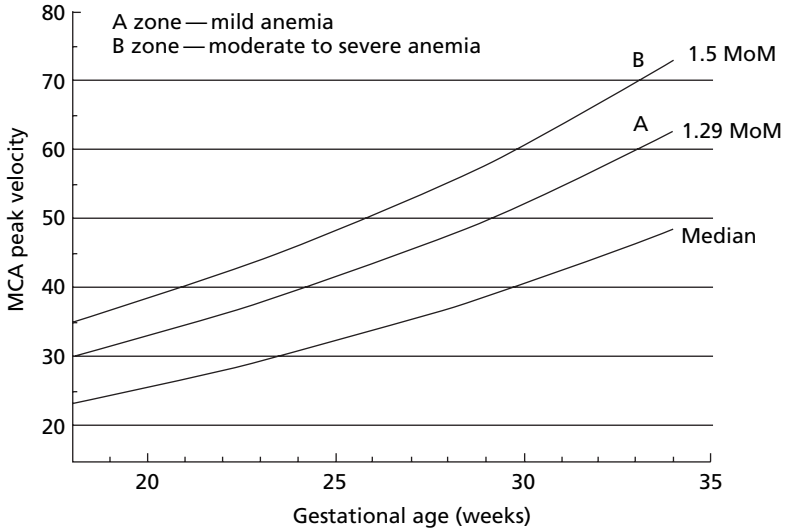


Fig. 70.1 Middle cerebral artery peak systolic Doppler velocity. (Reproduced with permission from Moise KJ. Modern management of Rhesus alloimmunization in pregnancy. *Obstet Gynecol* 2002;**100**:600–11, Elsevier Science Company, Copyright © 2002.)

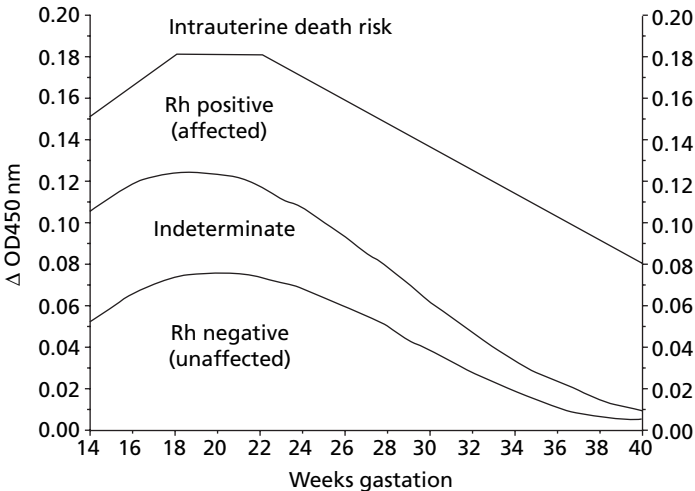


Fig. 70.2 Queenan curve for ΔOD_{450} values. (With permission from Queenan JT, Tomai TP, Ural SH, King JC. Deviation in amniotic fluid optical density at a wavelength of 450 nm in Rh-immunized pregnancies from 14 to 40 weeks' gestation: a proposal for clinical management. *Am J Obstet Gynecol* 1993;**168**:1370–6, Mosby, Inc., Copyright © 2001.)

Initiate antenatal testing with non-stress testing or biophysical profiles at 32 weeks' gestation. If repeat MCA velocities remain below 1.5 MoM or $\Delta OD450$ values remain below the Rh positive (affected) zone, perform amniocentesis at 35 weeks' gestation for $\Delta OD450$ and fetal lung maturity (use phosphatidylglycerol quantitation, lamellar body count, or the lecithin : sphingomyelin ratio, instead of the TDx-FLM test as the latter can be falsely elevated as a result of high amniotic fluid levels of bilirubin).

- If mature lungs are found and the $\Delta OD450$ value has not reached the Rh positive (affected) zone, induce at 37 weeks' gestation to allow for hepatic maturity in an effort to prevent hyperbilirubinemia.
- If immature lungs are found and the $\Delta OD450$ value has reached the Rh positive (affected) zone, treat with 30 mg oral phenobarbital t.i.d. and induce labor in 1 week. This will accelerate fetal hepatic maturity and allow for more efficient neonatal conjugation of bilirubin.⁶ In these cases, a unit of packed red blood cells cross-matched to the pregnant patient should be prepared prior to the delivery so that it is available in the event that the pediatrician must perform an emergency neonatal transfusion.
- If immature lungs are found and the $\Delta OD450$ value is not in the Rh positive (affected) zone, repeat the amniocentesis at 37 weeks.

MANAGEMENT OF A SUBSEQUENT ALLOIMMUNIZED PREGNANCY

(Previously affected fetus that has undergone intrauterine transfusions or an infant who has undergone neonatal transfusions.)

Maternal titers are *not* helpful in predicting the onset of fetal anemia after the first affected gestation. In cases of a heterozygous paternal phenotype, perform an amniocentesis at 15 weeks' gestation to determine the fetal red cell antigen status. If an antigen negative fetus is found and paternity is assured, no further testing is warranted. Begin serial MCA Doppler assessments or serial amniocenteses for $\Delta OD450$ (using the Queenan curve) at 18 weeks' gestation. Repeat at 1–2 week intervals.

If a rising value for MCA Doppler more than 1.5 MoM or a rising $\Delta OD450$ value into the Rh positive (affected) zone is noted, perform cordocentesis with blood in readiness for intrauterine transfusion for a fetal hematocrit of less than 30%. If the MCA Doppler or $\Delta OD450$ remains normal, follow the same protocol for antenatal monitoring and delivery as previously noted for the management of the first sensitized pregnancy.

TREATMENT

Since it was first introduced in 1963,⁷ the intrauterine transfusion (IUT) of donor red blood cells has clearly contributed to the survival of countless fetuses with severe HDFN worldwide. Today the direct intravascular transfusion (IVT)

using the umbilical cord for access is the technique most widely used in the USA. Typically, a unit of donor red cells that has been recently donated and lacking the putative red cell antigen is used. The donor should be negative for antibody to cytomegalovirus. The unit is cross-matched to the pregnant patient and then packed to a final hematocrit of 75–85% to allow a minimal blood volume to be administered to the fetus during the IUT. The blood is then leukoreduced with a special filter and irradiated with 25 Gy to prevent graft-versus-host reaction.

The patient is usually admitted to the labor and delivery suite for an outpatient procedure. Conscious sedation is used in conjunction with local anesthetic. Prophylactic antibiotics are given but tocolytics are rarely required. Continuous ultrasound guidance is used to find the umbilical cord insertion. After the initial puncture of the umbilical vein, a sample of fetal blood is sent for hematocrit and other values. A small dose of a paralytic agent is administered to cause cessation of fetal movement. Donor red cells are then transfused based on the initial fetal hematocrit and formulas to calculate the fetoplacental blood volume using ultrasound-estimated fetal weight.⁸ A final sample is obtained to measure the fetal hematocrit at the conclusion of the procedure. After the procedure, the patient undergoes continuous fetal monitoring until there is resumption of fetal movement. An ultrasound is performed the following day to assess fetal viability.

IUTs are rarely successful prior to 18 weeks' gestation; excellent rates of neonatal survival in today's special care baby units have led most centers to limit IUTs to gestational ages of less than 35 weeks. If the fetus is severely anemic and the gestational age is less than 24 weeks, the fetal hematocrit is only partially corrected with the first IVT.⁹ A subsequent procedure is planned 48 h later to correct the fetal hematocrit into the normal range. In other cases, the second procedure is usually planned 7–10 days after the first with an expected decrease in the fetal hematocrit of approximately 1% per day. Subsequent procedures are repeated at 2–3 week intervals based on fetal response.

After the last procedure, the patient is scheduled for induction of labor at 38–39 weeks' gestation to allow for fetal hepatic and pulmonary maturity. It is rare for these infants to require prolonged phototherapy or exchange transfusions. Breastfeeding is not contraindicated.

OUTCOME AND FOLLOW-UP

In experienced centers, the overall perinatal survival with IUT is 85–90%.¹⁰ Fetuses with hydrops have a markedly lower rate of survival, particularly if the hydrops does not resolve after 2–3 procedures. Suppression of fetal erythropoiesis results in prolonged bone marrow suppression after birth. These infants should be followed weekly with hematocrits and reticulocyte counts until there is evidence of reticulocytosis. Simple neonatal transfusions of red cells may be

required in as many as 50% of cases, particularly if the neonate becomes symptomatic from the anemia.¹¹

Neurodevelopmental follow-up of neonates transfused by IVT are limited in number. Most studies point to over 90% chance of intact survival.¹² Hydrops fetalis does not seem to impact on this outcome. Sensineural hearing loss may be slightly increased as a result of prolonged exposure of the fetus to high levels of bilirubin. A hearing screen should be performed during the early neonatal course and repeated by 2 years of age.

PREVENTION

Only RhD alloimmunization can be prevented through the use of a specific immunoglobulin (RhIG). Although this product is manufactured from human serum, clinical trials are underway with synthesized monoclonal antibodies. Prevention of alloimmunization to other red cell antigens is currently not possible as specific prophylactic immunoglobulins are not available. In some countries, such as Australia, Kell negative female children and women of reproductive age are cross-matched to receive Kell negative blood when they require a transfusion. This policy has not been adopted in the USA because of the low frequency of the Kell antigen in the general population.

Patients whose initial blood type at the first prenatal visit returns RhD negative, weak Rh positive (formerly called Du positive) have fewer RhD antigenic sites expressed on their red cells. For this reason they are not at risk for Rhesus alloimmunization and therefore do not require RhIG. If an RhD negative patient's initial antibody screen is negative, further diagnostic testing is unnecessary until 28 weeks' gestation. Unless the patient's partner is documented to be RhD negative, a 300 µg dose of RhIG should then be administered. A repeat antibody screen at 28 weeks is recommended by the American Association of Blood Banks (AABB), although the American College of Obstetricians and Gynecologists has left this to the discretion of the clinician.¹³

At the time of the delivery of an RhD negative patient, cord blood should be tested for RhD typing. If the neonate is determined to be RhD positive, a second dose of 300 µg should be administered within 72 h of delivery. Routine screening of all women for excessive fetomaternal bleeding at the time of delivery is now recommended by the AABB. Typically, this involves a sheep rosette test that is read qualitatively as positive or negative. If negative, one vial of RhIG (300 µg) is given as this will be sufficient to protect the patient from a 30 mL fetal bleed. If positive, the volume of the bleed is quantitated with a Kleihauer–Betke stain or fetal cell stain using flow cytometry. Blood bank consultation should then be undertaken to determine the number of doses of RhIG to administer. If RhIG is inadvertently omitted after delivery, some protection from sensitization has been shown with administration within 13 days. RhIG should not be withheld as late as 28 days after delivery if the need arises.¹³

Table 70.2 Other indications for RhIG administration.

Spontaneous abortion
Threatened abortion
Elective abortion
Ectopic pregnancy
Hydatidiform mole
Amniocentesis
Chorion villus biopsy
Placenta previa with bleeding
Suspected abruption
Intrauterine fetal demise
Blunt trauma to the abdomen (including motor vehicle accidents)
External cephalic version

Additional indications for RhIG are listed in Table 70.2. The use of RhIG for threatened abortion has not been well studied. If minimal vaginal bleeding is noted, it can probably be omitted; however, if significant clinical bleeding is present, a dose should be administered. Although a 50 µg RhIG dose can be used up to 13 weeks' gestation; in practical terms most hospitals no longer stock this preparation and the cost is comparable to the standard 300 µg dose. Repeat doses should be given at 12-week intervals if bleeding persists. A second indication for RhIG that is often overlooked is blunt trauma to the maternal abdomen, particularly at the time of a motor vehicle accident. Finally, if 300 µg RhIG is given late in gestation for external cephalic version or third trimester amniocentesis for fetal lung maturity, a repeat dose is unnecessary if delivery occurs within 3 weeks as long as a FMH in excess of 30 mL is not documented. The use of a repeat dose of RhIG after 40 weeks' gestation or its use after post-partum tubal ligation remains controversial.

CONCLUSIONS

The prevention and treatment of HDFN secondary to Rhesus alloimmunization represents a true victory of modern perinatal care. Advances in DNA technology will soon allow for routine non-invasive red cell typing of the fetus from maternal serum. Maternal immunomodulation will probably negate the need for intrauterine transfusion in the coming years.

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Early detection of preterm labor

Jay D. Iams

INTRODUCTION

Seventy-five percent of perinatal morbidity and mortality occurs in babies born before 37 weeks' gestation, especially before 32 weeks. Preterm infants are more likely to experience cerebral palsy, developmental delay, visual and hearing impairment, chronic lung disease, and poor school performance. Preterm birth has increased since 1990 by 14% to a rate of 12.5% in 2003. An increase in multiple births (e.g. a 38% rise in twin gestations) accounts for some of the increase, but the rate in singletons has also risen by 7% since 1990. In 2002, the preterm birth rate was 10.2% for singleton, 58.2% for twin, and 92.4% for triplet gestations. Approximately 20% of preterm births are *indicated*, in that they are ultimately caused by a maternal or fetal illness that places mother or baby, or both, in jeopardy if the pregnancy continues (e.g. maternal hypertension or pre-eclampsia, fetal growth restriction, or bleeding resulting from placenta previa or abruption). More commonly, preterm births occur *spontaneously*, after preterm labor (40%), preterm ruptured membranes (35%), or related conditions (5%). There are numerous risk factors associated with preterm birth but attempts to reduce the rate of preterm birth by interventions aimed at individual risk factors have not been successful. It is more likely that multiple factors combine to increase the chance of preterm delivery. Environmental exposures (e.g. to stress, genital infections, smoking, or nutritional deficits) and genetic factors in both mother and fetus (e.g. genetic variations that influence the response to inflammation) have been identified that are associated with increased risk of preterm birth and appear to govern the likelihood of spontaneous preterm birth.

Four biologic pathways have been identified that may lead to preterm cervical effacement, labor, or membrane rupture:

- 1 Intrauterine inflammation
- 2 Decidual hemorrhage
- 3 Uterine stretch or overdistention
- 4 Premature activation of the normal physiologic initiators of labor

Inflammation is a more likely pathway for births before 32 weeks; decidual hemorrhage is not necessarily associated with clinical bleeding and may occur at any time in pregnancy. Multifetal gestation, polyhydramnios, and uterine anomalies can cause increased uterine distention. Preterm labor after 32 weeks' gestation is often the result of premature activation of the maternal–fetal hypothalamic–pituitary–adrenal axis. The processes leading to spontaneous preterm birth most often occur slowly over a period of several weeks.

DIAGNOSIS

Early identification of women who will deliver preterm could allow intervention that might decrease the chance of preterm birth, or at least decrease the chance of neonatal mortality and morbidity. An efficient system to reduce the consequences of preterm birth has not yet been devised because both identification and intervention strategies are inadequate. However, there have been some promising recent developments.

Early detection of risk

The following are associated with an increased risk of preterm birth, but have been disappointing when evaluated to predict actual risk of preterm birth.

Clinical risk factors

A history of prior preterm birth, bleeding after the first trimester, maternal genital tract infection, and multifetal gestation have been associated with an increased likelihood of preterm delivery. A history of prior preterm birth confers a twofold increased risk (approximately 20% absolute risk) for one, and a fourfold increased risk for two or more previous preterm births. The sensitivity of clinical and historical risk factors for preterm birth is relatively low, ranging from 20% to 40% depending on the risk factor and the population studied.

Monitoring of uterine contractions

Although antepartum contraction frequency is greater among women who will deliver preterm, contraction frequency is not a sensitive or predictive marker to identify women with increased risk because the magnitude of the difference is too small to distinguish them from women who will deliver at term.

Biochemical markers

Maternal blood, saliva, and cervicovaginal secretions have been tested to look for biochemical markers of one or more of the four pathways cited above. Fetal fibronectin, an extracellular matrix protein that attaches the fetal membranes to the underlying uterine decidua, is not normally present in cervicovaginal

secretions between 22 and 36 weeks. When fibronectin is found between 22 and 36 weeks, the risk of preterm birth before 35 weeks, and especially before 28 weeks, is increased. However, the sensitivity of fetal fibronectin has been low, approximately 20–40%. Tests of markers in serum and saliva have also had low sensitivity.

Examination of the cervix

Preterm cervical effacement, has been consistently associated with an increased risk of preterm birth. It can be detected either by:

- *Digital examination*: expressed as either a Bishop score (a composite of cervical dilation, effacement, position, consistency, and station of the fetal presenting part) or the cervical score (cervical length in centimeters minus the cervical dilation at the internal os in centimeters, or
- *Endovaginal sonography*: recorded as cervical length in millimeters

Sonographic measurement of length is more reproducible and reveals premature effacement at the internal os more reliably, but requires more training and equipment than digital examination (Table 71.1).

When uterine contractions, fetal fibronectin, Bishop score, and cervical ultrasound were compared in women with increased risk, none had optimal positive predictive value or sensitivity but cervical assessment by ultrasound (length less than 25 mm) or Bishop score (5 or more) had better sensitivity than either fetal fibronectin or contraction frequency (Table 71.2).

Table 71.1 Comparison of sonographic and digital cervical assessment at 26–29 weeks for prediction of spontaneous preterm birth before 35 weeks' gestation.

	Sonographic assessment*		Digital assessment†	
	Length		Bishop score	Cervical score
	≤20 mm	≤25 mm	≥5	<1.5
Sensitivity (%)	31	49	32	36
Specificity (%)	95	87	93	95
Positive predictive value (%)	17	11	14	20
Negative predictive value (%)	98	98	98	98

Data from *Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous delivery. *N Engl J Med* 1996;334:567–72, and †Newman RB for the NICHD Maternal Fetal Medicine Network. The Preterm Prediction Study: Comparison of the cervical score and Bishop score for prediction of spontaneous preterm birth. *J Soc Gynecol Invest* 1997;4:152.

Table 71.2. Value of tests in predicting spontaneous delivery at less than 35 weeks.

Test	Week of gestation at time of testing		
	22–24	27–28	31–32
<i>Maximal nighttime contraction frequency $\geq 4/hr$</i>			
Sensitivity	8.6	28.1	27.3
Specificity	96.4	88.7	82.0
Positive predictive value	25.0	23.1	11.3
Negative predictive value	88.3	91.1	93.0
<i>Cervicovaginal fibronectin $\geq 50 ng/ml$</i>			
Sensitivity	18.9	21.4	41.2
Specificity	95.1	94.5	92.5
Positive predictive value	35.0	30.0	30.4
Negative predictive value	89.4	91.6	95.2
<i>Cervical length $\leq 25 mm$</i>			
Sensitivity	47.2	53.6	82.4
Specificity	89.2	82.2	74.9
Positive predictive value	37.0	25.0	20.9
Negative predictive value	92.6	94.1	98.1
<i>Bishop score $\geq 4^*$</i>			
Sensitivity	35.1	46.4	82.4
Specificity	91.0	77.9	61.8
Positive predictive value	35.1	18.8	14.7
Negative predictive value	91.0	92.9	97.8

* The Bishop score is a composite measure of cervical length, dilation, position, consistency, and the degree of descent (station) of the presenting part of the fetus. The results indicate the degree of readiness for labor; values from 0 to 4 indicate not ready for labor, and values from 9 to 13 indicate ready for labor. (From Iams JD, Newman RB, Thom EA, *et al.* Frequency of uterine contractions and the risk of spontaneous preterm delivery. *N Engl J Med* 2002;**346**:250–5).

TREATMENT AND PREVENTION

To have clinical value, tests to predict preterm birth should optimally lead to effective interventions that can prevent or reduce mortality and morbidity in babies born to women with positive test results, or should at least allow potentially expensive or harmful treatment to be avoided in women with negative test results.

A number of clinical risk factors and tests for preterm birth have been studied in randomized clinical trials aimed at surveillance, early detection and treatment to reduce preterm birth. The results of multiple trials are summarized in Table 71.3.

Table 71.3 Randomized controlled trials (RCTs) of interventions for risk factors for preterm birth.

Risk factor or population studied	Interventions tested in RCT	Outcome
Positive risk score	Nutritional supplementation	No benefit
Positive risk score	Social support	No benefit
Prior preterm birth	Antibiotics during pregnancy	Mixed, but mostly negative results
Prior preterm birth	Cervical cerclage	No benefit
Positive risk score	Education and self-detection of contractions	No benefit
Prior preterm birth (singletons)	Progesterone (17 α -OH-progesterone caproate)	33% reduction in preterm birth
Prior preterm birth (singletons)	Nurse contact and/or contraction monitor	No benefit
Twins	Nurse contact and/or contraction monitor	No benefit
Positive vaginal cultures	Antibiotics during pregnancy	No benefit; mixed if also + cultures
Positive fetal fibronectin	Antibiotics during pregnancy	No benefit
Short cervix	Cerclage (usually with antibiotics at surgery)	No benefit
Prior preterm birth and short cervix	Cerclage (usually with antibiotics at surgery)	Mixed but mostly negative results
Prior preterm birth	Antibiotics before next pregnancy	No benefit
Preterm labor in current pregnancy	Nurse contact and/or contraction monitor	No benefit
Preterm labor in current pregnancy	Maintenance prophylactic tocolysis	No benefit
Twins	Prophylactic tocolytic drugs	No benefit
Twins	Prophylactic bed rest	No benefit

Interventions aimed at identifying (by self-palpation or electronic uterine activity monitors) and suppressing increased uterine activity have not found a decline in preterm birth. Treatment of women with a short cervix, with or without a prior history of preterm birth, with cervical cerclage has not produced a consistent decrease in preterm birth in randomized trials.

Recent reports that women with a history of preterm birth who were treated with supplemental progesterone had significantly lower rates of recurrent preterm birth have raised hope that subsequent studies might also show benefit for women who have clinical or biophysical markers of risk, such as multiple gestation or a short cervix. No such studies have yet been reported.

Testing women with clinical risk factors for prematurity could be useful if the test result could be used to *avoid* unnecessary treatment. For example, reduced activity is often recommended for women with multiple gestations without evidence that it is helpful. Spontaneous preterm birth has been reported to be uncommon in women with twins when the cervical length exceeds 35 mm at 24–26 weeks' gestation. Similarly, women with a history of early preterm birth whose cervical length exceeded 25 mm between 18 and 26 weeks' had a rate of preterm birth of only 3.4%, compared with 10% among women randomly assigned to be treated with a prophylactic cerclage.

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Preterm labor—tocolysis

Sarah J. Kilpatrick and Jay D. Iams

INTRODUCTION

Preterm birth occurs in approximately 12% of pregnancies and is the most common underlying cause of perinatal morbidity and mortality in non-anomalous infants. Approximately 40% of preterm births are preceded by premature labor, 40% by preterm premature rupture of the membranes (PPROM), and 20% by medical or obstetric indications for delivery. Premature labor is defined as the onset of uterine contractions that lead to delivery before 37 weeks' gestation. Although tocolytic drugs have not reduced the incidence of preterm delivery, randomized trials for all tocolytics except magnesium have shown significant delay of delivery by 2 days. This delay allows antenatal treatment with corticosteroids to reduce neonatal morbidity and mortality, and permits transfer of the mother and fetus to a tertiary hospital for delivery if necessary. Thus, the true benefit of tocolytics for preterm labor is obtained when treatment is directed at pregnancies at the gestational ages that benefit from antenatal steroids. Delivery after 48 h of antenatal steroid exposure significantly reduces neonatal respiratory distress syndrome, intraventricular hemorrhage, and neonatal death in neonates less than 34 weeks. These significant benefits in neonatal outcome are observed from 24 to 34 weeks' gestation. After 34 weeks in a well-dated pregnancy, antenatal steroids offer no neonatal benefit. The National Institute of Child Health and Human Development (NICHD) recommends routine use of a single course of antenatal steroids (12 mg betamethasone i.m. every 24 h for two doses or 6 mg dexamethasone i.m. every 12 h for four doses) for pregnancies at risk of delivering within 1 week, between 24 and 34 weeks.

PATHOPHYSIOLOGY

Premature labor is best understood as the final common pathway in a multifactorial disease process. Putative mechanisms that lead to preterm labor include subclinical infection or inflammation, decidual hemorrhage, and overdistension of the uterus. A combination of obstetric, sociodemographic,

and medical factors interact to initiate persistent uterine contractions. In some individuals, a single risk factor is sufficient to produce labor, while in others a combination of lesser risk factors combine to allow the initiation of labor. In addition, there are many associated risk factors. The fact that the initiation of preterm labor may have different etiologies may explain why tocolysis has been shown to be effective for only 48 h. A history of preterm birth, multifetal gestation, and vaginal bleeding are the clinical risk factors most strongly associated with preterm delivery (relative risk [RR] of 4 or more) in the list below (in italics).

Risk factors important in the pathogenesis of preterm labor

1 Obstetric/mechanical/overdistension of uterus

- *Multifetal gestation*
- Abnormal or incompetent cervix
- Uterine anomalies
- Polyhydramnios

2 Inflammation

- Any acute intra-abdominal or systemic inflammation (appendicitis, pyelonephritis, surgery, major trauma)
- Urinary tract infection
- Sexually transmitted disease

3 Decidual hemorrhage

- *Vaginal bleeding*
- Cigarette smoking and other substance abuse (especially cocaine)
- Abruptio

4 Other risk factors

- *Prior preterm delivery*
- Type and duration of work
- Lower socioeconomic status
- Non-white race
- Young and older women
- Poor nutrition
- Poor prenatal care

DIAGNOSIS AND INITIAL EVALUATION

The diagnosis of preterm labor is made when persistent uterine contractions lead to change in cervical dilation or effacement, or both, before 37 weeks' gestation. Diagnosis is based on digital examination of the cervix and manual or electronic monitoring of uterine contractions. Although the diagnosis is straightforward in advanced preterm labor, (e.g. when the cervix is more than 3 cm dilated or 90–100% effaced), it is exceedingly difficult to make the diagnosis accurately with lesser degrees of dilation and effacement. Both contrac-

tions and modest cervical effacement and dilation occur frequently with advancing gestational age in normal pregnancies. Unfortunately, success in treatment declines steadily as the cervix effaces and dilates. This conundrum will continue to bedevil obstetricians until an improved method of early and accurate diagnosis is found. Because overdiagnosis is common in women with persistent contractions and cervical dilation less than 3 cm, evaluation of these women with endovaginal sonography to measure cervical length and detection of oncofetal fibronectin in cervicovaginal secretions have been proposed to improve accuracy of diagnosis. In women whose cervical length exceeds 30 mm and/or who have a negative fibronectin test result, the likelihood of delivering within 1 week is extremely small. If these adjunctive tests are used, then the women with normal results should not be treated. The positive predictive values of a short cervix or positive fetal fibronectin in women with symptoms are low, approximately 20–25%, but may be useful to select candidates for tocolytic treatment or transfer to a tertiary center when clinical data are equivocal.

Initial evaluation of preterm labor

1 Is preterm labor present?

Common symptoms and signs

- Persistent contractions, both painful and painless at a frequency of 6–8/h
- Spotting
- Back pain
- Menstrual-like cramps or pressure
- Cervical dilation of 2 cm or more or effacement of more than 80%
- Change in dilation or effacement on serial examinations without effacement of 80% or dilation of 2 cm has low predictive value

2 Is tocolysis for preterm labor appropriate?

- Is gestational age one that would benefit from antenatal steroids? (24–34 weeks)
- Are tocolytics warranted to transport the mother to a more appropriate hospital?
- Are tocolytics warranted to gain time to assess lung maturity?
- Are tocolytics likely to be successful? (cervical examination less than 5 cm)

3 Are there any maternal contraindications to tocolysis?

Does prolongation of pregnancy place the mother at risk?

- Significant hypertension
- Significant bleeding
- Cardiac disease
- Chorioamnionitis

Does tocolytic medication place the mother at risk? (see contraindications for each tocolytic)

4 Are there any fetal contraindications for tocolysis?

- Demise or lethal anomaly
- *In utero* fetal compromise
- Significant intrauterine growth restriction

5 Other possible indications for tocolysis

- External cephalic version
- Entrapped breech head at vaginal or caesarean delivery: nitroglycerin (50 µg IVP (intravascular push) slowly and titrated up by maternal blood pressure) may be useful for acute uterine relaxation during procedures such as removal of a retained placenta but long-term use as a tocolytic is not advised
- Prophylactic for cerclage placement or other intra-abdominal surgery

MANAGEMENT

Care is directed at maintaining good uterine perfusion pressure, detecting contractions, and assessing fetal well being.

- 1 Left lateral recumbent position
- 2 External fetal heart rate (non-stress test) and contraction monitoring
- 3 Intravenous line with lactated ringers (LR) or normal saline
- 4 Laboratory assessment
 - Complete blood count (CBC) with differential
 - Urinalysis and culture (consider obtaining catheterized specimen)
 - Fetal fibronectin if used must be obtained before any examinations with lubricants
 - Vaginal and rectal cultures for group B streptococcus
 - Cervical culture for *Neisseria gonorrhoeae* and chlamydia
 - Wet prep for *Trichomonas*, and bacterial vaginosis (BV)
- 5 Ultrasound assessment
 - Presentation
 - Amniotic fluid volume
 - Placental location
 - Estimated fetal weight and gestational age
 - Anatomy survey for anomalies if possible

TREATMENT**Tocolytic medications**

In general, tocolytics should be used acutely to delay delivery for 48 h. Choosing an initial tocolytic agent requires consideration of the mechanism of action, safety, and side-effect profile of each available agent (Table 72.1). A protocol for each drug may reduce risk. Magnesium remains the most commonly used parenteral tocolytic in the USA despite the absence of data from randomized controlled trials demonstrating its efficacy compared with placebo. Indometacin and nifedipine are becoming more common and have better

Table 72.1 Tocolytic medications.

Agent	Mechanism of action	Dose	Side-effects	Contraindications	Specific interventions
Indometacin	Prostaglandin synthetase inhibition	50 mg p.o., then 25–50 mg p.o. q 4–6h for 48 h Maximum dose: 300 mg/24 hrs	Maternal: gastric irritation Fetal: constriction of ductus, decreased urine output, decreased AFI	Any bleeding diathesis or platelet disorder, active peptic ulcer, creatinine > 1.0, AFI < 6.0 excluding cases of preterm premature ruptured membranes [PPROM], > 32 weeks (use other tocolytic)	Consider daily AFI Stop indocin if AFI < 6
Nifedipine	Calcium-channel blocker	Load: 20 mg p.o. q 30 minutes times three or until uterine activity subsides (maximum 60 mg/90 min) Maintenance: 10–20 mg p.o. q 3–8 h for 48 h Begin maintenance dose 3 h after last loading dose	Hypotension, tachycardia, headache, flushing	CHF, aortic stenosis, impaired liver function, heart block, SBP < 90, DBP < 60	Obtain BP/P before and every 15 min after each loading dose. Continue BP/P every 15 min for 1 h after loading dose is complete. Hold dose for SBP < 90 or DBP < 60

Continued on p. 480

Table 72.1 Continued.

Agent	Mechanism of action	Dose	Side-effects	Contraindications	Specific interventions
Terbutaline	β_2 sympathomimetic decreases free intracellular Ca^{2+}	0.25 mg s.c. q 3–4 h for short intervals only	Tachycardia, widened pulse pressure, increased glucose and lactate, decreased K^+ , arrhythmia	Moderate to severe maternal cardiac disease, pulmonary hypertension, uncontrolled diabetes, uncontrolled hyperthyroidism	
Magnesium sulfate	Intracellular calcium antagonism	4–6-g load, then 2–3 g/h i.v.	Vasodilation, muscle weakness, respiratory depression Magnesium toxicity: deep tendon reflexes disappear, respiratory depression, decreased urine output, cardiac arrhythmias including cardiac arrest	Heart block, myocardial damage, impaired renal function (urine output <30 mL/h; creatinine > 1.0), myasthenia gravis	Treatment for magnesium toxicity: Ca gluconate 10% (4.65 mEq/10 ml) 10 mL i.v. = 1 amp Push slowly over 1–2 min

CHF, congestive heart failure; DBP, diastolic blood pressure; i.v., intravenous; p.o., oral; PPRM, preterm premature rupture of membranes; q, every; SBP, systolic blood pressure; s.c., subcutaneous.

efficacy data than magnesium. Indometacin may be the most effective but also is known to reduce flow through the fetal ductus arteriosus and decrease fetal urine output. These effects are reversible and uncommon if treatment is limited to 48–72 h in patients at 32 weeks' gestation or less. Magnesium should not be combined with a calcium-channel blocker because of increased risk of reduction in maternal cardiac output. After the acute treatment of preterm labor there is no longer any role for maintenance tocolysis as multiple studies have shown neither significant pregnancy prolongation nor improved neonatal outcome with maintenance tocolysis (oral or subcutaneous terbutaline, ritodrine, magnesium).

Complications can be reduced through careful attention to fluid balance and early symptoms of pulmonary edema. Patients at highest risk for pulmonary edema are those with multiple gestations, prolonged treatment for more than 24 h, and/or underlying infection. If contractions do not decrease within 4–6 h to four per hour or less, the original diagnosis and possible underlying causes (e.g. amnionitis or abruption) should be re-evaluated. If amnionitis is thought to be likely, tocolysis should be stopped and the patient delivered.

Group B streptococcus prophylaxis

After obtaining appropriate vaginal, cervical, and rectal cultures, the patient should be treated with penicillin (clindamycin or erythromycin if penicillin allergic) for group B streptococcus (GBS) unless she is known to be GBS negative. If cultures are negative then the treatment may be stopped.

Antenatal steroids

Antenatal steroids should be given if the patient is between 24 and 34 weeks unless she has had a prior course this pregnancy or fetal lung maturity has been documented (12 mg betamethasone i.m. every 24 h for two doses or 6 mg dexamethasone i.m. every 12 h for four doses).

FOLLOW-UP

The duration of hospitalization is governed by cervical status, complicating diagnoses (e.g. urinary tract infection, other infections), gestational age, and home environment. In general, acute treatment should occur for 48 h and after that time the patient should be evaluated for discharge from the hospital. There are no prospective data to support the use of home uterine monitoring or the subcutaneous terbutaline pump after acute treatment of preterm labor. Adjunctive antibiotic treatment of women with preterm labor has not been effective in large prospective trials. Treatment of urinary tract infection, GBS, and chlamydia is appropriate. Maintenance tocolysis after the initial 48 h with any medication to suppress contractions has not been shown to reduce the rate of prematurity or to improve neonatal outcome.

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Premature rupture of the membranes

Brian Mercer

INTRODUCTION

Premature rupture of the membranes (PROM) complicates approximately 10% of pregnancies, and 3% of pregnancies delivering before term. It is responsible for one-third of preterm deliveries, and is more common as a cause of preterm birth in populations of lower socioeconomic status.

PATHOPHYSIOLOGY

Spontaneous membrane rupture occurs physiologically at term either before or after the onset of symptomatic contractions. This is believed to be related to progressive weakening of the membranes seen with advancing gestation, largely resulting from collagen remodeling and cellular apoptosis. When PROM occurs before term, the process of membrane weakening may be accelerated by a number of factors such as stretch, inflammation, and local hypoxia. Some clinical risk factors for preterm PROM are shown in Table 73.1.¹⁻³ In asymptomatic women, a short cervix on transvaginal ultrasound (relative risk 3.2) and a positive cervicovaginal fetal fibronectin (fFN) screen (relative risk 2.5) are also associated with increased risks of preterm birth resulting from PROM.³ However, routine screening with these modalities is not recommended as they fail to identify the majority of women delivering preterm because of PROM.

CLINICAL IMPLICATIONS

The hallmarks of PROM are brief latency from membrane rupture to delivery, increased risk of intrauterine and neonatal infection, and oligohydramnios.

Of women with preterm PROM managed conservatively to prolong gestation, approximately half will deliver within 1 week after membrane rupture. Latency increases with decreasing gestational age at membrane rupture, with approximately one-quarter remaining undelivered at least 1 month after membrane rupture near the limit of viability. Because the benefits of conservative management include time for acceleration of fetal maturity with antenatal corticosteroids (24–48 h latency required) and reduction of gestational

Table 73.1 Clinical risk factors for preterm premature rupture of membranes (PROM).

Risk factor	Odds ratio
Previous preterm PROM	3.3–6.3
Previous preterm delivery	1.9–2.8
Cigarette smoking	2.1
Bleeding during pregnancy	
During first trimester	2.4
During second trimester	4.4
During third trimester	6.4
More than one trimester	7.4
Acute pulmonary disease	1.8
Bacterial vaginosis	1.5

age-dependent morbidity (extended latency ≥ 1 week required), serious consideration should be given to expeditious delivery if the fetus is considered to be at low risk for gestational age-dependent morbidity, if antenatal corticosteroids are not administered, or if extended latency is not anticipated.

Clinical chorioamnionitis is common after preterm PROM and increases with decreasing gestational age at membrane rupture. Clinical chorioamnionitis and endometritis complicate 13–60% and 2–13% of pregnancies, respectively, with PROM remote from term. Positive amniotic fluid cultures are obtained from amniocentesis specimens in 25–35% of women with preterm PROM.⁴ Maternal sepsis is a rare but serious complication of conservatively managed PROM affecting approximately 1% women with PROM remote from term.

Fetal demise complicates approximately 1% of conservatively managed cases of preterm PROM. This risk increases in the face of chorioamnionitis, and when PROM occurs near the limit of potential viability. It is believed that in most cases demise results from umbilical cord compression, although loss resulting from fetal infection and placental abruption can occur. Cord prolapse is an uncommon complication of PROM, and unlikely if not evident on admission by visualization of the cervix with sterile speculum or suspected based on initial fetal heart rate monitoring.

Abruptio placentae complicates approximately 4–12% of patients with preterm PROM. Placental bleeding may occur before or after the onset of membrane rupture. The benefits of conservative management should be reassessed in the face of suspected placental abruption, with attempts at extended latency reserved only for those who have minimal bleeding and no change in maternal cardiovascular status, and whose fetus is at high risk for death because of extreme prematurity with immediate delivery.

DIAGNOSIS

Diagnosis of PROM can usually be made clinically based on a suggestive history combined with a sterile speculum examination. Demonstration of fluid passing per os is diagnostic of membrane rupture. Ancillary testing of vaginal fluid for an alkaline pH (more than 6.0–6.5) with nitrazine paper is supportive, but can be falsely positive (17%) because of the presence of blood, semen, alkaline anti-septics, or bacterial vaginosis, and can be falsely negative (9%) with prolonged leakage. The presence of a ferning pattern on microscopic examination of dried vaginal secretions can also be confirmatory and is less commonly falsely positive (6%) because of the presence of cervical mucous within the specimen (false-negative rate 13%). Repeat speculum examination after prolonged recumbency may be helpful if the diagnosis is suspected but initial examination is not confirmatory. Ultrasound evidence of oligohydramnios is supportive of a clinical diagnosis but is not diagnostic as low amniotic fluid can occur for other reasons (e.g. fetal growth restriction, urinary tract anomalies) and the amniotic fluid volume may be within normal limits despite membrane rupture. The diagnosis can be confirmed unequivocally through ultrasound-guided amnio-infusion of indigo carmine (1 mL in 9 mL sterile normal saline) followed by observation for passage of blue dye per vaginum.

EVALUATION

Initial evaluation of the woman presenting with preterm PROM includes cervical cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, anovaginal culture for group B streptococcus, and urinalysis with urine culture as appropriate.

If the diagnosis of PROM is suspected, digital cervical examinations should be avoided until the diagnosis of PROM has been excluded. Digital vaginal examinations after PROM have been shown to shorten the latency period from membrane rupture to delivery and increase the risk of chorioamnionitis, while adding little information regarding cervical dilation and effacement over that obtained by visual examination.⁵

Initial maternal uterine activity and fetal heart rate monitoring should be performed to evaluate for evidence of labor, umbilical cord compression, and for fetal well being if the limit of potential fetal viability has been reached. If conservative management is being considered, initial extended monitoring for approximately 12 h followed by intermittent monitoring at least daily is appropriate. A non-reactive fetal heart rate can be a sign of intrauterine infection, particularly if testing had previously been reactive.

Clinical assessment for chorioamnionitis including assessment of maternal and fetal heart rates, maternal temperature, uterine tenderness, and vaginal discharge. The combination of fever ($\geq 38.0^{\circ}\text{C}$ or 100.4°F) with uterine tenderness and/or maternal or fetal tachycardia in the absence of an other evident

source for infection is suggestive of chorioamnionitis and is an indication for delivery regardless of gestational age.

A maternal white blood cell count (WBC) above 16,000 cells/mm³ is supportive of suspicious clinical findings or chorioamnionitis. It is important to remember that there is significant variation in WBC count between patients and that the WBC count is elevated in pregnancy and for 5–7 days after administration of antenatal corticosteroids. As such, this test should not be used in isolation. It is helpful to obtain a baseline WBC count, when conservative management is considered, for initial assessment and for subsequent comparison.

Ultrasonographic examination should be performed to determine fetal position and presentation, exclude fetal malformations associated with PROM (e.g. hydrops fetalis, intestinal obstruction, diaphragmatic hernia may cause uterine stretch as a result of polyhydramnios), estimate fetal weight, assess amniotic fluid volume, and to perform a biophysical profile should initial fetal heart rate testing be non-reactive.

Ultrasound-guided amniocentesis to evaluate for intra-amniotic infection can be helpful if the diagnosis is suspected clinically but the diagnosis is not clear. Care should be paid to avoid the umbilical cord, which can be mistaken for a small amniotic fluid pocket if there is severe oligohydramnios. Amniotic fluid can be sent for Gram's stain, WBC (≥ 30 cells/mm³ considered abnormal), glucose (less than 16–20 mg/dL considered abnormal), and culture for aerobic and anaerobic bacteria.^{6,7} Mycoplasma is a common microorganism identified from amniotic fluid after PROM but is not visible on Gram's stain. Mycoplasma cultures are not available in all laboratories.

In general, women presenting with PROM at term do not require additional specific evaluations once the diagnosis is made, unless other complicating circumstances are present, or in the unlikely event that conservative management is being considered.

MANAGEMENT

Conditions that mandate delivery after preterm or term PROM include clinical chorioamnionitis, non-reassuring fetal testing, significant vaginal bleeding, advanced labor, and concurrent pregnancy complications indicating delivery (e.g. severe pre-eclampsia). In the absence of amnionitis, placental abruption, fetal distress, or advanced labor, conservative management of women with preterm PROM may be appropriate. A gestational age-based approach to conservative management should be considered. The patient should be appraised of available current data regarding neonatal morbidity and mortality according to gestational age at delivery,⁴ in order to make appropriate decisions regarding the potential benefits of conservative management as opposed to expeditious delivery.

Term: 37 weeks or more

While labor will spontaneously ensue within 12 h in 50%, and by 24 h in 70% of women with PROM at term, the risk of chorioamnionitis increases with the duration of membrane rupture (2% less than 12 h, 6% 12–24 h, and 24% by 48 h). Because of this, and because current data do not suggest an increased risk of infection or operative delivery with early induction, those with PROM at term are best served by labor induction and/or augmentation as needed, with cesarean delivery reserved for clinical indications. PROM is not a contraindication for preinduction cervical priming with prostaglandin E₂ gel.⁸ Group B streptococcus (GBS) prophylaxis should be administered to those with positive anovaginal cultures in the current pregnancy.⁹ GBS prophylaxis should also be initiated for those without a recent negative culture (less than 6 weeks) who have membrane rupture \geq 18 h. Women with intrapartum fever should receive broad-spectrum antimicrobial therapy, including agents effective against Gram-positive and Gram-negative organisms, regardless of GBS culture status.

Preterm: 34–36 weeks

Because women with PROM near term (34–36 weeks) are at relatively low risk of serious acute morbidity which is not likely to be reduced with the relatively brief anticipated latency at this gestation, and because antenatal steroids are not generally recommended for fetal maturation at this gestation, these women are best treated by expeditious delivery as for the term patient with PROM. Although there are risks of morbidity at this gestation, the risks of infection and umbilical cord compression outweigh the potential benefits of conservative management. As many of these women will not have had a recent anovaginal GBS culture and because of the increased risk of neonatal infection in low birth weight infants, intrapartum GBS prophylaxis should be given in the absence of a recent (less than 6 weeks) negative anovaginal GBS culture.

Preterm: 32–33 weeks

In the absence of indication for delivery, evaluate fetal lung maturity status on amniotic fluid collected from the vaginal pool or by amniocentesis (foam stability index \geq 47 or phosphatidyl glycerol [PG] positive, or lecithin : sphingomyelin [L : S] ratio \geq 2 : 1 or FLM II \geq 55 considered mature). If there is blood- or meconium-stained amniotic fluid, vaginal pool specimens for L : S ratio or FLM may be falsely immature. However, delivery should be considered in these women because of the potential for fetal compromise.

- 1 If testing reveals a mature fetal pulmonary profile, expeditious delivery according to the recommendations for PROM at 34–36 weeks
- 2 If testing reveals an immature lung profile or if fluid cannot be obtained:

- Induction of fetal pulmonary maturation with antenatal corticosteroids followed by delivery at 24–48 h, or at 34 weeks' gestation is recommended.
- If conservative management is pursued, broad-spectrum antibiotic treatment should be administered to reduce maternal and neonatal infections, to prolong latency in order to enhance steroid-induced and spontaneous maturation.
- Once antenatal corticosteroid benefit has been achieved, the patient should be assessed regarding the potential for extended latency (≥ 1 week) before 34 weeks' gestation. If the patient is more than 33 weeks' gestation at this time, it is unlikely that further delay of delivery to 34 weeks will result in substantial spontaneous fetal maturation. Delivery is recommended before complications ensue.
- During conservative management, maternal and fetal assessment should be initiated, as delineated below for PROM at 23–31 weeks.
- If antenatal corticosteroids and antibiotics are not given in this setting, serious consideration should be given to delivery before infection or other complications ensue.

Preterm: 23–31 weeks

Because the risks of neonatal morbidity and mortality resulting from prematurity is high with immediate delivery at 23–31 weeks' gestation, these women are generally best served by inpatient conservative management to prolong pregnancy and reduce gestational age-dependent morbidity in the absence of evident infection, abruption, advanced labor, or fetal compromise. Should the patient be initially admitted to a facility without resources for emergent care of the mother and a very premature newborn, she should be transferred to a facility capable of providing care for these patients if possible after initial assessment and before acute complications occur.

During conservative management, the following should be considered:

- 1 Initial extended continuous fetal and maternal monitoring (approximately 6–12 h) for contractions, non-reassuring fetal heart rate patterns, including umbilical cord compression.
- 2 At least daily clinical assessment for evidence of labor, chorioamnionitis, placental abruption. In addition, vital signs (temperature, pulse, blood pressure) should be documented at least each shift.
- 3 Antenatal corticosteroids for fetal maturation are recommended unless a full course has previously been given. Recent meta-analysis has suggested such treatment to be effective in reducing neonatal respiratory distress and intraventricular hemorrhage after PROM, without increasing the risk of neonatal infection.¹⁰ Either 12 mg betamethasone intramuscularly 24 h apart for two doses, or 6 mg dexamethasone intramuscularly 12 h apart for four doses is appropriate.

4 Broad-spectrum antibiotic therapy should be administered during initial conservative management of preterm PROM to treat or prevent ascending subclinical decidual infection in order to prolong pregnancy, and to reduce neonatal infectious and gestational age-dependent morbidity. Intravenous therapy (48 h) with ampicillin (2 g i.v. every 6 h) and erythromycin (250 mg i.v. every 6 h) followed by limited duration oral therapy (5 days) with amoxicillin (250 mg p.o. every 8 h) and enteric-coated erythromycin base (333 mg orally every 8 h) is recommended.¹¹ Shorter duration therapy has not been shown to offer similar neonatal benefits, and is not recommended. Although not specifically studied, recent shortages in antibiotic availability have led to the need for substitution of alternative antibiotic treatments. Oral ampicillin, erythromycin, and azithromycin are likely appropriate substitutions for the above agents, as needed. Although a large multicenter study has suggested that broad-spectrum antibiotic therapy might increase the risk of necrotizing enterocolitis,¹² this finding is at variance with those of the NICHD-MFMU trial finding a reduced stage 2–3 necrotizing enterocolitis with broad-spectrum antibiotic therapy in a higher risk population.

Isolated case reports have suggested success with conservative management, and broad-spectrum antibiotic treatment of women with PROM and amniocentesis confirmed intra-amniotic bacterial colonization. While this approach may be plausible, particularly for the asymptomatic woman with PROM near the limit of viability (23–29 weeks' gestation), such an approach has not been confirmed to be beneficial in randomized prospective studies of women undergoing routine amniocentesis after preterm PROM. Conservative management is not recommended if amniocentesis performed for equivocal clinical findings of intra-amniotic infection reveals positive results.

Management of the known GBS carrier after the initial 7 days of antibiotic therapy has not been well defined. In the absence of any studies addressing this issue, options include:

- 1** No further antepartum therapy, with intrapartum GBS prophylaxis of all known carriers
- 2** Continued narrow-spectrum GBS prophylaxis of all known carriers from completion of the initial 7-day course through delivery
- 3** Follow-up anovaginal culture after completion of the 7-day course, with continued narrow spectrum therapy against GBS until delivery
- 4** Follow-up anovaginal culture of those having extended latency after initial antibiotic treatment, with repeat treatment of women with subsequently positive cultures (as well as intrapartum prophylaxis for all known carriers)

At least daily non-stress fetal heart rate and contraction monitoring should be carried out to observe for evidence of subclinical contractions, fetal heart rather decelerations resulting from umbilical cord compression, sustained tachycardia, or evidence of fetal compromise. A biophysical profile score or

6/10 or greater may be helpful when the fetal heart rate pattern is not reactive. A fetal heart rate pattern that is reactive on initial testing but becomes non-reactive on follow-up tests, or a worsening biophysical profile score, should raise suspicion regarding the possibility of developing intrauterine infection or fetal compromise. Under such circumstances, prolonged monitoring and repeat biophysical testing should be considered.

White blood cell count monitoring can be helpful, but an elevated white blood cell count alone is not an indication for delivery. We perform an initial baseline white blood cell count for reference before administration of antenatal corticosteroids, and repeat testing if the initial result is elevated, or if equivocal clinical findings for intrauterine infection ensue. Repeat testing is not needed if the diagnosis of intrauterine infection is clear. Treat specific cervicovaginal pathogens and urinary tract infections.

Ultrasound should be performed every 3–4 weeks to assess fetal growth. It is not necessary to repeat amniotic fluid volume estimates frequently as persistent or worsening oligohydramnios is not an indication for delivery. Initial severe oligohydramnios has been associated with briefer latency to delivery, but this finding is an inaccurate predictor of latency or neonatal outcomes.

Data for efficacy of tocolysis of women with preterm PROM are not compelling. Treatment has been shown to reduce the likelihood of delivery at 24–48 h in some studies. However, such treatment has not been shown to improve neonatal outcomes. Tocolytic therapy should not be administered after preterm PROM if there is suspicion of intrauterine infection, fetal compromise, or placental abruption. Amniocentesis to exclude concurrent intra-amniotic infection may be helpful when tocolysis is being considered.

Because pregnancy and inactivity are risk factors for thromboembolic complications, preventative measures such as leg exercises, and/or antiembolic stockings, and/or prophylactic doses of subcutaneous heparin may be of value in preventing this outcome during conservative management with bed rest.

The patient who remains stable without evidence of infection, abruption, or fetal compromise should generally be delivered at 34 weeks' gestation because of the ongoing but low risk of fetal loss with conservative management and the high likelihood of survival without long-term sequelae with delivery at this gestational age. Assessment of fetal pulmonary maturity at 34 weeks is acceptable, with continued conservative management of those with immature studies after further discussion of the risks and benefits of further conservative management.

Amnioinfusion has not been shown to be of benefit in preventing fetal compromise, or extending latency after preterm PROM. During labor, amnioinfusion is not recommended routinely, and should be reserved for the indication of ameliorating significant umbilical cord compression (variable heart rate decelerations) that is unresponsive to maternal repositioning.

Preterm: less than 23 weeks

When PROM occurs prior to the limit of viability, a “best gestational age” determination should be made based on the earliest available ultrasound and menstrual history. These patients should be counseled with a realistic appraisal of potential fetal and neonatal outcomes. Regarding maternal morbidity, conservative management of mid-trimester PROM is associated with a high risk of chorioamnionitis (39%), endometritis (14%), abruption placentae (3%), and retained placenta with postpartum hemorrhage requiring curettage (12%). The risk of stillbirth during conservative management of mid-trimester PROM is approximately 15%, some of which is a result of non-intervention for fetal distress when delivery occurs before the limit of viability. Most of these pregnancies will deliver before or near the limit of viability, where neonatal death is either assured or common. The risk of long-term sequelae will depend on the gestational age at delivery. Persistent oligohydramnios is a poor prognostic indicator after PROM before 20 weeks, placing the fetus at high risk of lethal pulmonary hypoplasia regardless of extended latency.

Management options for women with PROM before 23 weeks include:

- 1 **Labor induction:** with the following according to individual clinical circumstances:
 - High-dose intravenous oxytocin
 - Intravaginal prostaglandin E₂
 - Oral or intravaginal prostaglandin E₁ (misoprostol)
- 2 **Dilation and evacuation:** intracervical laminaria placement prior to labor induction or dilation and evacuation may be helpful.
- 3 **Conservative management:** should conservative management be pursued, the following points should be considered:
 - The patient should be monitored initially for the development of infection, labor or placental abruption. Strict pelvic rest and modified bed rest with bathroom privileges should be encouraged to enhance the potential for membrane resealing, and to reduce the potential for ascending infection. Given the absence of data regarding the superiority of either, initial inpatient or outpatient monitoring may be appropriate according to individual clinical circumstances.
 - Serial ultrasound is recommended to evaluate for fetal pulmonary growth and for persistent oligohydramnios. Fetal pulmonary growth can be estimated by ultrasound measurement of the thoracic : abdominal circumference ratio or chest circumference. A low thoracic : abdominal circumference ratio in the setting of persistent oligohydramnios is highly predictive of lethal pulmonary hypoplasia after PROM.¹³ When identified before the limit of viability, this finding may help the patient regarding the decision between continued conservative management and delivery.

- Women with PROM before 23 weeks' gestation have been included in some studies of antibiotic therapy after PROM. Treatment as described above for women at 23–31 weeks is appropriate. However, this population has not been studied separately, and it is not known if treatment is beneficial.
- Once the patient with previable PROM reaches the limit of viability, many physicians will admit the patient to hospital for ongoing bed rest. The purpose of admission at this time is to allow for early diagnosis and intervention for infection, abruption, labor, and non-reassuring fetal heart rate patterns (see conservative management of PROM at 23–31 weeks above). Because these women remain at high-risk for early delivery, administration of antenatal corticosteroids for fetal maturation may be appropriate at this time. It is not clear that delayed administration of broad-spectrum antibiotics for pregnancy prolongation will assist this population.
- Novel treatments for membrane sealing after previable PROM, including serial amnioinfusion, membrane plugging with Gelfoam® (Pharmacia & Upjohn Co., Kalamazoo MI) or fibrin-platelet-cryoprecipitate plugs, and indwelling transcervical infusion catheter have been studied. Further research regarding the maternal and fetal risks and benefits of these interventions is needed before membrane sealing is incorporated in clinical practice.

SPECIAL CIRCUMSTANCES

Cerclage

When the cerclage is removed on admission for preterm PROM, the risk of adverse perinatal outcomes is not higher than for those women with preterm PROM without cerclage. Studies comparing cerclage retention with removal after preterm PROM have suggested trends towards increased maternal infection with retained cerclage; however, no individual study has reached statistical significance. Alternatively, no study has found a significant reduction in the infant morbidity with cerclage retention subsequent to preterm PROM, and one study found increased neonatal death resulting from infection with cerclage retention. As such, cerclage should generally be removed when PROM occurs. Should the cerclage be retained during attempts to enhance fetal maturation with antenatal corticosteroids, concurrent antibiotic administration should be considered to reduce the risk of infection and the stitch should be removed after antenatal steroid benefit has been achieved (24–48 h).

Herpes simplex virus

A history of herpes simplex virus infection is not a contraindication for expectant management of PROM remote from term. If herpetic lesions are present at the onset of labor, cesarean section is indicated. Alternatively, with PROM at

30 weeks or thereafter, the presence of primary or secondary herpetic lesions should lead to consideration of expeditious cesarean delivery.

Human immunodeficiency virus

Intrapartum vertical transmission of HIV increases with increasing duration of membrane rupture. Given the poor prognosis of perinatally acquired HIV infection, expeditious abdominal delivery after PROM at any gestational age after the limit of fetal viability is recommended. Vaginal delivery may be appropriate for women with HIV, if the viral titer is low. If conservative management of the patient with PROM at or before the limit of viability is undertaken, multi-agent antiretroviral therapy with serial monitoring of maternal viral load and CD4 counts should be initiated.

Resealing of the membranes

A small number of women will have cessation of leakage with resealing of the membranes. Under this circumstance, we continue monitoring in hospital for approximately 1 week after cessation of leakage and normalization of the amniotic fluid index to encourage healing of the membrane rupture site. These women are subsequently discharged to modified bed rest and pelvic rest, with frequent re-evaluation.

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Amnionitis

Sindhu K. Srinivas and George A. Macones

INTRODUCTION

Amnionitis (chorioamnionitis, intra-amniotic infection) is common, occurring in 1–5% of term deliveries and up to 25% of preterm deliveries. In fact, it is believed that amnionitis may be a causative factor in preterm births resulting from preterm labor or preterm premature rupture of membranes (PPROM).

Depending on the type and severity of the infection as well as the gestational age at which it occurs, amnionitis may lead to a variety of outcomes including spontaneous abortion, stillbirth, prematurity (and the various complications that might result from prematurity), neonatal sepsis, infectious maternal morbidity, and even sepsis and shock.

PATHOPHYSIOLOGY

It is believed that amnionitis results from an ascending infection from the lower genital tract into the amniotic cavity, although hematogenous and transplacental etiologies have also been proposed. In the early stages of an ascending bacterial invasion of the choriodecidual interface, there may be no maternal symptomatology (subclinical intrauterine infection). However, as the infection ascends and continues, clinical manifestations may become apparent.

Amnionitis is a polymicrobial infection and most commonly involves bacteria that are part of the normal vaginal flora. These bacteria include *Bacteroides* (25%), *Gardnerella* (25%), streptococcus species (25%), *Escherichia coli* and other Gram-negative rods (20%), and mycoplasmas.

In term patients, amnionitis seems to occur more as a consequence of multiple risk factors such as prolonged rupture of membranes or multiple vaginal examinations. However, in preterm patients it is believed that amnionitis might incite preterm labor or PPRM. There are multiple hypotheses regarding how amnionitis may trigger PPRM or premature labor. One theory is that the infection may trigger prostaglandin synthesis and release from amniotic membranes. A second hypothesis is that there is bacterial lipopolysaccharide

(endotoxin) release causing release of cytokines (e.g. interleukin 1 [IL-1], IL-6, tumor necrosis factor) which then increase the production of collagenases and matrix metalloproteinases (which can lead to membrane weakening).

RISK FACTORS

Many factors have been associated with amnionitis. Established risk factors include long labor, nulliparity, multiple vaginal examinations, internal fetal monitoring, length of internal monitoring, and maternal bacterial vaginosis infection, as well as other lower genital tract infections such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Ureoplasma urealyticum*. Other associated risk factors are cigarette smoking and history of prior preterm delivery or PPROM.

CLINICAL PRESENTATION

There are two main categories of patients in which amnionitis should be suspected:

- 1 Term pregnancies, in which there are clinical symptoms suggestive of infection. In this scenario, amnionitis is defined as maternal fever ($> 100.4^{\circ}\text{F}$ or 38°C) and one of the following additional findings:
 - Maternal tachycardia (> 100 b/min)
 - Fetal tachycardia (> 160 b/min)
 - Uterine tenderness
 - Leukocytosis ($> 18,000$ white blood cell count)
 - Foul-smelling vaginal discharge
- 2 Patients presenting with preterm labor or PPROM. Some patients who present with preterm labor or PPROM may also have clinical symptoms that strongly suggest amnionitis (same criteria as above). In subjects with preterm labor or PPROM who do not exhibit any of these classic signs or symptoms, physicians must still be concerned about a subclinical intrauterine infection. For women in preterm labor, amnionitis is extremely common in those who are failing first-line tocolytic therapy.

DIAGNOSIS AND MANAGEMENT

Patients at term

In patients at term, amnionitis is primarily a clinical diagnosis of maternal fever with one of the following additional signs: maternal tachycardia, fetal tachycardia, uterine tenderness, leukocytosis, or foul-smelling vaginal discharge.

Delivery is indicated when the diagnosis of amnionitis is made at term in order to minimize infectious morbidity to both the mother and fetus. If fetal heart monitoring is reassuring, labor should be induced and an attempt should be made at a vaginal delivery. If a non-reassuring fetal heart rate pattern is detected, a cesarean section should be performed. (Note that indications for

cesarean section are standard obstetric indications. Amnionitis in itself is not an indication for cesarean section.) Once the diagnosis of amnionitis is made, broad-spectrum antibiotics should be started immediately (i.e. 2 g ampicillin i.v. every 6 h and 1.5 mg/kg gentamicin every 8 h, or other broad-spectrum regimens).

Patients with PPRM

Patients who present with PPRM or preterm labor should be considered at high risk for having amnionitis. Overall, the management of patients with PPRM or preterm labor depends on gestational age at presentation and the presence or absence of clinical symptoms.

Preterm labor or PPRM with symptoms of amnionitis

Once diagnosis is made, delivery is indicated regardless of gestational age. Broad-spectrum antibiotics should be utilized. Vaginal delivery is preferred, with cesarean section reserved for standard obstetric indications.

Preterm labor or PPRM without clinical symptoms

This group is at risk of having amnionitis. Monitor closely for maternal symptoms (fever, uterine tenderness) or fetal symptoms (tachycardia, non-reactive non-stress test) of infection. Consider amniocentesis for diagnosis if vague or unclear clinical symptoms. If an amniocentesis is needed, send the transabdominally obtained fluid for culture (aerobic, anaerobic) and for the following tests: Gram stain, glucose concentration, and white blood cell count (WBC). In some institutions, IL-6 and leukocyte esterase may also be obtained. The gold standard for diagnosis is a positive amniotic fluid culture. Delivery should be strongly considered if bacteria are seen on Gram stain or if the amniotic fluid culture is positive. If any of the other parameters listed in Table 74.1 are abnormal, the entire clinical picture should be taken into account and delivery should not be pursued based on a single abnormal value. If amnionitis is diagnosed via amniocentesis results or based on high level of clinical suspicion, broad-spectrum antibiotics should be initiated and a move toward delivery should be undertaken.

Patients who present with fever without a clear source

These cases can be challenging to manage. Take care to entertain a wide differential diagnosis of which amnionitis should be considered. Other diagnoses include pyelonephritis, appendicitis, and gastroenteritis. The other clinical manifestations will help to distinguish between these diagnoses. If the diagnosis is uncertain, an amniocentesis may be appropriate to rule out amnionitis because the presence of an intrauterine infection would warrant delivery.

Table 74.1 Abnormal results in diagnosing amnionitis.

Amniotic fluid glucose < 15 mg/dL
Amniotic fluid WBC > 30 cells/ μ L
Amniotic fluid IL-6 \geq 7.9 ng/mL
Amniotic fluid leukocyte esterase \geq 1; positive reaction
Amniotic fluid Gram stain any organism on an oil immersion field
Amniotic fluid any positive growth of an aerobic or anaerobic microorganism

TREATMENT

Once the diagnosis of amnionitis is made either clinically or by amniocentesis, preparations for delivery should be undertaken. Additionally, given that amnionitis is polymicrobial in nature, broad-spectrum antibiotics should be initiated. The most common recommended regimen is 2 g ampicillin every 6 h and 1.5 mg/kg gentamicin every 8 h, although other regimens that offer similar coverage may be utilized. If the patient undergoes a cesarean section, clindamycin is added at cord clamp to protect against wound infection. Further, antibiotics should be used post cesarean section until the patient has been afebrile for 24–48 h.

COMPLICATIONS

In patients with amnionitis, an increased cesarean delivery rate (30–40%) is seen, mostly secondary to arrest disorders. Patients with amnionitis are also at increased risk of postpartum hemorrhage, endometritis, and post cesarean section wound infection.

PREVENTION

Several risk factors have been identified for amnionitis and care should be taken to avoid these when possible: extended duration of labor, prolonged rupture of membranes (>18 h), multiple vaginal examinations, and internal monitoring. Other risk factors associated with amnionitis that are not preventable include young maternal age, low socioeconomic status, and nulliparity.

Additionally, some infection control measures have been evaluated such as chlorhexidine vaginal washes, and have been found to be ineffective in preventing amnionitis. Antepartum treatment of bacterial vaginosis has also not been shown to prevent amnionitis. The effective preventive strategies that have been proven to decrease the incidence of amnionitis are active labor management, induction of labor after PROM at term, and the use of antibiotics in selected patients.

CONCLUSIONS

The diagnosis of amnionitis is typically clinical and based upon the presence of maternal fever (>100.4 F or 38 C) and one of the following additional criteria: maternal tachycardia (>100 b/min), fetal tachycardia (>160 b/min), uterine tenderness, leukocytosis ($>18,000$ white blood cell count), or foul-smelling vaginal discharge.

Amniocentesis for amniotic fluid culture is the best diagnostic test for sub-clinical amnionitis or in uncertain clinical presentations.

Maternal complications include bacteremia, labor abnormalities (mainly arrest disorders), and hemorrhage. In addition, cesarean section in the presence of amnionitis increases the risk of hemorrhage and wound infection.

Amnionitis has been linked to long-term neurodevelopmental delay and cerebral palsy in children. Continuous intrapartum fetal monitoring is recommended for cases of amnionitis in order to observe evidence of fetal compromise.

Immediate delivery has not been shown to improve outcome in cases of amnionitis where there is reassuring intrapartum testing and antibiotic administration. However, the true cure for amnionitis is delivery so induction should be expeditious and cesarean section should be performed for standard obstetric indications. Amnionitis in itself is not an indication for cesarean section.

Amnionitis is polymicrobial in nature. Broad-spectrum antibiotics should be initiated once the diagnosis is made to minimize maternal and neonatal morbidity. Antibiotics are recommended postpartum after a cesarean section until the patient has been afebrile for 24 h.

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Third trimester bleeding

Alan Peaceman

INTRODUCTION

Vaginal bleeding in the third trimester complicates 4% of pregnancies and should warrant further evaluation by a physician. A report of heavy bleeding mandates referral to the hospital.

PATHOPHYSIOLOGY

Although the origin of third trimester vaginal bleeding is most often the uterus, consideration of the lower genital tract is sometimes helpful. However, fewer than 5% of patients with third trimester bleeding display evidence of a cervical or vaginal source (e.g. cervical polyps, erosions, and carcinomas, as well as vaginal moniliasis). These conditions generally cause spotting or pinkish discharge rather than frank bleeding. Approximately 10% of patients with third trimester bleeding demonstrate sonographic evidence of placenta previa. The mean gestational age of bleeding from placenta previa is 34 weeks, commensurate with the beginning of development of the lower uterine segment. Most frequently, there is no identifiable precipitating cause—rather, the bleeding arises spontaneously, often while the patient is inactive. The mechanism for bleeding is unclear, but is likely related to the expansion of the lower uterine segment disrupting the attachment of the placenta. The placental bed blood flow then escapes through the nearby cervix, although clot can form just above the internal cervical os. In this situation, the blood loss is maternal. The fetus is uncommonly affected unless the blood loss of the mother is sufficient to cause hypotension or profound anemia. Risk factors for placenta previa include increased parity, maternal age, and prior cesarean section. The latter also increases the probability of coexistent placenta accreta (seen in 10% in patients with previa and one prior caesarean, as high as 50% with previa and two prior cesareans). The recurrence risk of previa has been reported to be 4–8%. A high index of suspicion must also be maintained for the presence of vasa previa. Although a rare cause of third trimester bleeding (1 in 3000 pregnancies), vasa

previa is associated with significant perinatal mortality resulting from umbilical vessel compression or rupture during labor, or at the time of rupture of membranes.

By far the most common cause (more than 80%) of third trimester bleeding is abruptio placentae. Most commonly, the hemorrhage occurs from peripheral placental bed vessels without evidence of intrinsic vasculopathy. This process causes vaginal bleeding without retroplacental clot formation, disruption of intervillous blood flow, maternal coagulopathy, or untoward hemodynamic effects. The precise mechanism underlying this form of hemorrhage is unknown. When the bleeding is confined to a relatively small portion of the periphery of the placenta, the patient is most often stable, as the remainder of the placental surface continues to perform the functions of nutrient exchange sufficiently. However, such vaginal bleeding can be an antecedent to preterm premature rupture of the membranes (PPROM) and preterm labor (PTL). The probability of PTL and PPROM increases with recurrent bleeding episodes and greater volumes of blood loss.

Clinically significant abruptio placentae resulting in retroplacental hematoma formation complicates 1 in 120 pregnancies. In general, this more severe form of hemorrhage is often associated with pre-existent decidual vasculopathy. In most cases, the abruption is "mild," presenting with modest vaginal bleeding and uterine irritability, but not with adverse hemodynamic or coagulation sequelae. However, abruptions that are more severe can result in heavier bleeding, hypofibrinogenemia and thrombocytopenia or frank coagulopathy, deterioration of the fetal condition or death, and maternal tachycardia or shock. High-frequency low-amplitude uterine contractions, pain, and tenderness are common in these severe cases, particularly in the 10–20% of abruptions that are centrally located and not associated with clinically apparent bleeding (concealed). The latter can lead to creation of a Couvelaire uterus, where blood begins to dissect into the myometrium. The most common predisposing clinical condition for severe abruption is chronic and/or pregnancy-induced hypertension (25–50%). Additional risk factors include cigarette smoking, cocaine use, and trauma. The recurrence risk for abruption is thought to be 5–10%.

DIAGNOSIS AND WORK-UP

The crucial step in evaluating third trimester bleeding is ultrasonography to delineate the placental location. This scan can be initially performed transabdominally and if the placenta is clearly located in the fundus, previa can be confidently excluded. In all other cases, strong consideration should be given to performing a transvaginal scan, as identification of the relationship between the placenta and the cervical os with transabdominal views can be confused by retained clot and various stages of bladder filling. Although vaginal examina-

tions have traditionally been discouraged until placenta previa has been excluded for fear of precipitating more significant bleeding, studies have shown that gradual advance of the vaginal probe to the level of the external os can be performed safely in this situation. The precise location of the placenta vis-à-vis the internal cervical os should be noted and the placenta classified as:

- 1 *Low-lying*: within 2–5 cm of the os
- 2 *Marginal*: within 2 cm but not covering the os
- 3 *Partial*: covering a portion of the os
- 4 *Complete*: entirely covering the os

The positive and negative predictive values of transvaginal ultrasound for the diagnosis of previa are 93% and 98%, respectively. Because hematomas are isoechoic with respect to the placenta for up to 1 week, ultrasound is often not effective in identifying a retroplacental clot associated with acute abruption placentae. Additional clinical and demographic criteria to aid in differentiating previa from abruption are listed in Table 75.1. In the presence of fetal tachycardia or a sinusoidal fetal heart rate pattern, loss of fetal blood should be considered, and a vasa previa searched for with color flow ultrasonography.

MANAGEMENT

Patients who report heavy third trimester bleeding (passage of clots or continuous flow of blood) should be referred immediately to the hospital. Initial steps in their evaluation should include assessment of maternal hemodynamic and coagulation status as well as confirmation of fetal viability, well being, and gestational age. A large-bore intravenous catheter should be placed, and laboratory studies obtained, including complete blood cell and platelet count, and fibrinogen level. When blood loss has been considerable, or coagulopathy has been identified, a cross-match for 4 units of packed red cells should be obtained, along with electrolytes, and a creatinine level. In addition, volume replacement should be initiated with crystalloid (e.g. Ringer's lactate), and a bladder catheter placed to record urine output.

Table 75.1 Clinical correlates with placental abruption and previa.

Variable	Previa (%)	Abruption (%)
Uterine pain	Uncommon	Common
Hypertension	<5	25–50
Contractions	<25	>75
Abnormal lie	35	<5
Intrauterine growth restriction	10–15	>80*

*In fetuses less than 36 weeks.

Continued frank hemorrhage with maternal hemodynamic compromise or coagulopathy, or fetal heart rate tracing abnormalities refractory to intravenous fluids, oxygenation, and maternal positioning, is an indication for immediate operative delivery regardless of etiology. Type O negative blood can be utilized for transfusion if type-specific cross-matched blood is not available for the mother. Such blood can also be made available for possible neonatal transfusion if neonatal anemia is encountered.

If the mother is hemodynamically stable and fetal status is reassuring, an ultrasound should be performed to confirm gestational age and evaluate for placenta previa. Continuous fetal heart rate monitoring is necessary until either delivery or maternal bleeding subsides. If a suspicion for previa exists, cervical examination should be avoided to prevent placenta trauma and the potential for increased bleeding. In the absence of a previa, a speculum examination should be performed to rule out the rare instances of lower genital tract sources. In general, the management paradigm presented in Fig. 75.1 can be utilized after initial evaluation and initiation of intravenous fluid therapy.

COMPLICATIONS

Abruptio placentae can be associated with hypovolemic shock resulting from blood loss per vagina or blood sequestered in the uterine cavity or myometrium (Couvelaire uterus). Failure to institute prompt fluid or blood component therapy, or both, may contribute to the risk of maternal death, acute tubular necrosis, shock liver, or adult respiratory distress syndrome. The decidua is a rich source of tissue factor (thromboplastin) and therefore it is not surprising that a coagulopathy develops in half of patients with moderate to severe abruptions. This condition is best treated by delivery and evacuation of the uterus, with fresh frozen plasma infusions given to replace coagulation factors until clinical coagulopathy, as manifest by continued oozing from raw surfaces, resolves.

FOLLOW-UP

In general, patients with stable placenta previa at less than 36 weeks' gestation should be managed expectantly. When significant bleeding occurs prior to 34 weeks, steroids should be administered to enhance fetal pulmonary maturity in case urgent delivery is necessary. In situations where bleeding is accompanied by regular uterine contractions, magnesium sulfate tocolysis can be considered if the patient is hemodynamically stable. This might be effective in stopping the bleeding if it has been initiated by uterine activity leading to changes in the cervix or lower uterine segment. Non-steroidal anti-inflammatory agents are best avoided because of the association with platelet dysfunction. In situations where the bleeding has stopped or is intermittent in small amounts, transfusion should be used to maintain maternal hematocrit at

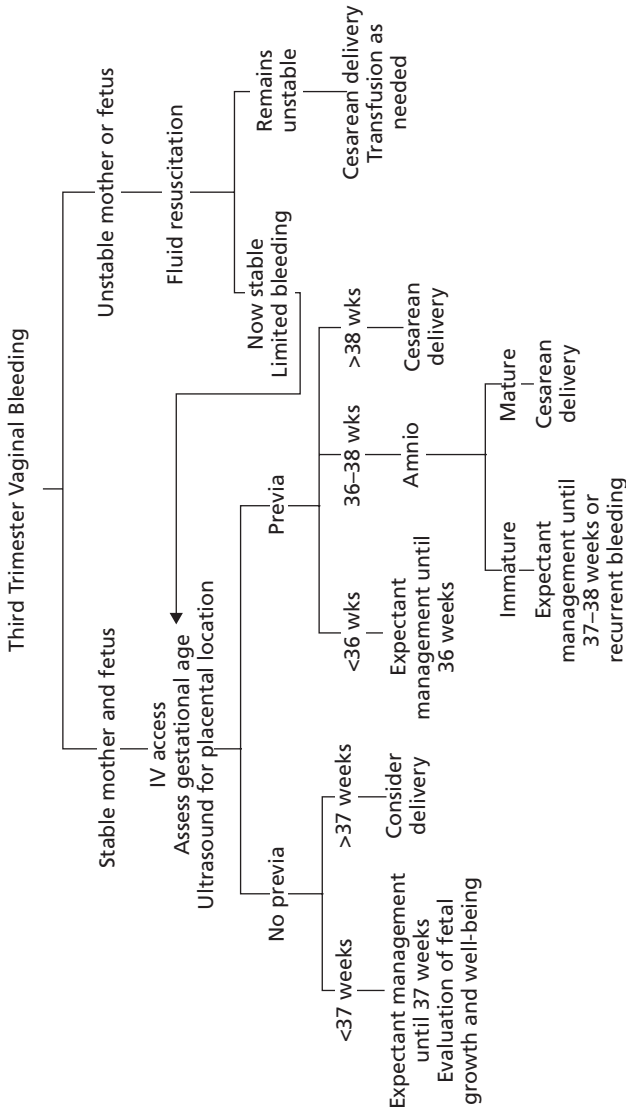


Fig. 75.1 Management of third trimester bleeding.

greater than 30%. This will provide reserve should increased bleeding occur suddenly. Most patients requiring more than one transfusion to maintain the hematocrit greater than 30% will not be stable long enough to justify continued transfusions, and delivery should be considered. If a patient with previa has cessation of bleeding for 4–7 days, management as an outpatient can be considered if rapid return to the hospital is possible. Although a situation could arise where heavy bleeding occurs and outpatient management results in delay in delivery, it is very uncommon for this to result in significant maternal or fetal morbidity or mortality. After 36 weeks' gestation, development of the lower uterine segment progresses and the risk of bleeding increases. At this time amniocentesis should be performed and the patient delivered if fetal lung maturity is demonstrated.

Patients with repetitive bleeding at less than 36 weeks without evidence of placenta previa are at increased risk for intrauterine growth retardation (IUGR), pre-eclampsia, preterm birth, and preterm premature rupture of membranes. Subsequent care of these patients should include evaluation for these complications. While the patient is bleeding, inpatient management and monitoring of the fetus and mother are indicated, with delivery indicated if either decompensate. Here too steroids should be used at less than 34 weeks to advance fetal pulmonary maturity. Tocolysis can be used as with previa if contractions are present and the mother is hemodynamically stable. If the bleeding has been mild and subsides for a number of days, consideration can be given to outpatient management, with readmission and reassessment if bleeding recurs. If bleeding does not recur and complications do not arise, patients can potentially be carried to term.

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Amniotic fluid embolus

Robert Resnik

INTRODUCTION

Since the entity was first described by Meyer,¹ amniotic fluid embolism has come to be recognized as a dramatic and dire event, responsible for more than 10% of maternal mortalities in the USA. The clinical presentation is that of a term or near-term patient, more frequently multiparous, in whom the sudden onset of agitation, dyspnea, anxiety, and respiratory arrest develops during labor, delivery, or in the first few hours postpartum. As many as half of patients will die during the initial resuscitative efforts. In those who survive the acute event, left ventricular failure may develop in a clinical picture consistent with adult respiratory distress syndrome as well as disseminated intravascular coagulation.

PATHOPHYSIOLOGY AND DIAGNOSIS

The pathophysiology of amniotic fluid embolism (AFE) has not been entirely clarified. However, combining data from animal models^{2,3} and humans,^{4,5} an understanding of the disease mechanism can be pieced together. Rapid infusion of amniotic fluid with particulate matter (often meconium) into the maternal circulation leads initially to an immediate and sharp increase in mean pulmonary artery pressure, pulmonary vascular resistance, and resultant systemic hypoxia resulting from disordered ventilation–perfusion. This is followed by a second phase of left ventricular failure. Recent data obtained from patients with AFE, monitored with pulmonary artery catheters, reveal a severe reduction in left ventricular systolic work index (LVSWI) and secondary increase in pulmonary wedge and diastolic pressures.⁵ Information collected from the National Amniotic Fluid Embolism Registry suggests that the syndrome is similar to anaphylaxis and septic shock, conditions also triggered by foreign toxins that enter the intravascular space.⁶

Thromboplastin-rich amniotic fluid triggers the intrinsic clotting system, with rapid defibrination and hemorrhage, thus aggravating an already complex cardiovascular picture. The differential diagnosis includes acute pulmonary

edema, pulmonary emboli from the peripheral venous circulation, and cardiac arrhythmias. During resuscitative efforts, it is advisable to obtain blood from the pulmonary artery via central lines to look for fetal squame cells (Attwood stain) and mucin (Giemsa stain).⁷ This observation will confirm the diagnosis in those patients who survive.

MANAGEMENT

Given this clinical picture, the following represents an appropriate management format:

- 1 Institute endotracheal intubation, with maintenance of oxygen flow rates dictated by monitoring arterial blood gases.
- 2 Cardiac resuscitative measures may be needed. Crystalloids should be administered to maintain intravascular volume and cardiac output. Inotropic agents may be required to treat hypotension and heart failure. The appropriate use of these agents necessitates continuous intensive cardiopulmonary monitoring. Use of a triple lumen pulmonary catheter is required.
- 3 Careful attention should be paid to blood loss following delivery and measurement of clotting factors. Blood should be obtained for measurement of clotting factors, partial thromboplastin time, platelets, fibrin split products, and fibrinogen. In addition, while awaiting these results, one should observe the time required for blood to form a solid clot in a red-top tube (normal, less than 8 min). In the presence of disseminated intravascular clotting, component therapy should be initiated with fresh frozen plasma or platelets, or both. (Fresh frozen plasma contains approximately 1 g fibrinogen/unit; each unit of platelets raises the platelet count by approximately 8000/ μ L.)

Patients who survive the cardiopulmonary event may have a 2- to 5-day course of mild to substantial respiratory insufficiency, probably resulting from adult respiratory distress syndrome, and complicated by pulmonary edema secondary to diminished left ventricular function. However, prompt and aggressive treatment during the initial phase is likely to decrease the reported maternal mortality of over 80%.

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Sepsis syndrome

F. Gary Cunningham

INTRODUCTION

The sepsis syndrome is induced by a systemic inflammatory response to bacteria or their byproducts such as endotoxins or exotoxins. Clinically, the syndrome is a continuum with septic shock as its worst manifestation. Shock from sepsis is characterized by hypotension, inadequate tissue perfusion, hypoxia, and metabolic acidosis. The presumptive diagnosis is made when chills and fever precede hypotension, tachycardia, tachypnea, oliguria, or mental confusion.

Antepartum pyelonephritis, chorioamnionitis and puerperal sepsis, and abortion-related infection are common causes of the sepsis syndrome in obstetrics and gynecology. Other causes include ruptured tubo-ovarian abscesses, perineal cellulitis in diabetics, and necrotizing fasciitis from surgical wound infections. Sepsis from one of these causes is more likely if the woman also has gynecologic cancer.

PATHOGENESIS

Endotoxin-producing bacteria such as *Escherichia coli* are the prototypical organisms that cause the sepsis syndrome. Exotoxins from group A streptococcal infections as well as from *Staphylococcus aureus* may cause a virulent lifethreatening toxic shock syndrome. Pelvic infections are polymicrobial and species of *Peptostreptococcus*, *Peptococcus*, *Streptococcus*, *Staphylococcus*, *Clostridium*, and *Bacteroides*, which elaborate less potent toxins, may also be involved.

Bacterial endotoxins or exotoxins evoke a systemic inflammatory response that includes secretion of proinflammatory cytokines from CD4 T cells. Leukocytes and platelets adhere to endothelial cells, which release proteases, oxidants, and cytokines such as tumor necrosis factor (INF α) and interleukins 1 and 8 (IL-1, IL-8). These substances in turn induce procoagulant activity, activate a number of genes, and up- or down-regulate cell receptors. They cause intense selective vasodilation with maldistribution of blood flow and volume. Vascular endothelium injury causes profound capillary leakage with interstitial fluid accumulation which may include pulmonary edema. Despite initially

elevated cardiac output, severely decreased systemic vascular resistance leads to hypotension. Further effects of hypoperfusion include renal tubular or cortical necrosis, myocardial necrosis, and capillary thromboses which are further aggravated by platelet aggregation.

WHO IS AT RISK?

Cancer, diabetes, HIV infection, and various kidney, heart, and liver diseases predispose the patient to sepsis syndrome. Cancer is a particularly important risk factor because necrotic tumor provides sites for bacterial growth; irradiation and chemotherapy cause immunosuppression; and long-term use of venous and urethral catheters fosters infection and sepsis.

DIAGNOSIS

Locating the infection site is critical. Clinical findings and laboratory studies help to rule out other causes of shock, such as hemorrhage, as well as to direct therapy (Table 77.1). Chest X-ray films, usually normal at the outset, may eventually disclose pneumonitis as a source for sepsis, but more likely will show pulmonary edema caused by endotoxin-induced alveolar capillary leakage. Abdominal radiographs may disclose intestinal obstruction, or extraluminal gas which suggests tissue necrosis or organ perforation. Urinalysis is used to diagnose pyelonephritis. Blood and infection-site cultures are taken if they might be useful in guiding further therapy. Abdominopelvic sonographic or computed tomography (CT) scanning may be helpful to either encourage or avoid laparotomy.

Table 77.1 Effect of shock on individual organs.

Central nervous system	
Cerebral	Confusion, somnolence, coma, combativeness
Hypothalamic	Fever, hypothermia
Cardiovascular	
Blood pressure	Hypotension (vasodilation)
Cardiac	Increased cardiac output with fluid replacement; myocardial depression with diminished cardiac output
Pulmonary	Shunting with dysoxia and hypoxemia; diffuse infiltrates and effusions from endothelial and epithelial damage
Gastrointestinal	Gastritis, toxic hepatitis, hyperglycemia
Renal	Oliguria, acute tubular necrosis
Hematologic	Thrombocytopenia, leukocytosis, coagulation activation

TREATMENT

When shock supervenes, proceed as follows:

- 1 Restore circulating volume to ensure adequate organ perfusion and correct acidosis
- 2 Institute empiric antimicrobial therapy
- 3 Surgically débride infected tissue; curette infected uterine contents; and drain abscesses
- 4 Monitor effects of therapy on vital functions and provide supportive care for organ-system dysfunction

Central to management of the sepsis syndrome is rapid intravenous administration of crystalloid solution to restore blood volume, improve perfusion, and correct hypotension and acidosis. Initial replacement may require 2–6 L to restore renal perfusion. Blood is given to maintain the hematocrit at or slightly above 30%.

In addition to closely monitoring respiratory rate, pulse, and blood pressure, measure urinary output—the most sensitive indicator of perfusion. Administer crystalloids and blood to maintain urine output at 30–60 mL/h. If vigorous volume replacement fails to restore urine flow promptly, or if there is evidence of cardiac or pulmonary dysfunction, then placement of a flow-directed pulmonary artery catheter may be considered. Such hemodynamic monitoring may be helpful to direct fluid therapy and determine the cause of pulmonary edema.

Even without overt pulmonary edema, respiratory insufficiency manifested by tachypnea and hypoxia requires prompt oxygen supplementation. If these signs persist, institute mechanical ventilation with positive end-expiratory pressure. If the patient has developed the acute respiratory distress syndrome (ARDS) then this step will be life-saving.

For renal infections, which are almost always caused by Gram-negative Enterobacteriaceae, give a combination of ampicillin or a cephalosporin with an aminoglycoside. Pelvic infections are typically polymicrobial and require broad-spectrum antibiotic therapy. Depending on allergies, give a beta-lactam congener that includes one of the penicillins or cephalosporins. An aminoglycoside is given for Enterobacteriaceae coverage because these are most often implicated in septic shock. Because bacteremia from pelvic sepsis is often caused by *Bacteroides fragilis* or other anaerobes, clindamycin or metronidazole is given for initial therapy of pelvic infections.

ADJUNCTIVE THERAPY

Septic shock is characterized initially by maximal vasodilation. Vasoactive drugs are not given unless volume expansion with crystalloids and blood fail to restore adequate renal perfusion and urine flow. In such cases, give 2–10 µg/kg/min of the beta-receptor stimulant dopamine hydrochloride ini-

tially to increase cardiac output and improve renal perfusion. If there is no improvement, then give incremental increases of up to 20–50 µg/kg/min as needed. Persistently depressed cardiac output at this stage is ominous. It is crucial to search for any persistent foci of bacteremia, to débride necrotic tissue, and to drain purulent material. Such areas are particularly common with necrotizing fasciitis from abdominal incisions, cellulitis after episiotomy, and perineal cellulitis complicating Bartholin gland abscesses in diabetics. Another troublesome condition is necrosis and dehiscence of the post-cesarean uterine incision which is usually also complicated by peritonitis.

A number of adjunctive therapies have been assessed over the last 15 years but, unfortunately, none has proven to be particularly beneficial. Because sepsis activates procoagulant production which causes microcirculatory thrombosis, various anticoagulants have been assessed in clinical trials. Recombinant activated protein C may be useful in some cases, for example purpura fulminans, but it can also incite hemorrhage.

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Counseling for fetal anomalies

Lorraine Dugoff

INTRODUCTION

The detection of a fetal anomaly can be an emotionally charged and stressful situation for the patient and her family as well as the healthcare provider. It is important for the healthcare provider to be supportive and provide accurate and complete information regarding prognosis and management options in a non-biased, non-directive manner. This chapter reviews the fundamentals in counseling a patient diagnosed with fetal anomalies.

PATHOPHYSIOLOGY

Congenital anomalies occur in approximately 1 in 200 liveborn infants and account for approximately 25% of deaths in a neonatal intensive care setting. The etiology of congenital anomalies is diverse. They can be isolated, such as a cleft lip, or part of a syndrome. Approximately 60% of major birth defects affect a single organ system. Specific causes for these isolated defects are often difficult to identify. Congenital anomalies can result from chromosome disorders, single gene or Mendelian disorders, and polygenic or multifactorial disorders. Most chromosomal syndromes, although genetic, are usually not hereditary. Single gene defects may be classified as autosomal dominant, autosomal recessive, or X-linked, depending on the mode of transmission. Multifactorial conditions result from a combination of genetic and environmental factors.

DIAGNOSIS

Prenatal diagnosis in the late 1960s and early 1970s primarily focused on the detection of chromosomal abnormalities using amniocentesis. With advances in the field of obstetric ultrasound came the ability to detect fetal structural anomalies. Currently, many isolated defects and genetic syndromes can be diagnosed prenatally using ultrasound. In addition, advances in the field of cytogenetics and molecular genetics have made it possible to detect microscopic chromosomal abnormalities and single gene disorders.

MANAGEMENT

Counseling a patient with detected fetal anomalies should include obtaining a family, pregnancy, and medical history, discussing the ultrasound findings, reviewing the fetal prognosis and risks, and discussing the options available.

Family, pregnancy, and medical history

The patient and her partner should be interviewed to determine their ethnicity, and whether they have a family history of mental retardation, birth defects, genetic syndromes, chromosomal abnormalities, stillbirths, recurrent pregnancy loss, or consanguinity. In some cases it may be helpful to obtain medical records to confirm or clarify a diagnosis. The pregnancy history should include any complications that occurred during the pregnancy as well as any exposures to potential teratogens including medications, alcohol, infections, high temperatures, and radiation. A medical history should be obtained, including conditions that are associated with birth defects such as diabetes mellitus, epilepsy, phenylketonuria, or a history of a viral infection during the pregnancy.

Review the ultrasound findings, fetal prognosis, and risks

When an anomaly is detected on ultrasound, a thorough anatomic survey is indicated to rule out additional abnormalities. When an abnormality is first identified, the patient should be told directly. You may say, "I think there may be a problem. I need to perform a more detailed examination. Please allow me the time. When I am finished with the ultrasound I will share the findings with you."

The following guidelines may be helpful in communicating the information to the patient or couple:

- Do not counsel the patient while she is still on the examination table. Allow her to get dressed and move to a private consultation room or office.
- Involve a genetic counselor; if one is not available, a perinatal nurse or social worker can help. These team members can provide invaluable support, help explain medical terms, and coordinate care and follow-up.
- Use simple, clear language when communicating the diagnosis and prognosis to the patient. Draw simple diagrams when possible.
- Be sensitive to ethnic, cultural, societal, and individual moral, philosophic, and personal beliefs which influence the way each patient reacts and responds to the information.
- Do not use adjectives that place a value judgment on the abnormality being described. What might be "minor," "simple," or "benign" to you might not be so to the patient.
- Leave the patient or couple alone for a few minutes to grieve and gather their thoughts.
- Acknowledge and validate the patient's or couple's feelings.

It is important to communicate the ultrasound findings and prognosis with the referring physician as soon as possible. In some cases, it may be helpful for the patient to speak with her physician while she is still in your office, as she may feel more comfortable speaking with a physician with whom she has a long-standing relationship. It is important to have ongoing communication with the referring physician. The patient's decision and follow-up arrangements should be discussed with her referring physician.

Discuss the various options

Management of patients with fetal anomalies can be complex and may require a multidisciplinary approach. Pediatricians and/or neonatologists, genetic counselors, geneticists, pediatric surgeons, radiologists, and social workers should be consulted when appropriate. It may be beneficial for the patient and her family to meet with a specialist from another field. For example, if a fetus has been diagnosed with a neural tube defect, it may be helpful to the patient and her family to meet with a pediatric neurosurgeon to discuss the surgical treatment and the outcome that might be expected.

In some cases, additional testing such as cytogenetic analysis, DNA testing, and fetal echocardiography may be indicated to confirm or identify a diagnosis. When appropriate, invasive testing options including chorionic villus sampling and amniocentesis should be discussed with the patient, including the risks and benefits associated with the procedure.

All appropriate management options should be discussed with the patient, including termination, fetal surgery, neonatal surgical options, and expectant management. It is critical to present these options in a non-directive manner. The patient needs to be given the opportunity to ask questions and take as much time as necessary for her to make a decision that is right for her and her family based on their religious, ethical, cultural, and social beliefs.

FOLLOW-UP

If a patient chooses to continue her pregnancy, appropriate follow-up appointments for ultrasound and specialty referrals should be arranged. When indicated, arrangements should be made for the patient to deliver at a tertiary care center. In many cases, a neonatal consultation and a tour of the labor and delivery unit and the nursery can be beneficial.

If a patient chooses to terminate her pregnancy, the various termination options including the risks and benefits of each option should be discussed. If the patient's referring physician does not perform pregnancy terminations, the patient should be provided with information regarding referrals for this service. If a patient chooses induction of labor, she should be informed that it is possible that the fetus may be born alive. The patient should be given the option to hold the baby after delivery and name him/her. The patient should be provided

with resources to help cope with her loss including a contact for a support group that deals with fetal loss. It is important to reassure the patient that she did not do anything to cause the abnormality as it is common for women to experience feelings of guilt.

In the event a patient chooses termination of pregnancy, she should be counseled and offered a fetal autopsy to be performed by an expert in the field in collaboration with a medical geneticist with experience in fetal dysmorphology. This may provide the family with more accurate information regarding the diagnosis and recurrence risks. In addition, photographs, radiographs, karyotype, and viral and bacterial studies should be obtained when indicated. In certain cases, fetal DNA and fibroblasts should be banked for future investigations. This may provide the family with prenatal diagnosis options for future pregnancies as genetic mutations associated with different genetic conditions are being discovered rapidly with advances in the field of molecular genetics.

Once all of the information has been collected including autopsy and karyotype results when applicable, a follow-up letter summarizing the findings, diagnosis (when known), recurrence risks, as well as any specific information regarding prenatal diagnosis options for a future pregnancy should be sent to both the patient and her referring physician. In addition, it is appropriate to offer the patient an opportunity to make an appointment for a consultation to review all of the findings and discuss future reproductive options.

COMPLICATIONS

Information initially communicated to the patient may not be accurately understood or retained. Patients may exhibit disbelief or denial. Allow time for the patient and her family members to absorb the information and ask questions and offer the patient the option to contact you in the future. It may prove helpful to provide the patient with diagrams, written material, or pictures.

PREVENTION

Unfortunately, many fetal anomalies are not preventable. Information regarding specific interventions should be provided if applicable, including treatment with folic acid to prevent recurrent neural tube defects, obtaining good glycemic control prior to conception in women with pre-existing diabetes mellitus, and information regarding teratogens. In addition, patients should be provided with information regarding prenatal diagnosis options for future pregnancies as well as preimplantation genetic diagnosis and donor eggs and/or sperm when appropriate.

CONCLUSIONS

There have been many advances over the last decade in the ability to diagnose fetal anomalies. It can be very challenging to make a diagnosis and counsel a

patient and her family regarding the prognosis, treatment options, and recurrence risks. In many cases it is helpful to use a multidisciplinary approach and involve genetic counselors, neonatologists, radiologists, medical geneticists, and other specialties as indicated. It is of utmost importance to provide counseling to patients with fetal anomalies using a non-biased, non-directive, supportive approach so that patients and their families can make decisions that are consistent with their own personal religious and/or ethical beliefs.

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PART 6

Labor and delivery

Maternal transport

Jerome Yankowitz

INTRODUCTION

One of the scientific triumphs of the 20th century was the dramatic reduction in mortality rates for many segments of the population. One area of medicine in particular that has enjoyed a sharp decline in mortality in the past century is maternal and neonatal care. Much of this success is attributable to the development of perinatal centers, which began in Scandinavia and the Netherlands in the late 1940s.¹ Urban hospitals in the USA were quick to emulate these centers. Mortality committees were also developed to devise strategies for improving outcomes in the perinatal period. Perinatal centers generally provide subspecialist care for high-risk obstetric patients, as well as the latest technology and expertise in neonatal intensive care. As technology has progressed, a greater variety of diseases have been successfully managed, with improvements in outcomes for younger and smaller infants, as well as pregnant women with coexisting medical problems. During the 1970s and 1980s, in an effort to extend the benefits of these perinatal centers to residents of rural areas, many states devised regionalized systems of perinatal care in which physicians working in community hospitals provide the bulk of perinatal care, but work in close conjunction with the tertiary care subspecialists.

An essential component of regionalized perinatal care is maternal transport. Before regionalization, many high-risk infants were transferred to tertiary perinatal centers after birth in order to receive intensive treatment. With the advent of regionalization, these neonatal transport programs were often strengthened, but were also joined by the option of maternal transport, allowing the mother to go to the tertiary center before delivery, either because of a concomitant maternal medical problem or if there might be reason to believe the neonate at risk for complications. In this way, the neonate began receiving intensive care immediately after birth with the ultimate goal of improved neonatal outcomes. This chapter outlines indications commonly used for maternal transport, as well as guidelines on its usage.

INDICATIONS FOR MATERNAL TRANSPORT

Many studies have reported the common reasons for maternal transport. Maternal factors are responsible for the majority of maternal transports.² Most of these transfers, however, are initiated with the health of the fetus in mind.³ A review by Giles⁴ revealed that over 40% of maternal transports occur because of more than one indication. Knox and Schnitker⁵ noted that many maternal transports are dependent on the possibility of a premature delivery.

Premature rupture of the membranes (PROM) was cited by many studies as a common indication for maternal transport.²⁻⁹ Giles⁴ noted that since the late 1970s there has been increased encouragement to attempt to prevent delivery en route by transporting pregnant women before active labor begins. Therefore, there appears to be a low threshold for transporting women who have experienced PROM, but are not yet in active labor.

Preterm labor was also cited by several authors as an indication for maternal transport.^{3-7,9,10} Several studies that have shown increased benefit for neonates of certain gestational ages or birth weights to be delivered at tertiary care centers support preterm labor as an indicator for transport. The recommendations for which infants should be transported have changed greatly within the past two decades. A 1987 study by Paneth *et al.*¹¹ recommended that infants less than 37 weeks' gestation or less than 2250 g be delivered in a facility with neonatal intensive care. In 1993, Strobino *et al.*¹² found that those infants less than 32 weeks would likely benefit from maternal transfer, a recommendation echoed by Walsh-Sukys and Fanaroff¹ in 1997, who also added the indication to transfer infants less than 1500 g. Most recently, in 2003, Lee *et al.*¹³ provided evidence that pregnancies over 29 weeks' gestation may not receive benefit from tertiary care, in the absence of other risk factors. For women in advanced preterm labor, Elliott *et al.*¹⁰ cautioned that other risk factors must be taken into account when deciding to transfer a pregnant woman, including the distance between hospitals, the expected time needed for transport, the personnel available to serve on the transport team, the facilities available at the referring hospital, and the speed of progression of labor.

Modanlou *et al.*¹⁴ generalized the indications for maternal transport with the statement that pregnant women are often referred antenatally to tertiary centers for chronic problems, while maternal transport often occurs for acute conditions that threaten the life of the fetus. Other acute conditions often responsible for maternal transport include antenatal bleeding,^{2,4,6,7,9,14} pre-eclampsia or eclampsia,^{2,4,7,8,14} chorioamnionitis,^{2,9} placental abruption,⁵ and abnormal or transverse lie.^{4,9} However, chronic conditions may become indications for maternal transport if they have gone undiagnosed because of a lack of prenatal care or if the severity increases suddenly. Examples of such circumstances include pregnancy-induced hypertension or chronic hypertension,^{8,9,14} multiple gestation,^{4,9,14} maternal diabetes,^{6,7,9,14} and Rh

sensitization.^{2,7-9,14} Other indications for transport cited less frequently include intrauterine death,^{7,9} fetal anomalies,⁹ need for cesarean section,^{7,9} maternal cardiac disease,¹⁶ sickle cell crisis,⁷ obstructed labor,⁷ incompetent cervix,⁸ post-date pregnancy,⁹ and placenta previa.⁸ Table 79.1 provides a summary of commonly cited indications and contraindications for maternal transport.^{5,15-17} Ultimately, the decision to transfer a pregnant patient must be made by physicians at both the referring and receiving hospitals, with full knowledge of the referring hospital's capabilities and with the primary goal of maintaining maternal safety.

Table 79.1 Indications and contraindications for maternal transport.

Maternal indications	Fetal indications	Contraindications
Premature rupture of membranes	Low gestational age	Maternal/fetal cardiovascular instability
Preterm labor	Cervical incompetence	Advanced cervical dilation (> 3 cm) not arrested by tocolytics
Pre-eclampsia/eclampsia/hypertension	Anomalies requiring surgery	Preterm contractions without other risk factor
Multiple gestation	Rh sensitization/hemolytic disorder	Delivery en route highly likely
Antenatal bleeding	Need for ventilation	
Serious infection	Fetal arrhythmia or bradycardia	
Poorly controlled diabetes	Unexplained intrauterine death	
Renal disease/decreased function	Non-reassuring fetal testing	
Drug overdose	Intrauterine growth restriction	
Trauma	Breech/transverse lie	
Acute abdominal emergencies	Severe oligohydramnios	
Collagen vascular disease (lupus)	Need for cesarean section	
Hepatic disease		
Cardiac disease		
Thyroid storm, thyrotoxicosis		
Malignancy		
Sickle cell crisis		

GUIDELINES FOR MATERNAL TRANSPORT

The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) have published guidelines for use when transporting patients, including information regarding personnel, equipment, transport procedures, and outreach education.¹⁸ Other authors have presented suggestions that may be useful in designing protocols for maternal transport, such as standardized equipment kits, personnel qualifications, and guidelines for treatment of common maternal conditions during transport.^{4,5}

Transport options are not, of course, limited to maternal transport alone, and it should not be assumed that every maternal–fetal pair that encounters a problem during late pregnancy should be transported to a tertiary center. Unless there is a substantial risk to the mother or infant, it may be ideal for the woman to receive treatment at the local hospital, by her local physician. This option allows for treatment by a familiar physician in a location close to home and to the support of family, as well as sparing the financial costs of transport and high-intensity care. In some cases, a telephone consultation with a specialist physician may be all that is needed.⁴ In other cases, it may be convenient for the specialist physician to travel to the local center to provide care. Maternal transport can be considered if there is an identified maternal or fetal risk for which the referring hospital is unequipped to treat, the maternal–fetal pair can be stabilized for transport, and both referring and receiving physicians agree that tertiary care is needed. Finally, neonatal, rather than maternal, transport may be necessary in cases of unexpected morbidities, advanced labor with delivery likely before transport can be completed, or any other reason that maternal transport is thought to be ill-advised.^{4,18}

The transport team should be composed of specially trained personnel who are familiar with a variety of emergency conditions that may occur in obstetric and neonatal patients.¹⁸ Each regional system should be directed by a tertiary care physician with training in high-risk obstetrics or neonatology. This consultant must be familiar with the latest technology in the field, as well as with the capabilities of the community hospitals in the region.⁴ The personnel who accompany the patient during maternal transport should include a wide variety of specialists, including physicians, neonatal or labor and delivery nurses, respiratory therapists, anesthesiologists and emergency medical technicians.¹⁸ It may be optimal for a team to be dispensed from the tertiary center in order to best deal with complications that occur en route; however, teams are often composed of personnel from the referring hospital. Indeed, it may provide relief to the patient to have her own physician or local nurses with her during transport.⁴ In any case, the members of the transport team must be individualized for each particular transport; for example, in the case of congestive heart failure a respiratory therapist may be essential.⁴ When transporting more

stable patients, emergency medical technicians can often provide safe transport in the absence of specialized personnel. The responsibility for the patient generally falls upon the referring hospital until arrival at the tertiary center, including during any time spent planning the transport. However, if the specialty center sends its own transport team, the responsibility may shift to the receiving facility at the time transport begins.¹⁸

The equipment needed for maternal transport should be considered carefully for each case, keeping in mind the maternal and fetal risk factors, distance to be traveled, type of transport vehicle, and resources available locally.¹⁸ An advantage of maternal over neonatal transport is the reduced need for extra equipment for neonatal transport.⁴ The AAP and ACOG guidelines broadly suggest for all transports: equipment for monitoring physiologic functions, temperature, and pulse oximetry, resuscitation and support equipment, portable medical gas tanks if ventilators are needed, and electrical equipment compatible with sources in the transport vehicle. Each piece of equipment should be tested regularly in the harshest conditions to be expected in the region.¹⁸ Other authors describe individual components of maternal transport kits that may be considered, such as standard medications, intravenous solutions, and supplies needed for delivery.⁴

The choice of transport vehicle often depends on the distance of the transport. Ambulance is likely the most effective for short-distance travel up to approximately 50–60 miles, except in urban areas with heavy traffic.^{4,18} Helicopter may be the most appropriate option for the 60–100 mile range, while aircraft should be considered for longer distances. When using air transportation, the pilot becomes an essential team member in the decision to transport. It must be remembered that the pilot has the final decision on whether an air transport will take place as he/she is responsible for the safety not only of the patient, but also of the entire crew and transport team.^{4,18}

The maternal transport itself should begin with a coordinated decision between referring and receiving hospitals on the utility of the transfer. The receiving physician should provide recommendations before the transport is initiated on such issues as use of tocolytics, antibiotics, steroids, and any other medication needed.^{5,17} Before transport can begin, necessary personnel, equipment, and medical records must be assembled for transport, as well as consent obtained from the patient. Table 79.2 provides an overview of the essential steps that must be considered for maternal transport to occur.¹⁷ During transport it is important to observe the patient continuously, as well as monitor vital signs, oximetry, ventilatory pressures, cervical status, uterine contractions, and fetal heart rates as appropriate. The transport team should also be prepared to handle an imminent delivery or perform procedures such as chest tube placement and intubation if the patient's clinical condition changes during transport.¹⁸ Another priority of the team is to provide supportive care for the patient

Table 79.2 Steps in maternal transport.

1	Notify perinatologist
2	Notify labor and delivery personnel
3	Notify neonatal intensive care unit personnel
4	Notify neonatologist
5	Notify relevant subspecialists
6	Notify admitting office personnel
7	Transfer patient's records

in order to decrease her anxiety. Constant communication with the receiving hospital is important in case the patient's condition changes en route.

A final responsibility of the regional center staff is to provide outreach education to the community hospitals in the region, as well as to the public.^{9,18} A study by Gibson *et al.*¹⁹ suggests the utility of establishing protocols by the regional center for maternal transport in the region in order to standardize procedures, enhance communication, and improve outcomes. Regional centers should also collect data on transport outcomes and community hospital capabilities, educate staff at referring centers on new technologies and treatments in high-risk obstetric and neonatal care, and inform the public about services provided and the structure of the regional network.¹⁸

CONCLUSIONS

The development of maternal transport systems has been a relatively recent advance in the field of perinatology, but has proved beneficial for a variety of maternal and fetal acute and chronic conditions in providing improved access to specialty care. In making the decision to transport a pregnant woman to a tertiary center, several factors must be taken into account including the patient's condition, the presumed risks to the neonate, and the capabilities of the referring hospital. Any decision for transport must be made jointly by the referring and receiving physicians. The development of protocols for maternal transport situations may help improve communication, as well as standardize the necessary procedures involved in order to maximize patient outcomes. It must be kept in mind, however, that each transport must be planned according to the needs of the individual patient.

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Medications in labor

Gary S. Eglinton and Isaac P. Lowenwirt

INTRODUCTION

All medications administered to a gravida affect her fetus. Medications pass across the placenta and affect the fetus directly, or they alter the maternal physiologic state and secondarily affect the fetus, or they act through both mechanisms. Many medications have the same effect on the fetus as on the gravida. It is possible for a medication to have a beneficial effect or no effect on one and a more pronounced or deleterious effect on the other. Nearly all medications may alter fetal heart rate patterns displayed by electronic fetal heart rate monitoring. Use of the smallest effective dose will protect both the gravida and her fetus from the risks of inadvertent overdose. It is important for the labor attendant to consider carefully the risk–benefit balance when administering any medication to a gravida.

The route of administration of a medication may be important in altering both maternal and fetal effects. In general, intravenous (IV) administration provides the most rapid and complete absorption, and the most rapid decay of effect for both the gravida and her fetus. Intramuscular (IM) administration results in slightly more variable bioavailability, slower onset, and more prolonged action. Administering a narcotic intravenously results in nearly immediate effect, but also potentially exposes the fetus to high levels of agent and metabolic byproducts almost immediately. If delivery is relatively imminent, yet narcotic administration seems indicated, IM administration will delay the time of onset of most effective analgesia for the parturient, while relieving the fetus or newborn of some of the burden of birth while acutely sedated. Subcutaneous administration results in less predictable uptake than is seen after IM or IV administration and is usually not the preferred parenteral route.

The parturient should receive physiologic fluids in labor if she is not taking an oral diet. There is a paucity of authoritative advice and it is difficult to identify research data to inform fluid management in labor and delivery. Physiology and surgery texts suggest that the “normal person” takes in approximately

2.5L/day water at basal activity level. Lying quietly consumes 0.022kcal/kg/min. If the energy cost of labor is only 0.01kcal/kg/min above basal (the same as playing an accordion while seated), then over 500kcal of heat must be exhausted in 12 h of labor. This requires approximately 1 L water. So the 24-h cost of labor plus basal needs is probably at least 4.5 L, far above some recommendations of 60–120 mL/h. Exercise physiology teaches us that muscular activity requires fluid support. One research group discovered that each of 28 obstetric units in their county administered IV fluid at 125 mL/h in labor. Their research randomized nulliparous patients to either 125 mL/h or 250 mL/h of Ringer's Lactate (RL) "or isotonic sodium chloride solution." With approximately 100 patients in each arm, the patients who received more fluid had shorter first stage labor ($P = 0.06$), shorter length of labor ($P = 0.06$), fewer required oxytocin ($P = 0.062$), and fewer had labor lasting 12 h ($P = 0.047$). These findings might not be strong enough to shape practice, but in the absence of better data, these results must be considered important. It also seems reasonable to acknowledge the energy cost of labor through provision of dextrose solution. D5RL is an appropriate fluid, with total IV infusion of approximately 125 mL/h (or more) for a normal patient. If the patient is larger, breathing heavily, perspiring or working harder, her replacement fluid and caloric requirements clearly exceed the minimum.

ANALGESIA

Meperidine hydrochloride (Demerol®), either alone or in combination with promethazine hydrochloride (Phenergan®), has a history of extensive use in labor. Common dosing is 50–100 mg meperidine and 25–50 mg promethazine IM every 3–4 h. Both medications can be given intravenously, but at reduced dosage of 25–50 mg meperidine (diluted to 10 mg/mL) and 25 mg promethazine. Because metabolic byproducts of meperidine may have half-lives of 8–21 h and will accumulate in patients with renal impairment and in premature fetuses/neonates, the risk–benefit ratio requires re-evaluation before repeated dosing. After IM administration, the half-life of active metabolites in the neonate is 63 h. The manufacturers recommend no more than 100 mg promethazine during 24 h of labor.

Morphine is available as the sulfate salt, a phenanthrene alkaloid of opium. The usual dose is 2–5 mg IV or 10 mg IM, repeated in 4 h as needed.

Fentanyl (Sublimaze®) is a synthetic opioid, highly lipid-soluble, and protein bound with no active metabolites. Its use for obstetric analgesia has increased because of its rapid onset and short duration of action. The analgesic potency is 100 times that of morphine and 800 times that of meperidine. The usual intravenous bolus dose of fentanyl is 50–100 µg. This dose may be repeated every hour as needed. Cumulative doses up to 600 µg given over the course of labor have not had deleterious effect on the incidence of respiratory depression,

neonatal vital signs, or Neurological and Adaptive Capacity Scores at 2–4 h and 24 h after delivery. Compared with equianalgesic doses of meperidine, fentanyl causes fewer maternal side-effects and fetal depression. Fentanyl has also been successfully used as intravenous patient-controlled analgesia (PCA) when epidural analgesia was contraindicated.

Butorphanol tartrate (Stadol®) and nalbuphine hydrochloride (Nubain®) are synthetic partial opiate agonists with opiate antagonistic effects. Neither should be used in opiate-tolerant individuals without prior detoxification. Probably, neither should be used in patients who have received opioids during the same labor. For labor, therapeutic doses of butorphanol are 1–2 mg IV or IM, maximum of 4 mg/dose, repeated in 4 h, as necessary. The manufacturer prefers alternative analgesia if delivery is anticipated within 4 h. Therapeutic doses of nalbuphine are 5–20 mg IV or IM (usually 10 mg, rarely up to a maximum of 20 mg), repeated in 3–6 h, as necessary. The maximum daily dosage is 160 mg.

REGIONAL ANALGESIA

The ideal labor analgesic techniques should provide pain relief with minimal maternal–fetal side-effects and low maternal–fetal drug exposure. The techniques should not cause lower extremity motor weakness, therefore allowing the parturient to ambulate and should not interfere with progress or course of labor. In addition, the best techniques should be sufficiently flexible to produce anesthesia for operative deliveries if necessary.

Epidural and combined spinal–epidural (CSE) analgesia as delivered today offers the parturient the most effective methods of pain relief while fulfilling many of these criteria. The effect of epidural and CSE on labor outcome has been the subject of many clinical investigations. Many confounding variables affect both the progress of labor and request for labor analgesia. Maternal, fetal, and obstetric factors may have a greater impact on progress and outcome of labor than does the epidural or CSE. However, anesthetic management can have a significant effect if more concentrated local anesthetic solutions are employed. The Comparative Obstetric Mobile Epidural Trial Group (COMET) in the UK published a randomized controlled study in 2001 showing that the use of dilute epidural infusion technique (0.1% bupivacaine and fentanyl 2 µg/mL) or CSE (with 2.5 mg bupivacaine and 25 µg fentanyl) significantly increased spontaneous delivery rate, thereby improving obstetric outcome. In 2005, Wong *et al.*, reported the results of a large randomized controlled trial using intrathecal administration of an opioid as part of CSE technique early in labor (cervical dilation <4 cm). Early and late regional analgesia recipients did not differ in their rates of cesarean and instrumental vaginal delivery. Early recipients enjoyed shorter labor, lower pain scores and fewer Apgar Scores (<7 at 1 minute). Given the benefit to obstetric outcome of dilute epidural infusion techniques and CSE, it would seem most appropriate to avoid intermittent bolus

techniques of more concentrated local anesthetics. It is with this background that we will focus on current regional analgesic techniques for labor.

Local analgesic medications

Bupivacaine (Marcaine®), a long-acting amino-amide local anesthetic, is the most commonly used local anesthetic for labor analgesia. Its popularity is based on its physiochemical properties of better preservation of motor function than lidocaine in low concentrations, its absence of tachyphylaxis in prolonged use, and its low cost. Epidural bupivacaine readily crosses the placenta but has no adverse neonatal effects in this setting. With doses of bupivacaine clinically used, the risk of systemic toxicity (central nervous system, cardiovascular system) is very low.

Ropivacaine (Naropin®) is a new amide local anesthetic structurally similar to bupivacaine with the same lipid solubility, pKa, and protein binding. In contrast to bupivacaine, which is prepared as a racemic mixture, ropivacaine is prepared as the pure L-isomer form. This change in chemical structure accounts for ropivacaine having lower cardiotoxic effects in cases of systemic toxicity than bupivacaine. Another purported advantage of ropivacaine is reduced motor blockade for a given degree of sensory block when compared with bupivacaine. When used in dilute concentrations for labor analgesia and adjusting for potency differences between the two local anesthetics, ropivacaine probably offers little or no motor-sparing advantages over bupivacaine. The large differences in cost (ropivacaine is much more expensive), along with the adoption of safer anesthetic practices and the use of dilute bupivacaine, have limited the acceptance of ropivacaine for widespread use in labor.

Levobupivacaine (Chirocaine®) is a new amide local anesthetic virtually identical to racemic bupivacaine in anesthetic potency. Prepared as the pure L-isomer, levobupivacaine is also less cardiotoxic than bupivacaine. The large difference in cost and the safety of dilute bupivacaine for labor have also limited the widespread use of levobupivacaine.

Epidural analgesia

Epidural analgesia offers the parturient the most effective and flexible form of pain relief and is currently the most common method utilized in the USA. By directly blocking the labor pain pathways (T10–L1, S2–S4), epidural provides superior analgesia when compared with parenteral opioids, without causing neonatal depression. The approach to solutions for initial bolus and subsequent infusions has been based on investigations of dose response, efficacy, and side-effects. Today's epidural techniques use a combination of dilute local anesthetic and opioid \pm ultra low dose epinephrine (1:500,000), thereby preserving motor function while minimizing maternal and neonatal side-effects. There are three methods of delivery of epidural analgesia.

Intermittent bolus technique: local anesthetic agents alone

A bolus dose of 10–15 mL 0.125–0.25% bupivacaine provides approximately 90 min of analgesia. Repeat doses are administered as needed.

The bolus dose of ropivacaine required to produce analgesia is 10–15 mL 0.2%.

The bolus dose of levobupivacaine required to produce analgesia is the same as bupivacaine (10–15 mL 0.25%).

Intermittent bolus technique: addition of opioid to local anesthetic

Fentanyl 50–100 µg or 10–15 µg sufentanil added to 10–15 mL 0.125% bupivacaine provides analgesia comparable with 0.25% bupivacaine, with increased maternal satisfaction secondary to reduced motor blockade. The duration of action is 90 min. The same dose of opioid could be added to 10–15 mL ropivacaine (0.075–0.1%) or 0.125% levobupivacaine.

Continuous infusion epidural techniques

Most obstetric anesthesiologists favor the use of continuous infusion epidural (CIE) in contrast to intermittent bolus technique. This approach avoids fluctuation in pain relief, while minimizing side-effects and improving time efficiency on a busy labor unit. Multiple studies have found significant advantages of CIE including less motor block, better ability to make expulsive efforts during second stage labor, fewer hypotensive events, and improved maternal satisfaction.

There are several infusion mixtures that are popular today. Representative mixtures are 0.0625–0.083% bupivacaine with 2 µg/mL fentanyl and 0.045% bupivacaine with 0.4 µg/mL sufentanil and epinephrine 1 in 500,000. Both infusions are maintained at 10–12 mL/h. We first activate the epidural with a 3-mL “test dose” of 0.25% bupivacaine (rule out intrathecal catheter placement), wait 5–8 min, and then bolus with 10–12 mL dilute infusion mixture. We then start the infusion at 10–12 mL/h. Breakthrough pain is treated with 5–8 mL 0.25% bupivacaine. Frequent requests for treatment of breakthrough pain (more than three injections) are associated with cesarean delivery for dystocia. 0.075–0.1% ropivacaine with opioid and epinephrine could be used in the same fashion as bupivacaine.

Patient-controlled epidural analgesia

Patient-controlled epidural analgesia (PCEA) for labor has gained popularity because it allows the parturient to self-medicate and titrate to the desired level of pain relief. With PCEA, patients may use less medication and have fewer anesthetic interventions for breakthrough pain, with outcomes similar to CIE. The ideal background infusion, incremental dose, and lockout remain unspecified. PCEA can be delivered with a low concentration, local anesthetic mixture of 0.0625% bupivacaine and 2 µg/mL fentanyl or 0.1% ropivacaine and

2 µg/mL fentanyl. Initial activation of epidural is the same as with CIE. In the absence of evidence-based infusion recommendations, the following are appropriate: basal infusion rate of 0–6 mL/h, demand dose of 3–5 mL, and a lockout interval of 10 min.

Side-effects and complications

The analgesic exposure risks of CIE and PCEA are reduced compared with a bolus technique because of the reduced drug exposure. If the epidural catheter is placed into or migrates into a blood vessel, the only side-effect seen would be loss of pain relief, not signs of systemic toxicity (seizures or cardiovascular collapse). Replacing the epidural catheter is usually all that is required.

Activation of the epidural with a 3-mL “test dose” of 0.25% bupivacaine and waiting 8–10 min allows the physician early detection of intraspinal injection, and the opportunity to prevent a high subarachnoid block. A solid motor block affecting lower extremity mobility would be evident. Once the continuous infusion is being delivered, onset of progressive motor blockade could be detected early enough to prevent hemodynamic or respiratory compromise from high block.

In approximately 3–6% of cases, inadequate analgesia may result because of the presence of anatomic factors (midline epidural connective tissue or compartments) or transforaminal catheter exit. This results in unequal spread of the analgesic agent. Early recognition and epidural catheter replacement solves the problem.

In comparison with intermittent bolus technique, the incidence of hypotension with CIE and PCEA is lower (less than 3%). Early recognition and treatment with hydration of crystalloid, lateral uterine displacement, and 5–10 mg of intravenous ephedrine quickly returns maternal blood pressure to baseline without compromising the fetus.

The incidence of postdural puncture headache (PDPH) after epidural varies between institutions and with the level of experience of the practitioner, but is usually less than 1%. If dural puncture occurs with the epidural needle, PDPH is likely to occur. Early detection and follow-up are important. Treatment with epidural blood patch is very effective.

Epidural fentanyl and sufentanil can cause truncal pruritus. As opposed to intrathecal opioids, symptoms are milder and treatment is rarely required. Diphenhydramine 25 mg IV or 80–120 µg naloxone IV can be used in severe cases.

Thermoregulatory changes occur with epidural which may result in hyperthermic effects. The incidence of maternal fever increases in nulliparous women with longer epidural use.

Despite the inherent safety of epidural techniques, vigilant staff, patient monitoring, frequent assessment of the epidural block, and a high index of

suspicion are essential for safe administration of labor epidurals. Proper resources and equipment on the labor floor are necessary. Epidural infusion devices should have safety features including adjustment controls that are locked, solution reservoirs that are kept in a lock box, and tubing that does not have an injection port.

Combined spinal–epidural analgesia

Combined spinal–epidural (CSE) analgesia has gained tremendous popularity over the last decade. The combination of epidural and spinal analgesia into one technique provides rapid pain relief with the additional flexibility of continuous infusions using an epidural catheter. In contrast to epidural, pain control upon injection of intrathecal opioids combined with local anesthetic is instant. There are specific patients who may benefit most from this technique: patients in early labor (less than 3–4 cm), patients who want to ambulate, and patients in the late stages of labor. The major advantage of CSE for patients in late labor is that they can be pain free and yet push effectively. Additionally, intrathecal opioids for labor are ideal for the parturient whose medical condition is such that it would be difficult for her to tolerate a sympathetic block (e.g. pulmonary hypertension, cyanotic heart disease, severe aortic stenosis).

Intrathecal medications

Morphine (Duramorph®) is a lipid-insoluble opioid with a long latency time (30–60 min) and long duration of action (140–240 min). A high incidence of side-effects, which extend into the postpartum period, has limited the use of intrathecal morphine in clinical practice. If morphine is used, 0.2–0.3 mg is the usual dose. The addition of a lipid-soluble opioid (fentanyl, sufentanil) speeds onset time to 5 min. Morphine alone is ineffective in providing adequate pain relief in advanced labor.

Meperidine (Demerol®) has opioid and local anesthetic properties. It is therefore more effective as a single agent in later stages of labor. The usual dose of meperidine is 10–15 mg. The duration of action is 120–160 min. A high incidence of nausea, vomiting, and hypotension has limited its use to patients who have local anesthetic allergy.

Fentanyl (Sublimaze®) is a synthetic, lipid-soluble, rapid-acting opioid frequently used for CSE. Fentanyl 25 µg provides 80–95 min of analgesia. The addition of a small dose of local anesthetic (2.5 mg bupivacaine) prolongs the effect of fentanyl, providing improved analgesia in advanced labor without increasing side-effects. Neonatal plasma fentanyl levels with clinical doses used for CSE are very low and have no observable effects on the fetus.

Bupivacaine (Marcaine®) is frequently used as an adjuvant agent with an opioid. The usual dose is 2.5 mg (1 mL 0.25%). The profound motor block it causes with frequent dosing limits its use as single agent.

Once the intrathecal medication has been administered, an epidural infusion is started using a dilute local anesthetic–opioid mixture. Bupivacaine 0.04–0.1% can be used with 2 µg/mL fentanyl or 0.4 µg/mL sufentanil, at 10 mL/h. This approach assures continuous analgesia with minimal side-effects.

Side-effects and complications

The side-effects of CSE technique are similar to those encountered with standard epidural analgesia but with varying incidence. They include pruritus, nausea, vomiting, hypotension, respiratory depression, urinary retention, fetal heart rate abnormalities, and PDPH.

Pruritus is the most common side-effect, with reported incidence much higher than with epidural (80%). Symptoms are usually mild, with few patients requiring treatment. Intrathecal morphine is associated with a much greater incidence of severe sustained pruritus than are fentanyl and sufentanil. Treatment is with 25 mg diphenhydramine IV or 80–120 µg naloxone IV.

Meperidine has a 25% incidence of nausea and vomiting. Fentanyl and sufentanil have a very low incidence (2–3%). Treatment with 5–10 mg metoclopramide IV, 4 mg ondansetron IV, or 80–120 µg naloxone IV is usually effective.

The incidence of hypotension with CSE is 5–10%, which is comparable with standard epidural analgesia. The difference between the two techniques is in the onset of hypotension. With CSE, hypotension occurs within 5 min of injection whereas with standard epidural with a long-acting agent, hypotension first presents in 20 min. The hemodynamic changes with CSE are mediated by opioid-induced preganglionic sympathetic block within the spinal cord, attenuation of spinally mediated pressor response, and fall in circulating catecholamines secondary to profound pain relief. Treatment of hypotension consists of maternal positioning, IV hydration with crystalloid, and ephedrine bolus.

Although rare, respiratory depression can occur with both lipid-soluble opioids (fentanyl, sufentanil) and lipid-insoluble opioids (morphine). In the case of fentanyl or sufentanil, respiratory depression would be seen in the first 20 min, reflecting rapid redistribution from the cerebrospinal fluid (CSF). Morphine causes a delayed respiratory depression secondary to rostral spread and would be seen 6–9 h after injection. Patients with prior opioid exposure, morbidly obese patients, and patients with preeclampsia on magnesium warrant caution when considering CSE technique. Monitoring of sedation scale, respiration, and oxygenation with pulse oximetry are recommended. Treatment consists of 0.2–0.4 mg naloxone IV. This dose may need to be repeated if a long-acting opioid was used (morphine, meperidine).

Use of a small-bore pencil-tipped spinal needle has reduced the risk of PDPH with CSE to 1%. This risk is comparable with standard epidural technique. If PDPH occurs, treatment with epidural blood patch is very effective.

Fetal bradycardia with CSE technique has a reported incidence of 3–20%. Several investigators have found similar incidence with standard epidural analgesia (intermittent bolus technique). The incidence of emergency cesarean delivery for fetal heart rate pattern abnormalities did not differ when comparing CSE with epidural analgesia. The mechanism of fetal bradycardia with CSE is different from standard epidural. With CSE, sudden catecholamine changes result in increased uterine tone that in turn decreases uteroplacental blood flow. Treatment with uterine displacement, discontinuation of oxytocin, and the use of pharmacologic means of relaxing the uterus (200–400 µg nitroglycerin IV or 0.25 mg terbutaline subcutaneously) are usually effective.

Rarely, distressing symptoms such as transient facial numbness, dyspnea, or dysphagia have been observed with sufentanil. The symptoms are attributed to cephalad spread of lipophilic opioids within the CSF. Symptoms do not usually result in clinically significant compromise in ventilation and usually resolve within 60 min. Treatment if necessary consists of improving oxygenation and ventilation.

SEDATION

In some cases of dysfunctional early labor or prelabor, sedation (or therapeutic rest) may be appropriate. Common medications for this purpose include 100–200 mg pentobarbital sodium (Nembutal®) orally or IM or secobarbital sodium (Seconal®). Because there is no effective antidote for the neonate, many prefer to use 100 mg meperidine IM or 10 mg morphine sulfate IM, especially if the patient is not at term and will remain under hospital supervision until the effect of the narcotic wears off.

ANTACID

Protection of the parturient from aspiration pneumonitis may include the use of 30 mL 0.3 M sodium citrate with citric acid (Bicitra®) before anticipated cesarean delivery. If more than 1 h has elapsed since the last dose of citric acid, she should receive another dose before induction of anesthesia.

Metoclopramide (Reglan®) is a dopamine antagonist that is structurally similar to procainamide. It is often used to treat maternal nausea and vomiting and to decrease gastric emptying time before surgery. Although placental transfer of metoclopramide occurs rapidly, adverse fetal effects with single doses have not been observed. Common dosing is 5–10 mg IV.

HYPERTENSION

Severe hypertension is persistent systolic pressure exceeding 180 mmHg, diastolic pressure exceeding 110 mmHg, or mean arterial pressure exceeding 130 mmHg. This degree of hypertension requires judicious treatment to protect the parturient from complications of acute severe hypertension, while at the

same time protecting the fetus from interruption of intervillous space blood flow caused by inadequate maternal blood pressure. Hydralazine hydrochloride (Apresoline®) is a direct vasodilator that lowers mean arterial pressure and systemic vascular resistance, and increases cardiac output and heart rate without affecting pulmonary capillary wedge pressure. It has been the preferred medication for management of acute severe hypertension in obstetrics for many years. Appropriate dosing is a 5- to 10-mg IV bolus repeated each 15–20 min until the diastolic pressure is between 90 and 100 mmHg.

Recently, labetalol hydrochloride (Normodyne®, Trandate®), a combined β and α adrenergic blocking agent, has become popular. Appropriate dosing is via IV bolus of 20, 40, 80, 80, 80 mg, at intervals of 10 min, as necessary (maximum 300 mg) to achieve the desired therapeutic effect. If the need for repeated boluses is prolonged, an alternative to continued bolus therapy is continuous IV infusion at 0.5–4 mg/min. In some patients it will not be possible to control blood pressure adequately and maintain the maternal pulse above 60 b/min on continuous IV infusion. Supplementing with occasional small boluses of hydralazine will likely result in satisfactory maintenance of both blood pressure and heart rate.

Another alternative to hydralazine is 10–20 mg of the oral calcium-channel blocker nifedipine (Adalat®, Procardia®). Dosing can be repeated in 20–30 min as necessary. The extended release form of nifedipine is not appropriate for this use. There is a significant sentiment that labetalol and/or nifedipine might be preferred over hydralazine. A recent meta-analysis calculated that hydralazine was associated with more maternal hypotension, more cesarean deliveries, more placental abruption, more maternal oliguria, more adverse effects on fetal heart rate, and more low Apgar scores at 1 min. The authors concluded that their results were not powerful enough to guide clinical practice, but their results demand attention.

Nicardipine (Cardene®) is a calcium-channel blocking agent with less negative inotropic effect than nifedipine and with more selective action on peripheral vasculature. It can be delivered by continuous IV infusion or bolus. Therapy is initiated at 5 mg/h IV (50 mL/h). If the desired result is not achieved, the infusion rate is increased by 2.5 mg/h every 5–15 min to a maximum of 15 mg/h. At goal blood pressure, the infusion is decreased to 3 mg/h. Side-effects include tachycardia and headache. Administration of either nicardipine or nifedipine with magnesium can cause severe hypotension, myocardial depression, and potentiation of neuromuscular blocking effects of magnesium.

Magnesium sulfate, as used in obstetrics is $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ USP. For arrest and prevention of eclamptic seizures, the recommended dose is IV loading of 4–6 g in 100 mL IV fluid administered over 15–20 min, followed by 2 g/h. Patients with high urine output might require more than 2 g/h to maintain therapeutic serum levels of 4–7 mEq/L (4.8–8.4 mg/dL or 2–3.5 mmol/L).

MgSO₄ · 7H₂O USP is available in a premixed 4% solution (40 g/L) intended for loading and continuous IV therapy. It is also available in 10-mL ampules of 50% solution (5 g/10 mL). Adding eight of these ampules to the commercially prepared 4% solution doubles the concentration when necessary to avoid volume overload. For recurrent seizures more than 20 min after completion of the initial IV bolus, an additional bolus of 2 g in 10 mL (20% solution) once for a small woman and perhaps twice for a larger woman will almost always prevent further seizures. In rare circumstances of continued seizures or excessive post seizure agitation, it might be necessary to administer sodium thiopental via slow IV push in a 2.5% solution of 75–250 mg over up to 10 min, or sodium amobarbital slowly IV up to 250 mg. To protect the airway, these patients are best managed with endotracheal intubation and positive pressure ventilation. Magnesium toxicity responds readily to 1 g calcium gluconate IV and discontinuation of the magnesium infusion. It might be necessary to repeat the calcium gluconate infusion. For significant respiratory depression, assisted ventilation may be necessary.

LABOR INDUCTION AND AUGMENTATION

Induction of labor may require preparation of an unripe cervix via prelabor ripening with prostaglandin E₂. There are two approved products containing dinoprostone, the naturally occurring form of prostaglandin E₂: Prepidil® and Cervidil®. Prepidil® is packaged with two cervical inserters to facilitate retention within the cervical canal, without instillation into the intrauterine extramembranous space. Prepidil® must be warmed naturally to room temperature before use. After administration, the patient should remain in the supine position for 15–30 min to minimize leaking. During use, uterine activity, fetal status, and character of the cervix should be monitored to detect untoward response. The dose can be repeated in 6 h as necessary, not exceeding three doses in 24 h. The recommended interval for administration of intravenous oxytocin after Prepidil® use is 12 h. There are reports of trials of combined use of Prepidil® and intravenous oxytocin simultaneously. As experience grows, this might become an acceptable clinical practice.

Cervidil® is a thin, flat, polymeric slab contained within a knitted polyester retrieval system that includes a long tape. The device contains 10 mg dinoprostone, released at 0.3 mg/h. Cervidil® is placed transversely in the posterior vaginal fornix immediately after removal from its container. Warming is not necessary. The patient should remain recumbent for 2 h following insertion to facilitate retention. Avoidance of coating the delivery system with lubricant also facilitates optimal release of the agent. Cervidil® is recommended for removal at the onset of active labor, or 12 h after insertion. The manufacturer has confirmed that there is enough agent to continue release of dinoprostone for another 12 h if there is a desire to continue ripening for another 12 h. During use, the patient requires monitoring of uterine activity, fetal status, and

the progression of cervical change. The manufacturer recommends removal of the device prior to amniotomy and if there is uterine hyperstimulation. Cervidil® is not recommended for use simultaneously with oxytocin. Oxytocin may be administered 30–60 min after removal of Cervidil®. There are reports of trials of combined use of Cervidil® and intravenous oxytocin simultaneously. As experience grows, this might become an acceptable clinical practice.

Prostaglandin E₁, misoprostol, is available as Cytotec®, indicated for treatment of peptic ulcer disease. Abundant randomized prospective clinical trials defined that misoprostol is equal to or superior to intracervical or intravaginal dinoprostone for cervical ripening and induction. Although the issue is contentious, use of this agent off label for cervical ripening or induction of labor is within the standard of care as of this writing. The starting dose usually should be one-quarter of a 100- μ g tablet (approximately 25 μ g), administered high in the vagina no more frequently than each 3–6 h. Oxytocin should not be administered less than 4 h after the last misoprostol dose. In some circumstances it might be appropriate to use 50 μ g misoprostol each 6 h. This higher dosing regimen has led to a higher frequency of complications.

Misoprostol should not be used for cervical ripening for women with a history of cesarean delivery or other major uterine incision. The American College of Obstetricians and Gynecologists (ACOG) guidance cautions against the use of any prostaglandin compound for cervical ripening after prior cesarean delivery.

Induction or augmentation of labor with dilute intravenous oxytocin requires caution and diligence to avoid significant fetal or maternal complication. Dilution of 10 units of oxytocin in 1 L of balanced solution results in a concentration of 10 milli Units (mU)/mL. The concentration may be higher (20 mU/mL) if conservation of infusion volume is important (severe preeclampsia). For induction or augmentation, there are proponents for both low-dose and high-dose regimens. Low-dose regimens begin the infusion at 0.5–1 mU/min or at 1–2 mU/min, and increase the infusion by 1-mU/min increments every 30–40 min, and by 2-mU/min increments every 15 min for the other low-dose regimen, to desired contraction effect. High-dose regimens begin at approximately 6 mU/min, with increments of approximately 6 mU/min every 15 min in one scheme, and each 20–40 min in another scheme. If there is hyperstimulation, after resolution, the increments should be 3 mU/min, with a further reduction to 1 mU/min increments for recurrent hyperstimulation. At Parkland Memorial Hospital (University of Texas Southwestern Medical Center, Dallas, TX), oxytocin is restricted from patients with a prior cesarean and a living fetus. There is no such restriction at the University of Alabama at Birmingham, or at the University of Texas at Houston, or in ACOG guidance.

INSULIN

For insulin-requiring diabetics, control of blood glucose between 60 and 110 mg/dL via continuous IV insulin infusion is optimal during labor and delivery. A simple regimen includes a mixture of 25 units recombinant human regular insulin in 250 mL normal saline. The mixture should then be shaken well, and 25 mL should be wasted by running out the IV tubing, to ensure adsorption of insulin by insulin receptor sites on the surfaces of the IV bag and tubing. The insulin mixture is administered by continuous pump at rates of 0.5 units/h or more, with increments of 0.5–1.0 unit/h as necessary to maintain desired glucose levels. While the serum glucose level is below approximately 140 mg/dL, the diabetic parturient should receive D5RL at 125 mL/h to avoid starvation during labor. Labor creates a metabolic demand that requires caloric support. Check her glucose values hourly by finger stick with test strips and automated meter at the bedside. Adjust the insulin infusion hourly and replace the IV D5RL with plain RL as necessary above a serum glucose value of approximately 140 mg/dL. Many early-stage diabetics (no end organ damage or vascular compromise) will require no insulin in labor while contracting and receiving D5RL as recommended.

TOCOLYTICS

As of this writing, tocolysis remains a controversial and contentious issue. It is likely that most patients in the USA subjected to tocolytic therapy are not in preterm labor and/or do not benefit from tocolysis. There are good reasons to question the efficacy of almost all proposed tocolytic regimens. Because efficacy has been difficult to document, it is important to pay careful attention to the possibility of fetal/neonatal and maternal harm.

Parenteral ritodrine, a beta-adrenergic receptor agonist, is the only agent that has been approved for tocolysis in the USA. In the collaborative trial of ritodrine by the Canadian Preterm Labor Investigators Group, ritodrine patients had a statistically lower risk of delivery within 24 h, 48 h and 7 days. The 95% confidence interval (CI) for delivery less than 32 weeks barely crossed zero (difference –9% in favor of ritodrine; 95% CI –18.6–0.2), so the difference was nearly significant at $\alpha = 0.05$. There was no difference in delivery less than 37 weeks, or in perinatal mortality. Because of its side-effect profile and modest efficacy, ritodrine did not enjoy wide popularity, and is no longer marketed in Canada or the USA.

Terbutaline is a beta-adrenergic receptor agonist used to ablate preterm contractions. It can be administered in doses of 0.25 mg subcutaneously each 20–30 min for three or four doses, possibly continuing for longer courses at longer intervals, such as each 3–6 h. Patients who stop contracting probably were not in labor, but they have been saved from the risks of potentially more dangerous interventions. Terbutaline also can be administered via continuous

IV infusion pump, initiating therapy at 2.5–5 µg/min, and increasing by 2.5–5 µg/min at 20–30 min intervals to a maximum of 25 µg/min, or cessation of contractions, or maternal intolerance. There is no evidence that treatment with terbutaline subcutaneously or IV as described, or with oral terbutaline or with continuous subcutaneous terbutaline pump is superior to placebo in preventing preterm delivery.

To demonstrate a reduction in preterm birth for beta-adrenergic receptor agonists as a group has required meta-analyses. Meta-analyses have also shown nearly statistically significant trends in diminution in low birth weight and respiratory distress syndrome, but not a reduction in neonatal mortality. The side-effect profile indicates that extreme caution is warranted with these agents.

Although there appears to be no level I evidence supporting the use of $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ USP over placebo for tocolysis, this is probably the most commonly used tocolytic in the USA at this time. The agent is commonly administered in the same fashion as for arrest and prevention of eclamptic seizures. The presumption is that the same therapeutic levels are important. The maternal side-effect profile for magnesium sulfate is well known and remarkable.

Indomethacin is the only tocolytic that has demonstrated efficacy in reducing preterm birth and delivery under 2500 g when compared with placebo. Regimens used have varied between studies, initiating treatment with 50 or 100 mg orally or rectally (suppositories are no longer available), followed by 25 or 50 mg each 6–8 h. Gestations over 32 weeks are not candidates, and treatment should not extend more than 48 h. The neonatal risks of exposure to indomethacin *in utero* remain controversial.

Calcium-channel blockers have been studied as tocolytics, but have not been compared with placebo. A recent meta-analysis evaluated trials comparing calcium-channel blockers (predominantly nifedipine) with other tocolytics (predominantly beta-agonists). The authors calculated that calcium-channel blockers improved the risk of delivery within 7 days, the risk of delivery before 34 weeks, and the frequencies of neonatal respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and jaundice. Calcium-channel blockers also showed a dramatic reduction in important maternal side-effects. There are many regimens for nifedipine tocolysis, including both capsules and tablets, administered orally or sublingually, whole, or crushed and dissolved in water. One useful regimen is 30 mg orally, followed by 20 mg orally in 90 min. Another regimen uses 10 mg orally every 20 min for a maximum of four doses, followed by 20 mg orally each 4–8 h. The range of daily doses in the evaluated studies ranged from 30 to 160 mg until contractions stopped. In the trials evaluated, nifedipine therapy continued, but there have been no trials to evaluate whether continuation is required after initial success. Nifedipine can be continued using either standard formulation or extended release

formulation. Given the demonstrated superiority of calcium-channel blockers over beta-agonists, it is unlikely that either class of agent will undergo a future large comparison with placebo.

Clinical management of preterm labor with tocolytic agents requires continued attention to the evolving literature. Which tocolytic agent is the “best” is not clear as of this writing. Our sense is that in 2005, expert opinion possibly favors nifedipine, and some advisers would favor indometacin before 32 weeks’ gestation. Some experts still believe that tocolysis is an unproven concept that should only be applied within an experimental protocol.

UTEROTONIC AGENTS

During cesarean delivery, a high dose of oxytocin, 80 units in 500 mL RL, infused over 30 min immediately after delivery of the infant has reduced the need for other uterotonic agents, when compared with a standard oxytocin infusion. A standard oxytocin infusion to maintain adequate uterine contraction after delivery of the placenta is 10 units in 500 mL RL or other satisfactory crystalloid, infused over 30 min, or 20 units in 1000 mL, infused at a rate of 10 mL/min.

Methylergonovine maleate (Methergine®) can be administered as 0.2 mg IM once, and can be repeated each 2–4 h, to a maximum of five doses. Some references include IV administration as an option, but others caution against it because of the possibility of severe complications, so it would be wise to avoid IV administration. Hypertension and pre-eclampsia are relatively strong contraindications, with the possibility of severe complications.

Carboprost tromethamine is the tromethamine salt of 15 methyl prostaglandin $F_{2\alpha}$ (Hemabate®). A single 0.25 mg (250 μ g) 1 mL ampule is administered deep IM, and repeated each 15–90 min as necessary, to a maximum of eight doses (2 mg). In clinical trials, 73% of cases responded to a single injection. Typical prostaglandin side-effects include diarrhea, hypertension, emesis, fever, flushing, tachycardia, and arterial oxygen desaturation.

Other uses of ecboolic agents that have been recommended by authors, but not compared in trials include placement of a 20-mg prostaglandin E_2 suppository in the rectum or in the lower uterine segment, or 1000 μ g misoprostol placed in the rectum.

MID-TRIMESTER PREGNANCY TERMINATION

Dinoprostone vaginal suppositories (Prostin E_2 ®), 20 mg, are indicated for termination of pregnancy from 12th through the 20th menstrual weeks, and for uterine evacuation after missed abortion or fetal demise up to 28 menstrual weeks’ gestation. The suppository is inserted high in the posterior vagina, with the patient remaining supine for 10 min after insertion. The product should remain frozen at -20°C (-4°F) until immediately before use, when it should be

brought to room temperature. The dose is repeated each 3–5 h, depending upon clinical response. Because of common side-effects, patients often are pretreated with antipyretic, antiemetic, and antidiarrhea medications. Uterine rupture has been reported in association with Prostin E₂® used in this fashion after prior cesarean.

The prostaglandin E₁ analogue misoprostol (Cytotec®) is not approved for this indication, but there is a large body of literature supporting its use. Many regimens have been used, with high efficacy. Medical uterine evacuation is easier with more advanced gestation and with greater interval after fetal demise. Successful doses of misoprostol have ranged from 200 to 600 µg vaginally each 12 h, or 400 µg vaginally each 3 h. Uterine evacuation is more successful if preceded by 200 mg mifepristone orally, 36–48 h prior to administration of misoprostol. Success ranged from 90% for mifepristone followed by 200 µg vaginal misoprostol every 3 h to 97% for mifepristone followed by 800 µg vaginal misoprostol, then 400 µg orally every 3 h for a maximum of four doses. Uterine rupture has been reported in association with misoprostol used in this fashion after prior cesarean, and in a patient without known uterine scar.

Concentrated oxytocin infusion can be used for uterine evacuation between 16 and 24 weeks' gestation. Patients with the cervix dilated less than 1 cm receive as many intracervical hygroscopic dilators (Dilapan®) as will fit comfortably. They then receive half of a 20-mg Prostin E₂® vaginal suppository every 6 h. Concomitantly they receive an infusion of high-dose oxytocin in 500 mL D5NS over 3 h, followed by 1-h rest on D5NS infusion containing no oxytocin. The high-dose oxytocin regimen increases in each successive 3-h infusion period, beginning with 50 units in the first 500 mL bag, and ending with 300 units in the final, or sixth 500 mL bag. This is a 24-h regimen. In a randomized comparison, this regimen was more successful than using Prostin E₂® vaginal suppositories every 4 h.

None of the regimens above has a 100% success rate. If the first regimen chosen does not succeed after 24 h, it probably is wise to reassess the clinical situation and change to an alternate method.

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Intrapartum fetal heart rate monitoring

Roger K. Freeman

RATIONALE FOR INTRAPARTUM FETAL HEART RATE MONITORING

Intrapartum fetal heart rate (FHR) monitoring was developed in the mid-1960s after patterns of heart rate change in relation to uterine contractions had been described by Hon, Caldero-Barcia and Hammacher.^{1,2,3} At the time of FHR monitoring development it was believed that most cases of congenital neurologic abnormalities were caused by fetal hypoxia proximate to birth. When the method was first developed, there were numerous non-randomized studies comparing electronically monitored patients with either historic controls or with low-risk patients who were monitored by auscultation, which was not rigorous. It was clear early on that the intrapartum fetal death rate was significantly less in electronically monitored patients than in the non-randomized controls, even if the controls were low risk and the electronically monitored patients were high risk. In the mid-1970s, Haverkamp *et al.*⁴ carried out the first prospectively randomized controlled study where the study group was openly electronically monitored and the control group had the electronic fetal monitor covered up so the caregivers could not use the information in patient management. The control group was monitored by auscultation with a rigorous protocol of listening every 15 min in the first stage of labor and every 5 min in the second stage by a dedicated nurse assigned to each patient. The results of this study and of several more randomized prospective trials revealed no benefit to electronic fetal heart rate monitoring during the intrapartum period when compared with intensive auscultation.⁵ Several of the studies also found higher cesarean section rates in the electronically monitored group. The only statistically significant benefit was shown in the large Dublin trial where the electronically monitored patients had neonates with fewer seizures, but on follow-up the incidence of cerebral palsy was not different between the electronically monitored patients and those with intensive auscultation.⁶

In retrospect, it has been pointed out that even with the introduction of electronic fetal monitoring in the majority of laboring patients, there has been no

reduction in the incidence of cerebral palsy.⁷ This finding has indicated to some that the technique has no benefit. However, if we accept the reduction in term intrapartum deaths in electronically monitored patients compared with those with non-intensive auscultation from the original non-randomized trials,⁸ and also compare the marked increase in perinatal survival over the past 30 years, we must conclude that some fetuses that used to die intrapartum now survive damaged and some that used to survive damaged now survive intact. Thus, electronic intrapartum fetal monitoring has probably been of some value. Nevertheless, it is clear that the vast majority of non-reassuring patterns do not result in neurologic damage and to the epidemiologist this high false-positive rate makes the technique invalid.⁹ However, if the technique was perfect, intervention based on the fetal monitor pattern would prevent all cases of cerebral palsy resulting from intrapartum hypoxia and there would be zero correlation with neurologic outcome, rendering the technique not predictive of future outcome, which is the standard used by epidemiologists.

PATTERN INTERPRETATION

Five periodic fetal heart rate patterns have been described.¹⁰

- 1 FHR acceleration with an amplitude of 15 b/min and a duration of 15 s from onset to offset is seen in most patients beyond 32 weeks' gestation and signifies good fetal oxygenation and an umbilical arterial pH of ≥ 7.20 . If accelerations are not present spontaneously, one can evoke FHR accelerations with fetal scalp stimulation after membrane rupture or with vibroacoustic stimulation before membrane rupture. This technique can be useful when following a problematic FHR pattern where spontaneous or evoked accelerations may allow one to avoid intervention.¹¹
- 2 Early deceleration is a uniform pattern with slow onset and offset that is a mirror image of the contraction. This is believed to be caused by fetal head compression and is mediated as a vagal reflex. It is not associated with fetal hypoxia or acid-base change and requires no intervention.
- 3 Variable deceleration is a pattern characterized by rapid onset and rapid offset and usually has an amplitude of 30–40 b/min or more. It is believed to be caused by umbilical cord compression giving rise to a vagal response. Unless the deceleration is prolonged beyond 40–60 s on a repetitive basis, is associated with a rising baseline rate or decreased FHR variability, or the return to baseline is prolonged, it is considered reassuring and does not require intervention. However, if cord compression is sufficient to produce more than transient fetal hypoxia, the findings of tachycardia, decreased variability, and/or slow return to baseline indicate that hypoxia may be more than transient and intervention may be indicated.
- 4 Late deceleration is characterized as a uniform decrease in FHR beginning after the peak of a contraction of normal duration and with a return to

baseline after the contraction is over. The onset and offset are gradual. It is believed to be caused by decreased oxygen transfer across the placenta which may be a result of decreased uteroplacental blood flow or maternal hypoxemia. Initially, late deceleration is usually associated with average FHR variability and is believed to be caused by a vagal reflex but as hypoxia increases, and the fetus develops metabolic acidosis, the variability decreases and at this point the mechanism for the late deceleration is believed to be brought about by myocardial depression.

- 5 Prolonged deceleration usually lasts more than 2 min and its onset may be similar to a late deceleration or a variable deceleration. This pattern is usually seen with a sentinel event such as a prolapsed cord, ruptured uterus, or sudden complete abruption.

MANAGEMENT OF PATIENTS WITH NON-REASSURING FHR PATTERNS

Fetal heart rate monitoring is very sensitive and if there is normal variability with a normal baseline rate associated with FHR accelerations and no decelerations, one can be reassured that there is no significant hypoxia in the fetus and no intervention is indicated. Persistent late deceleration with decreased variability, persistent severe variable deceleration with decreased variability, or prolonged decelerations with decreased variability have been designated by the NICHD study group as patterns consistent with hypoxia sufficient to result in neurologic damage in some infants.¹² These patterns indicate rapid intervention in an attempt to “rescue” the hypoxic fetus. Unfortunately, non-reassuring patterns that fall between the completely reassuring and the three patterns described by the NICHD as being consistent with severe hypoxia have very poor correlation with outcome and it is more difficult to interpret and manage patients with these patterns. For this reason it is recommended that when such a pattern is encountered, it is advisable to use an ancillary method to evaluate the fetus. Methods that may allow one to avoid intervention safely with these non-reassuring patterns include fetal scalp or vibroacoustic stimulation, fetal scalp blood pH sampling, or fetal pulse oximetry.

FETAL INFLAMMATORY RESPONSE TO MATERNAL CHORIOAMNIONITIS

Recent reports have indicated that fetal inflammatory response to maternal infection may result in the elaboration of proinflammatory cytokines that may be responsible for damage in the periventricular areas of the premature fetal brain resulting in spastic diplegia. In term infants this fetal inflammatory response may result in damage to the same cortical and subcortical watershed areas of the motor cortex that are affected by prolonged intermittent hypoxia resulting in spastic quadriplegia. Fetal heart rate patterns have not been

described in these situations but in this author's anecdotal experience there are commonly findings of tachycardia with decreased variability, usually in association with maternal fever, and inconsistent deceleration patterns may be present. While antibiotics are advisable when maternal chorioamnionitis is suspected, there have been no strategies that have proven effective in preventing neurologic damage resulting from the fetal inflammatory response.^{13,14}

MEDICOLEGAL IMPLICATIONS OF INTRAPARTUM FHR MONITORING

While there may be disagreement on the overall value of intrapartum FHR monitoring, in the courtroom the fetal monitor strip is usually the main focus when a lawsuit alleges negligence in cases of cerebral palsy believed to be caused by intrapartum fetal asphyxia. Thus, there are important considerations for the obstetrician when there is concern at the time of birth about the neonatal condition. The determination of a cord arterial pH of greater than 7.0 indicates that fetal hypoxia proximate to birth cannot be implicated as a cause of later neurologic damage. The presence of chorioamnionitis and funisitis may indicate that later neurologic damage could be caused by a fetal inflammatory response to maternal infection. Thus, when delivery of a depressed infant occurs or when fetal heart rate patterns have been of concern, it is often helpful to obtain fetal cord arterial blood gases and to save the placenta in order to determine later the likely cause of any neurologic developmental problems.

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Abnormal labor

Alan Peaceman

INTRODUCTION

Dystocia, from the Greek meaning difficult or abnormal labor, is the term given to laboring patients whose progress in labor stalls prior to delivery. Some practitioners use this term for all patients delivered by cesarean section for inadequate progress in labor. Dystocia is the leading indication listed for cesarean delivery in nulliparous patients, and accounts for approximately one-third of all cesarean sections performed. Conversely, dystocia is very uncommon among multiparous patients, occurring in less than 2% of women with prior vaginal deliveries. The frequency of cesarean section for dystocia has risen dramatically over the past three decades, occurring in less than 2% of labors in 1970 and 8–10% of labors currently. This increased frequency is a major reason for the rise in the primary cesarean section rate in this country, which has also fueled the rise in repeat cesareans being performed. The diagnosis of dystocia is described by a number of other conditions, including failed induction of labor, active phase arrest of dilation, and second stage arrest of descent, but these terms relate more to the timing of the diagnosis rather than the cause. Rates of dystocia vary markedly between practitioners, hospitals, states, regions of the country, and countries, which is likely to be more a result of differences in labor management strategies rather than differences in patient characteristics. Success in decreasing the incidence of dystocia among nulliparous patients would have a major impact on the overall rate of cesarean birth.

DEFINITION

Part of the reason for variation in rates of cesarean delivery for dystocia is because the definition of dystocia is not established. No discreet endpoint exists in the latent phase to describe the length of time when vaginal delivery is no longer accomplishable, and agreement does not exist regarding the length of time for active phase arrest before intervention is appropriate. For nulliparous patients, Friedman¹ described the upper limit of normal for the length of the latent phase as 20 h, and the lower limit of normal for rate of cervical dilation

in the active phase as 1.2 cm/h. These figures were derived from analysis of 500 patients more than 50 years ago, with a cesarean section rate of 1.8%, and a forceps rate of 51%. Further, management of labor, including use of oxytocin and regional anesthesia, are much different today.

A number of investigators have questioned the applicability of Friedman's findings in today's labor units. In 2002, Zhang *et al.*² found a markedly different labor curve, with labors being much slower today. They found that rates of dilation less than 1 cm/h were not uncommon among women delivering vaginally, and many patients without any dilation noted for 2 or more hours still delivered vaginally. The recommendation that 2 h of arrest in the active phase may be sufficient for a diagnosis of dystocia has also been challenged. Among nulliparous women with active phase arrest for 2 h, Rouse *et al.*³ found that 74% of patients still delivered vaginally if oxytocin was continued for at least another 2 h. In our labor unit, we found that nulliparous women had an average rate of dilation in the active phase of 1.7 cm/h, with the lower 5th percentile being 0.7 cm/h. Further, 39% of patients delivering vaginally had a rate of dilation less than 1.2 cm/h, the lower limit of normal described by Friedman.

CAUSES OF DYSTOCIA

The main causes of dystocia are listed in Table 82.1. Inefficient uterine action is the most common cause, and it is composed of a number of clinical situations. Induction of labor has been associated with a twofold increase in the rate of cesarean section, and some increased risk persists even after the patient reaches 4 cm dilation. This risk is even higher among patients starting induction with an unfavorable cervix, and cervical ripening does not necessarily lower this risk. For patients undergoing induction of labor and those who present in spontaneous labor, some cases of dystocia could be avoided with increased or longer uterine stimulation with oxytocin. While most patients who

Table 82.1 Causes of dystocia.

<i>Inefficient uterine action</i>
Induction
Inadequate stimulation of contractions
Failure of uterine response to stimulation
<i>Malposition</i>
Occiput posterior
Asynclitism
Inadequate cephalic flexion
<i>Cephalopelvic disproportion</i>

deliver vaginally have at least 200 Montevideo units as measured by intrauterine pressure catheter, individual patients may progress only with more stimulation. In other situations, more frequent or more intense contractions cannot be attained, often because of intrauterine infection or fetal intolerance to labor as perceived by interpretation of the fetal heart rate monitor, and dystocia is the result.

Malposition of the cephalic presentation is also a significant factor that can lead to dystocia, especially in the second stage. Arrest of descent occurs less frequently if the largest diameter of the fetal head is aligned with the largest diameter of the maternal pelvis. This is not necessarily a recurring issue in future pregnancies, and may explain why many patients with arrest of descent can have a subsequent successful trial of labor with a similarly sized fetus. Some studies have associated an increased frequency of malposition with epidural anesthesia, but more recent studies with more dilute concentrations of local anesthetic, with or without narcotic, have challenged this association.

Cephalopelvic disproportion (CPD) is a commonly used reason given for dystocia. Risk factors include both large fetal size and small maternal pelvic size. However, there are no established criteria for this diagnosis, and it is often made based on the lack of progress in the presence of regular uterine contractions without regard to position of the occiput. X-ray pelvimetry has not been found to be helpful in clarifying the diagnosis. In the absence of a contracted pelvis, such as seen with android pelvic architecture or pelvic deformity, the diagnosis of CPD is uncertain, and dystocia could be more a function of fetal position or uterine action.

Complications associated with dystocia can occur and should be anticipated. Prolonged labors have higher rates of intrauterine infection, and are associated with an increased risk of uterine atony after delivery. On rare occasions, obstructed labor can lead to a constriction ring in the uterus, or rupture of the uterus. Compression of the sigmoid colon during prolonged obstructed labor is still a cause of rectovaginal fistula formation in underdeveloped regions of the world. Of more relevance to developed nations, the rising rate of cesarean delivery for a diagnosis of dystocia has led to an increased number of pregnancies occurring among patients with a prior abdominal delivery. This in turn has led to the increase in complications seen with vaginal birth after cesarean section (VBAC), as well as major hemorrhage associated with placenta accreta.

MANAGEMENT

Principles for labor management in an effort to reduce or manage dystocia include the following:

- 1 Induction increases the risk of dystocia over spontaneous labor. Elective induction should be undertaken with caution in the nulliparous patient, especially with an unfavorable cervix.

- 2 Interventions to stimulate contractions with prolonged latent labor are often unsuccessful. When a patient in the latent phase has amniotomy and labor stimulation, the labor frequently is similar to induced labor. Another option is maternal sedation if exhaustion is present.
- 3 Amniotomy can stimulate contractions, and should be performed prior to a diagnosis of dystocia.
- 4 Uterine rupture is a rare event in nulliparous labor. Most mothers and fetuses tolerate labor stimulation with oxytocin without complication.

A suggested technique for managing term nulliparous labor is the active management of labor. Patients are counseled not to present to the hospital unless membranes rupture spontaneously, or contractions are at intervals of 5 min and painful. The diagnosis of labor is more certain if complete cervical effacement or 4 cm dilation is achieved in the presence of regular, painful contractions. At this point, amniotomy is performed, and fetal monitoring initiated. Cervical examinations are performed every 1–2 h, with the expectation being that the rate of dilation be at least 1 cm/h. If this rate of change is not seen, labor augmentation with oxytocin is begun in the absence of a contracted pelvis and non-reassuring fetal status. A dilute solution of oxytocin is administered by an infusion pump, at a rate of 6 mU/min. The rate of infusion is increased by increments of 6 mU/min until a target of 9–10 contractions per 20-min window of time is achieved, to a maximum of 42 mU/min. On occasion, the fetal heart rate tracing is not reassuring at this contraction frequency, and a lower infusion rate may be effective and better tolerated. None the less, numerous studies have demonstrated that this higher rate of infusion is as safe as lower rates, and frequently more effective at achieving vaginal delivery.⁴ Intrauterine pressure catheters are not required if external monitoring of contraction frequency is feasible. The infusion rate is decreased or stopped if a non-reassuring fetal heart rate pattern appears. As long as progress in dilation continues, labor is allowed to continue. However, if at some point no further dilation occurs for 2–4 h, cesarean delivery can be performed. In the second stage of labor, oxytocin is used in a similar fashion for failure of descent. If arrest of descent occurs for more than 1 h with contractions of the target frequency, operative delivery is performed.

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Breech delivery

Martin L. Gimovsky

INTRODUCTION

The management of labor and delivery for the fetus presenting as a breech has long been recognized as a complex clinical challenge. Breech presentation complicates approximately 3–4% of labor and deliveries at term and is even more frequent earlier in gestation.

Perinatal morbidity and mortality are significantly increased in infants born from breech presentation. Moreover, the adverse outcome is primarily attributable to increased rates of congenital anomalies, frequency of premature birth, and labor and delivery related asphyxia and trauma. Frequently, these three major contributors are interrelated. In addition, the subset of problems associated with breech presentation is fundamentally different from the risks seen with breech labor and delivery.

DIAGNOSIS

Early diagnosis of breech presentation increases the options available for management. Because breech presentation has a tendency to recur, the past obstetric history is a logical starting point. Women with multiple leiomyomas, previous uterine surgery, and grand multiparity are more likely to have breech-presenting fetuses in the third trimester. During prenatal care, assessment of fetal lie should be performed routinely after 36 weeks. Clinical suspicion and Leopold maneuvers, liberally supplemented with ultrasound, are commonly used in making the diagnosis. When a fetus is confirmed to be in breech presentation after 36 weeks' gestation, we recommend the following approach.

MANAGEMENT

Discussion with the patient and her family about the inherent problems seen in association with breech labor and delivery. Although an 18–20 level II ultrasound will exclude most anomalies, bedside scan at the time of presentation to

labor and delivery is warranted to estimate fetal weight, the attitude of the fetal cervical spine, and placental location. A biophysical profile and careful determination of the amniotic fluid index should also be obtained. This same evaluation should be performed regardless of whether the patient is for a trial of labor or a cesarean section.

With appropriate consent, we proceed with external cephalic version when a breech fetus is diagnosed after 36 weeks. A beta-mimetic agent is used routinely. A prior cesarean section is not considered a contraindication to an attempt at version. If version is successful, we perform fetal surveillance twice weekly until labor ensues.

If version is unsuccessful, contraindicated, or not acceptable to the patient, we discuss with the patient a potential trial of labor by protocol, and by cesarean section. The vast majority of patients and physicians will opt for cesarean section, particularly if the diagnosis of malpresentation is made before the onset of labor. ACOG Committee Opinion 265 cites the Term Breech Trial (Hannah *et al.* 2000) in support of this common practice. Controversy exists regarding the management of a patient presenting in advanced labor with breech presentation. Additionally, when a second twin presents as breech, one option includes vaginal breech delivery by breech extraction or by assisted breech delivery.

When the specific circumstances of an individual patient allow for a trial of labor, we recommend the following guidelines. A selective trial of labor may be chosen on a case-by-case basis, provided:

- 1 The estimated gestational age of the fetus is 37–42 weeks
- 2 The fetus is estimated to weigh 2000–3500 g at the onset of labor
- 3 The fetus is in the frank or complete breech presentation
- 4 Computed tomographic (CT) pelvimetry and/or bedside ultrasound confirms that the fetal head is not hyperextended and that the arms are flexed upon the fetal chest in addition to excluding women with a borderline or small pelvis. If CT is performed, the following criteria are useful in excluding a borderline bony pelvis:
 - Anteroposterior (AP) diameter at the pelvic inlet is more than 11 cm
 - Transverse diameter at the pelvic inlet is more than 12 cm
 - Interspinous diameter at the mid-pelvis is more than 10 cm

During the trial of labor:

- 1 Continuous electronic fetal heart rate monitoring is employed, supplemented by acoustic stimulation or tactile stimulation as indicated to assess fetal acid–base balance when necessary.
- 2 The Friedman curve is carefully followed with hourly evaluation of the progress of labor. Greater than 1.2 cm/h in the nullipara, and greater than 1.5 cm/h in the multipara, are guidelines for the minimal acceptable rates of progression in active labor. Oxytocin is utilized as indicated by uterine activ-

ity. Failure to progress, or any borderline situation, calls for prompt cesarean section.

The second stage of labor is managed in the delivery room or in the operating room as a “double set-up.” Support from anesthesiologists, pediatricians, and the operating room staff rounds out a team of two gowned and gloved obstetricians.

The delivery itself is treated with watchful waiting. The less force employed by the accoucheur, and the greater the reliance on force from the patient, the more likely the fetal body will maintain flexion in the delivery process. This will minimize the risk of traumatic birth. Continuous fetal monitoring in the delivery room, as well as the availability of a portable ultrasound machine, is advisable.

The fetus is encouraged to deliver with the back anterior in so far as possible. A Mauriceau maneuver or one of its variants allows for easy delivery of the aftercoming head. If necessary, forceps are easily applied to the fetal head as a pelvic application. An episiotomy is made after the buttocks have crowned. A cord sample for acid–base analysis is obtained and analyzed as indicated by the need for neonatal resuscitation.

At cesarean section delivery, the same fundamental principles apply. Upon entering the abdominal cavity, the fetus is palpated and the degree of uterine rotation determined. At term delivery, a transverse uterine incision usually suffices. In opening the uterus, great care is taken to avoid fetal laceration. Our approach is to employ Allis clamps to elevate the myometrium away from the fetus. A simple snap is then used to rupture the membranes. The fetal buttocks are positioned at the incision. The primary operator calls for direct fundal pressure to assist the delivery of the body. When the fetal scapula is reached, the shoulders are delivered by rotation and the arms swept downward if necessary. The aftercoming head is also delivered by direct fundal pressure to maintain cranial flexion.

At preterm delivery, the choice of transverse or vertical uterine incisions is determined by individual circumstances upon entry to the abdominal cavity. A vertical or “classic” incision is called for if premature rupture of membranes has occurred, the fetus is less than 30 weeks, or has an estimated fetal weight of less than 1000 g. As with vaginal delivery, undue haste is to be avoided.

CONCLUSIONS

Regardless of the mode of delivery, the breech fetus challenges the clinician to balance the risks of operative delivery (cesarean section) to the mother, with the risks of vaginal delivery to the fetus. In either situation, injury to mother or child is infrequent. It should be noted (and the family fully informed) that on an individual basis, a breech infant may also sustain injury at cesarean section delivery. On occasion, a mother may suffer serious morbidity whether a

cesarean section or a trial of labor is chosen. A balanced approach starting with early recognition during the antepartum period should include consideration of external cephalic version followed by cesarean section for the majority of patients. The protocol recommended above offers an alternative approach to minimize the risks to *both* mother and fetus.

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Vaginal birth after cesarean section

James R. Scott

INTRODUCTION

The cesarean delivery rate in the USA has dramatically risen from 5% in 1970 to more than 30% in some hospitals today. Many believe the current cesarean rate and rising rates in other countries are too high, and vaginal birth after cesarean section (VBAC) has long been promoted as one way to lower them. Despite more than 1000 citations in the literature and the recent emphasis on evidence-based medicine, randomized trials to prove definitively that maternal and neonatal outcomes are better with either a trial of labor (TOL) after cesarean or repeat cesarean delivery have not been carried out. Contemporary issues that affect VBAC rates include the right for women to have a cesarean section with no medical indication (“on request or demand”), the possibility of future pelvic support disorders after vaginal delivery, and medicolegal risks should uterine rupture occur. Consequently, deciding between TOL and repeat cesarean is a challenge for both physicians and patients.

PRELABOR COUNSELING

The decision for a TOL after a previous cesarean versus repeat cesarean involves balancing the risks vs benefits for each route of delivery. (Fig. 84.1) Trial of labor in a carefully selected patient with a low transverse cesarean scar is usually desirable, but recent studies have alerted physicians and patients to potential adverse events. Most studies on VBAC have been conducted in university or tertiary level centers under ideal conditions with staff coverage and in-house anesthesia. Yet many women in the USA are delivered in smaller community hospitals where obstetricians and anesthesiologists may not be available at night and on weekends. Although patients were carefully selected in initial studies, the list of obstetric conditions reportedly appropriate for VBAC rapidly expanded. Usually derived from small series, they included unknown uterine scar, twins, post-term pregnancy, and suspected macrosomia. Attention to the possibility of an adverse outcome is important before attempting VBAC in these settings, and common sense should prevail.

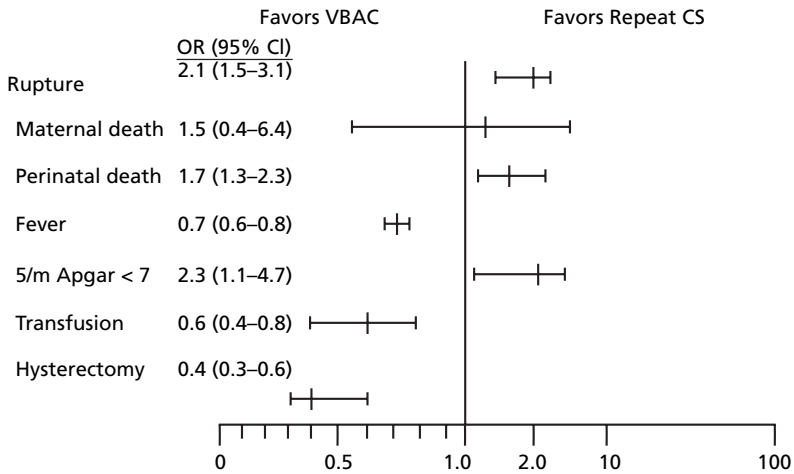


Fig. 84.1 Odds ratio graph comparing morbidity of trial of labor with elective repeat cesarean delivery. (Reproduced with permission from the American College of Obstetricians and Gynecologists. *Vaginal Delivery After Previous Cesarean Birth (Practice Patterns No. 1)*. Washington DC: ACOG.)

It is reasonable to encourage women to undertake TOL in a safe setting, but potential complications should be honestly discussed. Thorough, impartial, and fact-based counseling beginning early in pregnancy provides the best setting for TOL. Medical records should be obtained to review the circumstances surrounding the indication for the previous cesarean(s) and to confirm the type of uterine incision.

Vaginal delivery is associated with fewer complications, is less expensive, has a faster recovery, and for many women there is an important satisfaction factor. Published series indicate that approximately 60–80% of TOL after a previous cesarean result in successful vaginal births. However, these rates often represent a selected population. Patients inappropriate for TOL usually have been excluded, so the exact percentage of women undergoing TOL is not known. A woman who has delivered vaginally at least once before or after her previous cesarean is more likely to have a successful TOL than the woman who has not yet delivered vaginally. The chance for success for those with a previous diagnosis of dystocia is consistently lower (40–70%) than for those with non-recurring indications. Clinical judgment is also important because no scoring system is totally reliable in predicting a successful TOL. For example, successful VBAC is more likely for a woman whose indication for the first cesarean was breech presentation than it is for a woman less than 5 ft (1.5 m) tall whose first 4300 g infant was delivered by cesarean because of a deep transverse arrest.

Conversely, repeat cesarean may be more practical and safe in certain settings. It can be scheduled, is predictable, avoids a failed TOL with its frustration and morbidity, and essentially eliminates uterine rupture with its potential catastrophic outcome and litigation. However, elective cesarean carries with it a likelihood of more cesareans with their future risks. Placenta previa and accreta are examples of significant problems associated with multiple cesareans. Taken together, previa and accreta occur in less than 5% of women with no prior cesarean, but the prevalence progressively increases with each cesarean and is as high as 67% with four or more previous cesareans. Severe bleeding associated with these conditions now account for over half of peripartum hysterectomies. These are difficult cases, often requiring extensive preoperative preparation, and associated with extensive surgery, bladder and ureter injury, excessive blood loss, and even maternal death.

Criteria most predictive of a safe and successful trial of labor

- 1 One (or two) prior low segment transverse cesareans
- 2 Clinically adequate pelvis and normal fetal size
- 3 No other uterine scars, anomalies, or previous rupture
- 4 Patient enthusiasm and consent
- 5 Spontaneous labor
- 6 Physician available capable of monitoring labor, the fetus, and performing a cesarean
- 7 Anesthesia, blood bank, and personnel available for emergency cesarean

Potential contraindications

- 1 Prior classic or T-shaped incision, or previous uterine surgery
- 2 Contracted pelvis and/or macrosomia
- 3 Medical or obstetric condition precluding vaginal delivery
- 4 Patient refusal
- 5 Unripe cervix, induction and augmentation
- 6 Inability to perform emergency cesarean because of lack of available obstetrician, anesthesia, staff or inadequate facility

The final decision for TOL versus repeat cesarean should be made by the physician and patient after careful consideration and discussion (Fig. 84.2). A plan of management should then be documented in the prenatal record. If a decision for TOL is made, the patient deserves support and encouragement. However, this does not mean that the plan cannot be altered if the situation changes.

MANAGEMENT OF LABOR AND DELIVERY

Each hospital should develop a protocol for management of these patients. Epidural anesthesia is not contraindicated. In fact, adequate pain relief may

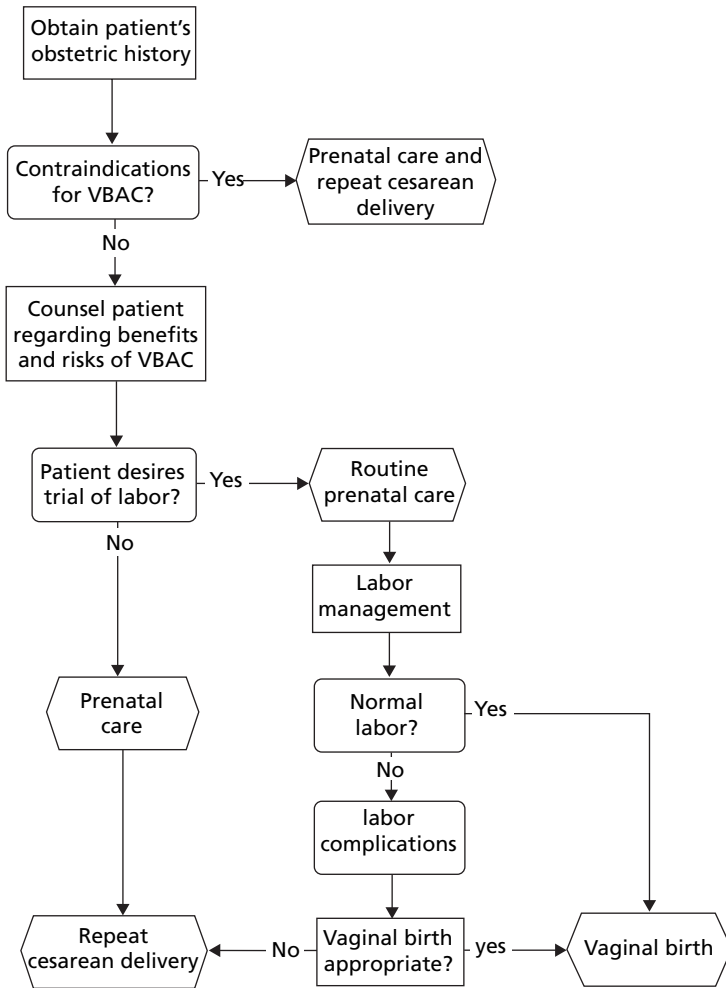


Fig. 84.2 Flow sheet showing one management scheme for vaginal birth after cesarean. (Reproduced with permission from Porter TF, Scott JR. Cesarean delivery. In: Scott JR, Gibbs RS, Karlan BY, Haney AF, eds. *Obstetrics and Gynecology*, 9th edn. Philadelphia: Lippincott Williams & Wilkins, 2003: 449–60.)

allow more women to choose TOL. The safety of induction of labor with prostaglandin gel and augmentation with oxytocin remains controversial, and misoprostol is contraindicated. Once labor has begun, the patient should be promptly evaluated and monitored; continuous electronic monitoring is usually preferable. It is important for personnel to be familiar with the potential complications of VBAC and to watch closely for fetal heart rate (FHR)

abnormalities and inadequate progress of labor. These women are at high risk for labor problems in view of the 20–40% rate of unsuccessful TOL. Timely diagnosis and prompt management of labor abnormalities are essential in any woman with a uterine scar to avoid the added risk of obstructed labor.

There is nothing particularly unique about delivery of the infant after TOL. The necessity for routine exploration of the uterus after successful VBAC is controversial. If there is excessive vaginal bleeding or signs of hypovolemia, immediate assessment of the scar and entire genital tract is mandatory. There is an increased incidence of infection and morbidity in patients who require cesarean because of a failed TOL.

UTERINE RUPTURE

Rupture of the uterine scar is the most serious complication of VBAC, and it can be life-threatening for both mother and baby. During labor, the rupture usually involves the previous scar and lower uterine segment but may be stellate and extend intraperitoneally or retroperitoneally. Associated factors include excessive amounts of oxytocin, dysfunctional labor, more than one cesarean delivery, multiparity, and even a previous non-pregnant uterine perforation. However, in most cases the reason rupture occurs is unknown, and adverse outcomes occur even in appropriate VBAC candidates. The rate of rupture is related to the type and location of the previous incision. The risk of uterine rupture with a classic or T-incision is 4–9%, with a low transverse incision it is 0.5–1.5%, and the risk with a low vertical incision is estimated to be between 1–4%.

DIAGNOSIS

Uterine rupture is sometimes difficult to diagnose, and close surveillance is necessary. Signs and symptoms may progress gradually or rapidly. The most common presenting sign is fetal distress. A FHR pattern with subtle variable decelerations may rapidly evolve into late decelerations, bradycardia, and undetectable fetal heart tones. Uterine or abdominal pain most commonly occurs in the area of the previous incision but may range from mild to “tearing” in nature. Uterine contractions often diminish in intensity and frequency. Vaginal or intra-abdominal bleeding produces anxiety, restlessness, weakness, dizziness, gross hematuria, shoulder pain, and shock. This clinical picture has sometimes been mistaken for abruption. Loss of station of the presenting part on vaginal examination is diagnostic.

TREATMENT

Any of these findings warrant immediate exploratory laparotomy. The condition of the infant is dependent on the severity of the rupture and relationship to the placenta and umbilical cord. The outcome is not always favorable even when delivery occurs within 30 min. The combined rate of fetal death and

severe long-term neurologic impairment when rupture occurs is as high as 20–25%. Repair of the uterus is possible in the majority of patients. In others, hemorrhage from extension of the rupture into the broad ligament or extensive damage to the uterus requires hysterectomy.

CONCLUSIONS

VBAC was enthusiastically supported by many groups during the past two decades. With more experience, it became apparent that there are rare but significant risks to the mother and infant. Poor perinatal outcome associated with uterine rupture is now a common cause of litigation. Most problems occur when the patient is not under direct observation or the diagnosis of uterine rupture is delayed. The latest ACOG Practice Bulletin recommends that a physician capable of performing a cesarean should be “immediately available.” Although outcomes from TOL and elective repeat cesarean are relatively equivalent, one may be better than the other for an individual case. With careful selection and close attention during labor, the majority of women can successfully deliver vaginally. In situations where attempted VBAC is not safe or the patient does not want it, elective cesarean is a reasonable alternative.

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Shoulder dystocia

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INTRODUCTION

Shoulder dystocia is an obstetric emergency that can lead to permanent disability and death of the neonate and occasional severe morbidity for the mother. The reported incidence varies from 0.2 to 3.0%. The higher incidences have been reported in publications and may reflect the trend to larger infants in the last two decades. However, the majority of infants who experience shoulder dystocia will be of normal birth weight. This emergency can occur with any pregnancy and each delivery attendant should have a management plan when the situation arises.

PATHOPHYSIOLOGY AND DIAGNOSIS

Shoulder dystocia occurs when the descent of the anterior shoulder is obstructed by the pubic symphysis. In a normal delivery after expulsion of the fetal head, external rotation occurs, returning the head to a right angle position in relation to the shoulder girdle. The fetal shoulder during descent is an oblique pelvic diameter. After expulsion and restitution, the anterior fetal shoulder should emerge from the oblique axis under the pubic ramus. The retraction of the fetal head against the maternal perineum accompanied by difficulty in accomplishing external rotation has been called the “turtle sign” and is usually diagnostic of shoulder dystocia. In other instances, external rotation may be accomplished by the birth attendant, but there is resistance to the delivery of the anterior shoulder with the usual amount of downward traction on the fetal head. This situation also implies the presence of shoulder dystocia. In some cases there is also obstruction to the descent of the posterior shoulder by the sacral promontory.

Shoulder dystocia occurs because of a relative disproportion between the fetal size and maternal pelvic capacity. Fetal weight shows the strongest correlation with the risk of shoulder dystocia; however, fetal body configuration is an important factor. Increased trunk and chest circumferences relative to head circumference have also been shown to be a factor. Because shoulder dystocia

Table 85.1 Risk for shoulder dystocia based on fetal weight, diabetic status, and method of delivery.

Fetal weight (kg)	Non-diabetic (%)	Diabetic spontaneous (%)	Diabetic assisted delivery (%)
4.00–4.25	5	8	12
4.26–4.50	9	12	17
4.51–4.75	14	20	27
4.76–5.00	21	24	35

is so closely related to fetal weight, the factors associated with shoulder dystocia are mainly those known to accelerate fetal growth or fetal disproportion. No single associated condition or combination of antenatal factors allows for clinically useful positive predictive values for shoulder dystocia or fetal injury. Risks for shoulder dystocia based on known (but not estimated) fetal weight are listed in Table 85.1.

MANAGEMENT

There are no randomized clinical trials to guide physicians in the selection of maneuvers and in which order to perform them. The lone published random trial found that prophylactic shoulder dystocia maneuvers did not reduce the incidence of shoulder dystocia. The best evidence available shows fetal injury to be associated with all described maneuvers to relieve shoulder dystocia. Some maneuvers are associated with increased risk of fetal injury and should be avoided: strong lateral downward traction on the fetal head and uterine fundal pressure.

When faced with a shoulder dystocia, the following sequence of maneuvers represents the best evidence available to deliver the infant without increased risk of injury. Recent studies have shown that a previously uncompromised fetus may be able to withstand 5–7 min of shoulder dystocia without suffering permanent injury from lack of oxygen.

Avoid forceful lateral traction on the fetal neck (more than 30° from the axis of the fetal spine). Have the mother stop pushing and instruct her to push only when asked to do so by you. Inform those in the room that there is a problem with the delivery of the shoulders. Ask someone to note the time. Have the mother positioned in the McRoberts position. This can be done having the mother grasp her posterior thigh and flexing the legs against her abdomen or by having birth attendants flex the mother's legs in a similar position. The McRoberts position causes cephalic rotation of the pubic symphysis and flattening of the sacrum, both of which will aid in relieving both anterior and posterior shoulder impaction.

If gentle downward traction with maternal pushing fail to deliver the fetus after the assumption of the McRoberts position, have an assistant apply suprapubic pressure in an oblique diameter, beginning with pressure applied opposite the side the fetal face. If the fetus is facing the mother's right side, pressure should be applied from the mother's left side with force intended to "shove" or collapse the shoulder. Gentle downward traction on the fetal head during a maternal push should again be attempted to determine whether the shoulder is now able to be delivered.

If McRoberts position and suprapubic pressure fail to effect delivery, attempt to deliver the posterior arm. Posterior arm extraction, when successful, will replace the bisacromial diameter with the axilloacromial diameter, thereby reducing the obstructing diameter in the pelvis. Insert a hand along the posterior shoulder and grasp the forearm if possible. Bring the forearm across the chest and through the vagina. Grasping the fetal hand may also be carried out to accomplish this. It is usually easiest to do this using your hand that is opposite the fetal face. If the fetus is facing to the mother's right (LOT), then try using your left hand to grasp the fetal arm. The mother should not be pushing during this maneuver.

If the head is tightly retracted against the maternal perineum, it may be necessary to perform episiotomy or proctoepisiotomy in order to insert your hand into the vagina to extract the fetal arm. If the posterior arm is wedged against the fetal body and the maternal sacrum, the humerus may need to be fractured in order to free the arm. This can be accomplished by positioning your index finger on the midshaft over the triceps muscle and flexing your finger. A tactile sensation or an audible click may be appreciated when the humerus is fractured. The arm can then be maneuvered into a position for extraction across the fetal chest.

After delivery of the posterior fetal arm, gentle downward traction on the fetal head will usually result in delivery of the baby. If after delivery of the posterior fetal arm, delivery of the baby cannot be accomplished, perform rotation of the posterior shoulder 180° to the anterior position while simultaneously rotating the anterior shoulder 180° to the posterior position. If the fetus is facing the mother's right side, rotation should be attempted in a counterclockwise direction as a first step.

Some physicians are more comfortable attempting rotation before attempting to deliver the posterior arm. Two types of rotational maneuvers are generally attempted: Wood and Rubin rotations.

The Wood rotational maneuver is rotating the fetal posterior shoulder by placing your index and middle fingers on the ventral surface (that facing the fetal face) and rotating the entire fetal body. If the fetus is in the LOT position, this would be accomplished with your left hand and rotation would be in a counterclockwise direction. Often after a 90° rotation, it will be

necessary to replace your left hand with your right hand to complete a 180° rotation.

The Rubin maneuver is accomplished by rotating the anterior shoulder under the pubic symphysis. If the fetus is in the LOT position, you would use your right hand to perform this maneuver. Another type of Rubin maneuver would be to rotate the posterior shoulder in a clockwise direction by placing pressure on the dorsal surface of the posterior shoulder.

If neither rotational maneuvers nor extraction of the posterior arm is possible, bilateral shoulder dystocia may be present, in which the anterior arm is lodged behind the symphysis pubis and the posterior shoulder is lodged high in the pelvis at or near the sacral promontory.

It may be impossible to deliver the fetus with the previously described maneuvers. In this case, either cephalic replacement or hands and knees position (Gaskin maneuver) could be selected. In the Gaskin maneuver, the mother's position is rotated 180° from supine position to one in which the mother is positioned on her hands and knees, with the maternal back pointing toward the ceiling. This change in maternal position is thought to allow for a change in fetal position within the maternal pelvis. An attempt is now made to deliver the posterior shoulder by gentle downward (toward the floor) traction followed by delivery of the anterior fetal shoulder by gentle upward traction. If this is not successful, an attempt can be made to deliver the posterior arm as described above.

If the mother cannot assume the "all fours" position or delivery cannot be accomplished in this position, cephalic replacement may be necessary. To accomplish delivery using cephalic replacement the fetal head must be returned to the occiput anterior position. The fetal head is then flexed by simultaneously putting downward pressure on the occiput with one hand and inward pressure on the fetal maxilla and face with the other hand. Once the fetal head is reintroduced into the vagina, emergency cesarean section should be performed. A fetal heart beat should be documented if at all possible before performing cesarean delivery.

EXTRAORDINARY MANEUVERS

Symphysiotomy should be performed only by individuals who have knowledge and experience in this procedure. It should be uncommonly used in the USA.

Abdominal rescue

If all maneuvers have been attempted and you are unable to replace the fetal head, low transverse uterine incision can be performed, the anterior shoulder manually rotated into the oblique diameter by the surgeon doing the uterine incision, and vaginal delivery accomplished. This requires at least two skilled delivery attendants and should rarely be used.

Table 85.2 Post delivery note.

Type of delivery (spontaneous, forceps, vacuum)
Indication of instrumental delivery if performed
Station of the delivery if instrumental delivery
Position of the fetal head on restitution (LOT or ROT)
Description, sequence, and result of maneuvers used to relieve shoulder dystocia
Total time elapsed from diagnosis to delivery
Complete umbilical cord blood gases (optional)
Condition of the infant with particular attention to the Moro reflex
Information provided to the patients

DOCUMENTATION

Documentation of delivery maneuvers and the timing and sequence of these maneuvers is an essential part of patient management and risk management in the event of fetal injury. In order not to forget an important element of documentation, the use of a preprinted form listing all the important elements in Table 85.2 is strongly suggested for use in all cases of shoulder dystocia, regardless of apparent fetal injury at the time of delivery.

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Twins, triplets, and beyond

Jacquelyn K. Chyu

INTRODUCTION

Multifetal pregnancies are considered high risk because of a significant increase in both maternal and fetal complications compared with singletons. These patients require close monitoring and frequent follow-up throughout pregnancy as well as careful planning at the time of delivery. The rate of multiple births has increased dramatically over the past two decades, with a 77% increase in twins and a 459% increase in triplet and higher order births. Although triplets and higher order multiples are increasing at a faster rate, twins represent 94% of all multiple gestations (Martin *et al.* 2002). Multiple gestations represent only 3% of all pregnancies in the USA, yet account for 14% of all infant deaths (Luke and Martin 2004). Compared with singletons, the perinatal mortality is increased 10-fold. The increased risk of perinatal morbidity and mortality results largely from preterm delivery, intrauterine growth restriction (IUGR), and congenital anomalies. In addition, maternal complications including hyperemesis, pre-eclampsia, hydramnios, and postpartum hemorrhage are also common.

The terms *monozygotic* and *dizygotic* refer to the number of ova responsible for the multiple gestations. A monozygotic pregnancy is a single fertilized ovum that splits into two distinct fetuses after a variable number of divisions. Monozygotic pregnancies are genetically identical. Dizygotic pregnancies originate from the fertilization of two separate ova that are therefore genetically dissimilar. The frequency of monozygotic twins is constant worldwide at 4 in 1000 births. In contrast, the frequency of dizygotic twins varies by maternal age, parity, family history, maternal weight, nutritional state, race, and the use of infertility drugs. In the USA, two-thirds of twins are dizygotic and one-third is monozygotic.

PATHOPHYSIOLOGY

Some investigators have speculated that pregnancies with multiple gestation result from increased maternal serum levels of gonadotropins. Infertility drugs

act by increasing the serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which produces multiple ovulations. The result is an increased frequency of dizygotic twinning. Clomiphene citrate (Clomid®) is associated with a twin gestation in 10% of pregnancies and menotropins (Pergonal®) in 30–50% of pregnancies. Gonadotropin levels fluctuate depending on maternal age, weight, nutrition, parity, and heredity. Studies of women who have had spontaneous dizygotic twins have yielded conflicting data on serum gonadotropin levels.

Even more uncertain is the origin of monozygotic conceptions. It has been hypothesized that monozygotic twins may result from exposure to teratogens during embryonic development.

PLACENTATION

Multiple gestations should be described in terms of placentation rather than the terms *identical* or *fraternal*. Determination of chorionicity in multiple gestation is essential for proper management of the pregnancy. In the USA, 20% of twin pregnancies are monozygotic and therefore at increased risk for twin–twin transfusion syndrome, cord entanglement, vascular anastomoses, and conjoining. In monozygotic pregnancies, the placentation is determined by the time at which division of a single ovum occurs, resulting in a central membrane consisting of two amnions and two chorions, two amnions only, or no central membranes. The most common is monozygotic/diamniotic. A good rule to remember is that monozygotic placentas are always monozygotic. Dizygotic pregnancies consist of two placentas, which can be fused or separate and are described as dichorionic/diamniotic.

Determining monozygotic versus dizygotic

- 1 *Placental number*. If two placental disks are seen, the pregnancy is dichorionic (dizygotic).
- 2 *Fetal sex*. If the fetuses are opposite sex, the pregnancy is dichorionic (dizygotic).
- 3 *Dividing membrane*. If fetuses are same sex with a single placenta, evaluate the thickness of the dividing membrane. If the membrane is thick (more than 2 mm) or has three to four visible layers, consider dichorionic/diamniotic. If membrane is thin, consider monozygotic/diamniotic. Remember that with severe oligohydramnios of one twin, a stuck-twin, the dividing membrane may not be visible. Consider monoamniotic gestation if no membrane is seen.
- 4 *Postpartum*. Confirm chorionicity by examining the placenta after delivery including gross and histologic examination. Genetic studies may be needed in same sex, dichorionic pregnancies to determine zygosity.

The same guidelines apply in triplets or quadruplets, but monozygotic and dichorionic placentas may coexist.

DIAGNOSIS

Delayed diagnosis of multiple gestation can result in an increased rate of complications. Therefore, early ultrasound to establish a diagnosis is essential.

- 1 *Clinical examination.* Suspect multifetal gestation if uterine size is greater than dates and multiple fetal heart tones are detected, and after use of infertility drugs.
- 2 *MSAFP.* Draw at 15–20 weeks and consider multiple gestation if elevated.
- 3 *Ultrasound.* False-negative and false-positive diagnoses are possible. An ultrasound examination should begin transabdominally; a second fetus in the uterine fundus can be missed by a transvaginal approach because of the limitation in depth of ultrasound transmission related to the higher frequency transvaginal probe. Obese patients present a challenge. A fetus can be missed if it is under the patient's ribs or deep in the pelvis. Determine the number of fetuses, number of placentas, fetal sex, and evaluate the thickness of the dividing membrane. Transvaginal ultrasound can detect fetal heart tones 1–2 weeks earlier than transabdominal ultrasound.

MANAGEMENT

Antepartum

Early ultrasound

An early ultrasound is important to confirm expected date of confinement (EDC) and assess chorionicity. If fetal size discrepancy exists use biometry of the larger fetus for dating considerations.

Medications and nutritional requirements

Folic acid (1 mg/day) and 60 mg/day elemental iron. Counsel the patient regarding the additional caloric requirements of twin pregnancy. The recommendation of the American College of Obstetricians and Gynecologists (ACOG) is an intake of 300 kcal greater than singleton gestation and a weight gain of 35–45 lb (16–20 kg).

A daily intake as high as 3500 kcal for the gravida with normal prepregnancy weight (body mass index [BMI] 19.8–26.0) has been suggested, comprised of 40% carbohydrate, 20% protein and 40% fat.

Aneuploidy screening

The risk for aneuploidy in multiple gestation is based on age alone and this approach is still supported by ACOG. Maternal age of 33 can be used as an indicator of increased risk because the risk of either or both fetuses in a twin pregnancy approaches the risk at age 35 in a singleton pregnancy. A detailed second trimester ultrasound is also useful in risk assessment. The use of other screening methods varies by institution. The combination of maternal age and nuchal translucency (NT) has been reported to detect 88% of fetuses with Down syn-

drome with a false-positive rate of 5% of fetuses in twin gestation. Second trimester serum screening is accomplished by using mathematical models and yields an approximately 51% detection rate with a 5% false-positive rate. The combination of NT and first trimester biochemistry (PAPP-A and beta hCG) has resulted in a 75% detection rate at a false-positive rate of 9% of pregnancies with a rate of one Down syndrome fetus detected for three chorionic villus sampling procedures. NT measurement compared with serum screening offers the advantage over serum screening alone of targeting the specific fetus at risk.

MSAFP screening to determine neural tube defect risk

MSAFP levels are approximately double in twins compared with singletons. A level greater than 4.0 multiples of the mean (MoM) in twins is associated with an increased risk of neural tube and ventral wall defect and should be addressed with a detailed sonographic survey of these structures. Amniocentesis is offered if an open defect is suspected or examination is inadequate.

Preterm birth prevention

Early cervical examination with frequent, serial examinations. A normal cervical length in the second trimester by endovaginal ultrasound examination is 4 cm; a short cervix measuring 2.5 cm at 23 weeks' gestation is associated with an increased risk of preterm labor and delivery under 32 weeks and this risk rises linearly with shorter measurements. Routine bed rest beginning at 24 weeks for all patients is controversial, but limit activity if a short cervix is identified. Prophylactic cerclage is not indicated without risk factors being present but may be used for patients with incompetent cervix. Prophylactic tocolytics are not indicated. Preterm labor (PTL) precautions should be explained to the patient. Administer antenatal steroids if delivery is expected within 7 days and the gestational age is between 24 and 34 weeks.

Multifetal pregnancy reduction

The goal of multifetal pregnancy reduction (MPR) is to reduce the number of live fetuses present in the uterus and thereby decrease the risk of preterm delivery in multiple gestations. The procedure is usually performed transabdominally by injecting potassium chloride into the region of the fetal thorax. MPR is usually performed between 9 and 13 weeks' gestation. Although the benefit of the procedure for triplet gestation remains controversial, the majority of MPR procedures are performed to reduce triplets to twins. A large series of 1000 cases demonstrated that the pregnancy loss rate before 24 weeks remained constant at approximately 5.4% in the hands of an experienced operator, with the starting number of fetuses ranging from two to five. Those pregnancies finishing with two or three fetuses delivered on average at the same gestational age reported for non-reduced twins and triplets (i.e. 35.3 and

33.5 weeks, respectively). Because the procedure is performed in the first trimester before detailed anatomic fetal ultrasound can be performed, the finding of a remaining anomalous fetus may result in a subsequent termination.

Selective termination

The management options available in the event of discovering an abnormality of one fetus is often an important consideration in the decision-making process involved in formulating a screening and/or diagnostic strategy. These options are expectant management (do nothing), termination of the pregnancy (both abnormal and normal fetuses), or selective termination of the abnormal fetus or fetuses. Selective termination is usually performed in the second trimester after the results of screening and diagnostic studies, by transabdominal fetal intracardiac injection of potassium chloride. This procedure can be performed only in pregnancies with separate chorions because of the effects of profound hypotension in the remaining fetus as a result of fetal demise in a mono-chorionic situation. Results of a large series of 200 cases demonstrate an overall unintended pregnancy loss rate less than 24 weeks of 4%. Of these, 2.4% occurred in twins and 11% in triplets or greater. The only factors affecting loss rate were greater number of starting fetuses and reduction of more than one fetus. The gestational age at delivery overall was 37 weeks, but the risk of delivery under 28 weeks was higher with selective termination performed at or less than 20 weeks gestation (4.5%), compared with 2.5% when performed at more than 20 weeks. Importantly, the overwhelming majority delivered at a gestational age more than 32 weeks. In monochorionic pregnancies, consider selective fetoscopic photocoagulation.

Prenatal diagnosis

There is an increased incidence of congenital anomalies, especially in monozygotic pregnancies. Perform comprehensive ultrasound examination at 18–20 weeks' gestation. Offer amniocentesis for karyotype based on maternal age and sonographic findings suggestive of aneuploidy. Amniocentesis may be performed on one sac if monozygosity is certain; otherwise, amniocentesis for karyotype should be performed on all sacs. Indigo carmine dye may be used to confirm proper needle placement. Chorionic villus sampling (CVS) offers the advantage of early diagnosis. Sampling accuracy of CVS in multiple gestations performed between 10 and 12 weeks with loss rates similar to amniocentesis have been reported.

Diabetes screening

Glucola is recommended at 24–28 weeks. Use same criteria for 3-h glucose tolerance test (GTT) to establish the diagnosis of gestational diabetes.

Fetal growth assessment

Serial ultrasound examinations every 4 weeks beginning at 24 weeks' gestation are used to assess fetal growth. Use singleton growth charts until 32 weeks. Increase antepartum testing schedule if discordance is greater than 25%. Consider delivery if there is IUGR at beyond 32 weeks.

Antepartum testing

Carry out non-stress tests (NSTs) twice a week if there is greater than 25% discordant growth. A biophysical profile (BPP) is recommended if NST is non-reactive. Doppler studies are helpful in confirming IUGR and/or twin-twin transfusion syndrome.

Monoamniotic pregnancy

This diagnosis is associated with increased perinatal mortality secondary to cord entanglement. Consider administering steroids and delivery by cesarean section at 34 weeks' gestation. Deliver before 34 weeks if any evidence of IUGR or discordance greater than 25% accompanied by abnormal NST, BPP, or Doppler studies.

Triplets and beyond

Spontaneous delivery of triplets usually occurs at 33–34 weeks' gestation and average fetal weight is 1800 g. Fetal growth is identical to singletons up to 27 weeks, but slows for remainder of the pregnancy. Use triplet ultrasound biometric tables to assess growth. Discordance is more common. Delivery is by cesarean section.

For quadruplets, spontaneous delivery occurs at 30–31 weeks, with average fetal weight of 1200–1500 g. Marginal and velamentous cord insertions and single umbilical artery are more common.

Vanishing twin syndrome

A twin disappears 13–78% of the time when twins are diagnosed before 14 weeks. Good prognosis for coexisting normal pregnancy.

Twin-twin transfusion

This occurs only in monochorionic pregnancies. Most monochorionic pregnancies have vascular anastomoses, clinically significant when arteriovenous communication. Donor twin becomes anemic, IUGR, and oligohydramniotic, and recipient becomes polycythemic and develops congestive heart failure and polyhydramnios. Perinatal mortality up to 70%. Poor prognosis if:

- 1 Diagnosed earlier than 28 weeks
- 2 Severe polyhydramnios
- 3 Fetal hydrops

Ultrasound diagnosis:

- 1 Same-sex twins, single placenta
- 2 Thin dividing membrane
- 3 Discordant growth
- 4 One twin oligo, one twin poly (stuck-twin)
- 5 Hydrops in one twin

Manage with aggressive serial amnioreduction. Consider radiofrequency laser ablation of communicating vessels if severe. Monitor with NSTs and ultrasound.

Congenital anomalies

Occur in 1.4% of singletons, 2.7% of twins, and 6.1% of triplets. Anomalies unique to multiple gestations include acardia and conjoined twins. Monozygotic twins have an increased risk of sirenomelia, neural tube defects, and cloacal extrophy but no increased risk of aneuploidy. If one fetus has a major malformation diagnosed in the second trimester, consider selective termination.

Single fetal demise

Incidence of fetal death of one twin after 20 weeks ranges from 2.6% to 6.8% and may be as high as 17% in triplets and higher order multiples. The concept of an increased risk of clinically significant maternal coagulopathy after demise of one fetus of a multiple gestation has been refuted and is not generally accepted. Obtain baseline platelet count, prothrombin time (PT), partial thromboplastin time (PTT) and fibrinogen level; if these are normal, no further surveillance is necessary. The main risk to the surviving fetus is prematurity. Because of vascular anastomoses of monochorionic pregnancies, the agonal hemodynamic changes associated with the demise of one fetus renders a risk of multicystic encephalomalacia to the viable twin. Delivery after single fetal demise does not improve outcome. Monitor with weekly NSTs and serial ultrasound examinations for fetal growth and cervical length. Although considered investigational, fetal brain magnetic resonance imaging (MRI) 2–3 weeks after single fetal demise may help to determine the presence of cerebral insult.

Delivery

ACOG recommend delivery by 40 weeks' gestation, although prospective risks of fetal death suggest that it is reasonable to consider delivery at 39 weeks for twins and 36 weeks for triplets. Three factors must be evaluated to determine the route of delivery for a patient with multiple gestations: gestational age, estimated fetal weights, and fetal presentations (Table 86.1).

Table 86.1 Frequency of presentation. (Reproduced by permission from MacLennan AH. Multiple gestation: clinical characteristics and management. In: Creasy RK, Resnik R, eds. *Maternal–Fetal Medicine: Principles and Practice*. Philadelphia: WB Saunders, 1994: 589–601.)

Presentation	Frequency (%)
Vertex/vertex	40
Vertex/breech	26
Breech/vertex	10
Breech/breech	10
Vertex/transverse	8
Miscellaneous	6

Table 86.2 Maternal complications in multifetal pregnancies.

Preterm labor
Hyperemesis
Polyhydramnios
Urinary tract infection
Postpartum hemorrhage
Cesarean delivery
Cholestasis
Pre-eclampsia
Placental abruption
Placenta previa
Vasa previa
Anemia

Vertex/vertex

A vaginal delivery is indicated for all estimated fetal weights. Oxytocin can be used for induction or augmentation.

Vertex/non-vertex

Route of delivery determined by estimated fetal weights (EFWs). If the EFW is greater than 2000 g, twin A is delivered vaginally and twin B by external version or total breech extraction. If the EFW is less than 2000 g, an external version can be attempted and, if successful, vaginal delivery; if unsuccessful, cesarean delivery.

Non-vertex/either

Cesarean section for delivery for all estimated fetal weights. Risk of interlocking twins.

Table 86.3 Fetal complications in multifetal pregnancies.

Prematurity
IUGR
Perinatal mortality
Congenital anomalies
Discordant growth
Umbilical cord entanglement
Locking twins
Twin transfusion syndrome
Vanishing twin

Triplets and beyond

Cesarean section for delivery, regardless of estimated fetal weights.

Continuous electronic fetal monitoring should be used throughout labor. There is no maximum time between delivery of twin A and twin B if fetal well being is confirmed. Be prepared for cesarean delivery at all times throughout labor. Ultrasound should be available during delivery to evaluate the position of baby B after delivery of baby A. Vaginal birth after cesarean (VBAC) is not contraindicated in multifetal pregnancies.

COMPLICATIONS

For lists of maternal and fetal complications in multifetal pregnancies, see Tables 86.2 and 86.3.

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Post-term pregnancy

Manuel Porto

INTRODUCTION

Since Clifford introduced the postmaturity syndrome in the mid-1950s, a series of seemingly synonymous terms have been used to describe pregnancies that extended beyond the estimated date of confinement (EDC). Postdate, post-term, and prolonged pregnancy are the terms that have been used almost interchangeably by obstetricians for nearly half a century. Traditionally, they have been defined by some to indicate pregnancies that have extended beyond 42 completed weeks' gestation from the first day of the last menstrual period (LMP), based in part on data that noted perinatal morbidity and mortality were significantly increased after 294 days. As recent studies have challenged the classic definition, I prefer to differentiate these terms and the management of such pregnancies accordingly.

DEFINITIONS

Consider **postdate pregnancy** as an inclusive term to describe all patients whose pregnancy extends beyond 41 menstrual weeks (287 days) from the LMP, without regard for the accuracy of the assigned gestational age. Up to 27% of all pregnancies may reach this milestone. **Post-term pregnancy** is the term I use to define those pregnancies that continue beyond 41 weeks with well-established pregnancy dating, generally by first or early second trimester ultrasound or known date of conception (e.g. fertility treatment). There appears to be justification for these more liberal criteria, as there is increasing evidence to suggest that adverse perinatal outcomes may increase after 41 completed weeks. **Prolonged pregnancy** is the term I reserve for those well-dated pregnancies that extend beyond 42 completed weeks. This group should represent only 3–5% of all pregnancies. Finally, the **postmaturity syndrome** refers to the dysmature neonatal product of a prolonged gestation.

MANAGEMENT

Reducing the incidence

Accurate gestational age determination will minimize the need for interventions in post-term pregnancy. Traditionally, standards for reliable EDC calculation have included historical and physical examination data. However, recent studies suggest that the use of first trimester ultrasound (crown–rump length) can significantly reduce the incidence of post-term and prolonged pregnancies, even in patients with a certain LMP and first trimester uterine size consistent with dates. Variability in the date of conception in relation to the LMP suggests that there may be benefit to first or early second trimester ultrasound dating in any pregnancy where the conception date is uncertain. At 40 completed weeks' gestation, perform a digital pelvic examination and consider membrane stripping (sweeping) to reduce the post-term pregnancy rate.

Exclude high-risk cases

Patients with hypertension, pre-eclampsia, growth restriction, pregestational diabetes, or multiple gestation should not be permitted to reach postdate or post-term pregnancy status. In well-controlled class A1 gestational diabetes, consider the pregnancy post-term at 40 completed weeks and manage as described below.

In uncomplicated postdate pregnancies (poorly documented dates), begin twice weekly antepartum testing at 41–42 weeks with the non-stress test (NST) and amniotic fluid index (AFI), often called the modified biophysical profile (BPP). Alternatively, the traditional BPP or contraction stress test (CST) can be utilized. Umbilical artery Doppler assessment does not appear to have a role in postdate testing. Induction of labor should be considered if the cervix is favorable (i.e. more than 2 cm dilated, Bishop score more than 6, or positive fetal fibronectin), antepartum testing becomes non-reassuring (non-reactive NST, AFI less than 5 cm), or the patient reaches 43 completed weeks' gestation.

Post-term pregnancies (well dated) begin twice weekly, modified BPP testing by 41 weeks' gestation. Induction should be employed when the cervix becomes favorable, antepartum testing becomes non-reassuring, or the pregnancy becomes prolonged (42+ weeks with good dates).

Induction options

Induction options include vaginal or intracervical prostaglandin gel (PGE₂), misoprostol, intracervical Foley balloon catheter, laminaria tents, and oxytocin among others. I favor the Foley catheter in cases where induction is precipitated by non-reassuring fetal testing, as it rarely produces uterine hyperstimulation. In other cases, vaginal misoprostol appears to be more efficacious than prostaglandins or oxytocin. Patients with a prior low transverse cesarean

section who do not enter spontaneous labor by 42 weeks are not candidates for induction, and should be scheduled for repeat cesarean delivery.

Intrapartum management should include continuous electronic fetal heart rate monitoring. Because of the increased incidence of macrosomia in post-term fetuses, be prepared for shoulder dystocia and avoid midpelvic delivery for prolonged second stage of labor with an estimated fetal weight in excess of 4000 g. Non-reassuring fetal heart rate patterns can often be clarified by fetal pulse oximetry, scalp or acoustic stimulation. If fetal intolerance of labor leads to operative intervention or thick meconium is noted at delivery, full umbilical cord blood gases should be obtained. At delivery, have an experienced newborn resuscitation team available when amniotic fluid meconium is present and suction the nasopharynx with a Delee trap immediately after delivery of the fetal head.

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Primary postpartum hemorrhage

Monica Longo and Gary D.V. Hankins

INTRODUCTION

Obstetric delivery is associated with the potential for acute, massive blood loss. Worldwide more than 125,000 women die annually from primary postpartum hemorrhage. This diagnosis remains one of the top five causes of maternal mortality in both developed and developing countries.

INCIDENCE AND ETIOLOGY

The precise incidence of postpartum hemorrhage (PPH) is unknown. The classic definition of PPH is bleeding in excess of 500 mL following the third stage of labor. Notwithstanding, when blood loss has been accurately measured at uncomplicated vaginal deliveries, it has averaged 600–650 mL while at uncomplicated cesarean sections it has averaged 1000 mL. The normal intravascular expansion of both plasma volume and red cell mass is such that the parturient without medical complications can sustain such blood losses and suffer no hemodynamic instability. The normal intravascular volume expansion during pregnancy thus allows for loss of 1–1.5 L blood at delivery without any significant hemodynamic alterations. The woman with pre-eclampsia, however, does not undergo the normal volume expansion and may poorly tolerate even a “normal” blood loss at delivery, and have profound shock with a physiologic blood loss well tolerated without the pre-eclampsia.

Ultimately, the diagnosis of PPH rests on the judgment of the clinician that blood loss has been significant enough to alter the management of the woman. PPH is classified as primary or early if it occurs within the first 24 h of delivery, and secondary or late if it occurs from 24 h after delivery through 6 weeks postpartum. Because the overwhelming majority of PPH is primary, we will confine our comments in this chapter to its diagnosis and treatment.

ANTICIPATION

A thorough understanding of the causes of PPH and the predisposing risk factors will enable the clinician to initiate preventive measures early. The most

Table 88.1 Causes of postpartum hemorrhage.

Etiology	Predisposing risk factor
Uterine atony	Uterine overdistention (polyhydramnios, multiple gestation, macrosomia) Rapid or prolonged labor Grand multiparity Uterine relaxing agents, (magnesium sulfate, nifedipine, beta-mimetics, indometacin, nitric oxide donors) Use of oxytocic agents for labor induction (oxytocin, prostaglandin E ₂) Chorioamnionitis Halogenated anesthetics Leiomyoma uteri
Retained products	Retained membranes Placenta accreta, increta, or percreta Retained succenturiate lobe
Lower genital tract trauma	Episiotomy (fourth degree or sulcus extension) Forceps/vacuum delivery and vaginal wall or cervical lacerations Fetal macrosomia Precipitant delivery
Uterine rupture	Obstructed labor Prior uterine surgery (myomectomy, reunification procedure, cesarean section) Use of oxytocic agents Use of prostaglandins
Uterine inversion	Magnesium sulfate Excessive traction on the umbilical cord
Coagulopathy	Amniotic fluid embolism Pregnancy-induced hypertension Abruptio placentae Sepsis Retained dead fetus Inherited coagulopathy

common cause of PPH is uterine atony. Other causes of PPH and associated risk factors are listed in Table 88.1. For example, a gravida with twins whose labor has been hypotonic despite the infusion of significant amounts of oxytocin carries multiple risk factors for PPH. The clinician should ensure that this patient has adequate intravenous access, and that the full obstetric team anticipates and is prepared to deal with obstetric hemorrhage.

MANAGEMENT

Recognition of risk factors and early institution of preventive measures is the cornerstone for successful management of obstetric hemorrhage. All gravidas should have blood type, Rh, and antibody screen performed as a routine part of antepartum care. The majority of women will have a negative antibody screen and can safely be given emergency release type and Rh-specific blood if they present with life-threatening hemorrhage. In such cases, waiting for the blood bank to provide cross-matched blood can prove to be fatal. In women with identified risk factors (Table 88.1), large-bore (i.e. 16 gauge or larger) intravenous access should be obtained before delivery, hydration should be maintained, and uterotonic agents should be readily available in the delivery room.

When PPH does occur, the first steps in management are to:

- 1 Stabilize the woman's vital signs
- 2 Stop the hemorrhage

Summon help to the bedside and clearly designate specific responsibilities to individual members of the healthcare team. One named individual should be responsible for monitoring and recording blood pressure, pulse, and respirations. This individual can also be responsible for fluid management and tracking the woman's input as well as her output to include both urine and ongoing blood loss. Another individual should be appointed the responsibility of gaining and maintaining intravascular access. Delay in gaining venous access may result in complete peripheral vascular collapse and the virtual impossibility of gaining peripheral lines. If so, an individual skilled with central line placement should be urgently called to assist.

Initial fluid resuscitation can be performed with crystalloid solution given at a ratio of 3 mL crystalloid for each milliliter of estimated blood loss. For example, with an estimated blood loss of 1500 mL the woman would be resuscitated with 4500 mL of crystalloid solution. When acute blood loss approaches 1500–2000 mL, red blood cell transfusion will almost always be necessary. This is especially so if the hemorrhage has not been stopped and blood loss is ongoing, as well as in the woman with pre-eclampsia. A Foley catheter should be inserted early in the process to allow ongoing assessment of oliguria. Oliguria, defined either as less than 30 mL/h or less than 0.5 mL/kg/ideal body weight, is an excellent indicator of hypovolemia and the need to further expand the intravascular compartment.

Assessment of uterine tone is always the next step in the management of primary PPH because uterine atony is overwhelmingly the dominant cause of primary PPH. If the uterus is atonic, immediate attention is given to mechanical (massage) and pharmacologic maneuvers (Table 88.2) to contract the uterus. The utility of bimanual uterine massage, in conjunction with evacuation of clot from the uterine cavity while simultaneously assessing for retained products of conception, intrauterine or intracervical lacerations, will

Table 88.2 Oxytocic agents used to treat uterine atony.

Agent	Dosage and administration
Oxytocin	10 units IM or IMM or dilute IV solution
Methylergonovine	0.2 mg IM
15-Methylprostaglandin F _{2α}	0.25 mg IM or IMM*
Misoprostol	800–1000 µg PO or PR

IM, intramuscular; IMM, intramyometrial; IV, intravenous; PO, oral; PR, rectal.

effectively establish tone in the majority of women and produce near immediate cessation of blood loss. Once tone has been established mechanically it can be maintained using a variety of pharmacologic agents. Oxytocin is the usual first-line treatment and is a very versatile drug. If intravenous (IV) access has been established it can be given as a dilute intravenous solution by placing 10 or 20 units into 1 L Ringer lactate or normal saline. At this concentration of oxytocin, and using an 18-gauge needle and standard IV pole and gravity administration alone, every oxytocin receptor in the uterus will be saturated. Oxytocin can also be given as 10 units intramuscularly (IM) or as a direct intrauterine injection. This is particularly useful in instances where IV access has not been achieved. Oxytocin should not, however, be given as an undiluted IV bolus (e.g. 1 amp IV push) as at this concentration it is a vasodilator and in the setting of hemorrhage could cause a precipitous drop in blood pressure. Additionally, as a concentrated bolus injection, oxytocin can cause cardiac arrhythmias, especially in the setting of a woman who is hypotensive, acidemic, and hypoxemic as may exist with acute obstetric hemorrhage and overt or borderline shock.

The next pharmacologic agent will depend, at least in part, on the specific clinical circumstances of the patient being treated. For instance, methylergonovine is a powerful uterotonic, but it is contraindicated in women with pre-eclampsia, poorly controlled hypertension, or those who have recently been treated with an α -adrenergic agent such as ephedrine. Methylergonovine should never be administered intravenously! Another powerful uterotonic is 15-methylprostaglandin F_{2α}. This drug is generally recommended to be redosed at 15-min intervals via the IM or intramyometrial route. However, when the hemorrhage is profound, the drug can be administered with even smaller interval time between doses. The newest uterotonic is misoprostol, given as 800–1000 µg rectally or orally. While this drug looks promising as a treatment for uterine atony and postpartum hemorrhage, we recommend it only as the third or fourth tier intervention until more clinical trials have established not only its efficacy, but also its safety.

If the uterus is firmly contracted, the next step in management is to rapidly inspect the perineum, vagina, and cervix for lacerations. A mass at the external cervical os or in the vagina may represent a partial uterine inversion and go unrecognized unless the clinician is aware of this possibility. If no lacerations are observed and supracervical bleeding continues, especially in the setting of a well-contracted uterus, then careful bimanual examination and manual uterine exploration should be repeated. Attention should be given to the contour of the uterine cavity, particularly along any previous uterine scars. An irregular cavity or large defect may indicate retained placenta or disruption of the uterine wall from accreta or increta or uterine rupture. In cases of uterine rupture intermittent, uterine atony is a frequent finding with the uterus contracting well to mechanical manipulation but with continued bleeding. In this setting, exploratory laparotomy may be required in order to diagnose the uterine rupture as palpation frequently fails to identify the defect. The vaginal or cervical lacerations can be packed for partial and temporary control of further blood loss while preparation is made for more definitive treatment. Surgical repair and hemodynamic stabilization often must occur concomitantly, as stabilization cannot be effected until the bleeding is controlled. Inertia of the healthcare team can prove lethal with a primary PPH.

In patients in whom medical therapy fails, and where the hemorrhage did not occur in the setting of a cesarean section where laparotomy has already been performed, intervention to disrupt the blood supply to the uterus may be necessary and life-saving. If bleeding is no longer so brisk as to represent an immediate threat to life, vascular catheterization and selective embolization of the uterine arteries or their branches may be an option if there are available resources, including a skilled interventional radiologist. Failing this, laparotomy is the last resort. Surgical options may include any combination of uterine artery ligation, utero-ovarian artery ligation, or infundibulopelvic ligament ligation. Importantly, fertility is not compromised by these procedures even when performed bilaterally and when both the uterine as well as infundibulopelvic ligaments are ligated. Ligation of the hypogastric arteries is generally an act of futility and carries an unacceptably high rate of complications. Finally, subtotal or total hysterectomy may be necessary. The choice of procedure will depend on many factors, including the age and parity of the patient, their desire for future childbearing, the rate of hemorrhage, and the experience of the surgeon.

BLOOD AND COMPONENT THERAPY

It is again emphasized that transfusion with packed red blood cells is often a necessary life-saving maneuver. Other products such as fresh frozen plasma or cryoprecipitate may also be required and may be indicated on the basis of either the clinical suspicion of or laboratory confirmation of a coagulopathy. Prophylactic transfusion of clotting factors is not recommended. Clinically,

coagulopathy is suspected on the basis of diffuse oozing throughout the surgical field as well as from peripheral sites such as venipunctures, Foley catheters, or nasogastric tubes. Platelets are generally recommended to maintain a count greater than 50,000/ μ L in a patient in whom surgery has been performed or is anticipated. Provided the indirect Coombs test is negative, type-specific or O negative blood can be used on an emergency release basis. One unit of packed cells will replace approximately 500 mL whole blood and should raise the hematocrit by approximately 3%.

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Postpartum endometritis

Jonathan Hodor

INTRODUCTION

Postpartum endometritis is an inflammatory process involving decidual tissue of the endometrium (endometritis) and/or the myometrium (endomyometritis). It occurs in response to a polymicrobial invasion of the endometrial cavity by vaginal flora. The incidence is less than 3% of vaginal deliveries but may be as high as 50% after a cesarean section. The many risk factors associated with postpartum endometritis include the following:

- 1** Cesarean delivery after a protracted labor with prolonged rupture of membranes, primarily in association with serial cervical examinations. The increased association with cesarean delivery is often attributable to contamination of the uterine activity from uterine and cervical manipulation. Note that the risk of postpartum endometritis is lower after an electively scheduled cesarean section.
- 2** Prolonged labor and/or prolonged rupture of membranes.
- 3** Multiple cervical examinations.
- 4** Manual removal of the placenta. In a prospective randomized study conducted by Magann *et al.*,¹ endometritis was noted to be significantly more common following manual placental removal from an exteriorized uterus, compared with spontaneous removal with the uterus *in situ*. Atkinson *et al.*² also concluded that manual removal of the placenta was associated with an increased rate of postcesarean endometritis despite the routine use of prophylactic antibiotics.
- 5** Underlying infection:
 - Chorioamnionitis
 - Bacterial vaginosis
- 6** Internal monitoring of fetal heart rate and uterine activity.
- 7** Retained products of conception (after a spontaneous delivery, spontaneous abortion, or elective abortion).
- 8** Presence of foreign bodies.
- 9** Other contributing risk factors include:

- Anemia
- Obesity
- Diabetes
- Malnutrition
- Immunocompromised status
- Low socioeconomic status of the patient
- Operator inexperience and/or skill
- Operative time greater than 1 h
- General anesthesia
- Blood loss greater than 800 mL

PATHOPHYSIOLOGY

Polymicrobial infection (aerobes and anaerobes) has a major role in the development of postpartum endometritis (Table 89.1). The primary route of uterine cavity contamination is by way of an ascending infection from the vaginal flora. Gram-positive cocci include primarily group B streptococci; Gram-positive bacilli such as *Clostridium* and *Listeria*; Gram-negative cocci include *Neisseria gonorrhoeae*; Gram-negative bacilli include *Escherichia coli*, *Klebsiella*, and

Table 89.1 Polymicrobial infection leading to postpartum endometritis. Adapted from data in Rosene *et al.*⁸ and Creasy and Resnik.⁹

Isolates	Percentage of isolates	Isolates	Percentage of isolates
Gram-positive aerobes		Gram-positive anaerobes	
Group B streptococci (<i>S. agalactiae</i>)	2–14	<i>Clostridium perfringens</i>	3–7
Group D streptococci (<i>S. faecalis</i>)	2–18	<i>Peptostreptococci</i> and <i>peptococci</i>	20–90
<i>S. epidermis</i>	7	Gram-negative anaerobes	
<i>Staphylococcus aureus</i>	5	<i>Bacteroides fragilis</i>	3–20
Diphtheroids	2	<i>Bacteroides bivius</i>	10–25
Group A streptococci (<i>S. pyogenes</i>)	1–2 Rare	<i>Bacteroides melaninogenicus</i>	
Gram-negative aerobes		<i>Fusobacterium</i> spp.	5–20
<i>Gardnerella vaginalis</i>	25–38	Genital mycoplasmas	5–20
<i>Escherichia coli</i>	5–40	<i>Ureaplasma urealyticum</i>	
<i>Enterobacterium</i> spp.	1–2	<i>Mycoplasma hominis</i>	50–100
<i>Proteus mirabilis</i>	2–5		20–35
<i>Klebsiella</i> spp.	5–10	<i>Chlamydia trachomatis</i>	3

Proteus. Suspect group B streptococcus (GBS) if symptoms develop within 1–2 days postpartum, *E. coli* if symptoms develop 3–4 days postpartum, and *Chlamydia* if symptoms develop more than 7 days postpartum. Note that group A beta-hemolytic streptococcus is a rare cause of endometritis in the setting of prophylactic antibiotic therapy.

DIAGNOSIS

Diagnosis is primarily based on clinical criteria usually developing within 5 days of delivery. These include the presence of persistent fever ($\geq 100.4^{\circ}\text{F}$ or 38°C) on two separate occasions, at least 4 h apart, after the first 24 h postpartum; uterine tenderness; abdominal tenderness usually limited to the lower abdomen; change in lochia (profuse/foul smelling); and leukocytosis (often in association with a left shift and bandemia). It is important to recall the physiologic leukocytosis seen during the early postpartum period and to correlate this laboratory finding with the patient's clinical symptoms. High fever, abdominal pain, ileus, hypotension, and sepsis are often seen in the presence of severe disease.

If endometritis is suspected, obtain blood cultures in all febrile patients following delivery, as 10–20% of patients will become bacteremic. The most common isolate from a positive blood culture will be *Bacteroides*. Collection of endometrial and/or cervical cultures is controversial.

It is also important to consider other sources of infection:

- Abdominal incision
- Breast
- Epidural site
- Episiotomy site
- Pulmonary (i.e. atelectasis)
- Urinary tract

Ultrasonographic findings of the uterine cavity may be normal to non-specific. Findings may include intracavitary echogenic material and the presence of endometrial fluid and/or thickening and irregularity. Clinical correlation is recommended. The ultrasound or a computed tomography (CT) scan of the abdomen and pelvis may be helpful in detecting a pelvic abscess, septic pelvic thrombosis, or infected hematoma in patients who fail to respond to antibiotic therapy within 48–72 h.

TREATMENT

Treatment is with broad-spectrum parenteral antibiotics with beta-lactamase coverage (Tables 89.2 and 89.3). Intravenous (IV) antibiotic regimens should continue until clinical improvement is observed and the patient has been afebrile for a minimum of 24–48 h. If no improvement is seen within 48–72 h of first-line therapy, consider the presence of resistant organisms (i.e.

Table 89.2 Antibiotics.

Antibiotics "first-line"	IV dose	Frequency	Other
Clindamycin (Cleocin®)	900 mg	Every 8 h	
+			
Gentamicin (Garamycin®)	1.5 mg/kg	Every 8 h	(in patients w/normal renal function)
Clindamycin (Cleocin®)	2700 mg	Every 24 h	
+			
Gentamicin (Garamycin®)	5 mg/kg	Every 24 h	
Clindamycin (Cleocin®)	900 mg	Every 8 h	In patients unresponsive to first-line therapy
+			
Gentamicin (Garamycin®)	1.5 mg/kg	Every 8 h	
+			
Ampicillin (Omnipen®/Marcillin®)	2 g	Every 4 h	
(or)			
Claforan®	2 g	Every 8 h	
(or)			
Vancomycin (if penicillin-allergic)	1 g	Every 24 h	
Metronidazole (Flagyl®)	500 mg	Every 8 h	Greater anaerobic coverage.
+		(IV or PO)	Not for use in breastfeeding mothers
Gentamicin (Garamycin®)	1.5 mg/kg	Every 8 h	
+			
Ampicillin (Omnipen®/Marcillin®)	2 g	Every 4 h	

enterococci or *Bacteroides*) and/or the presence of other causes of persistent fever (i.e. retained products of conception, pelvic abscess, pelvic thrombophlebitis, wound infection, or drug-induced fever). Use of alternative regimens is therefore recommended. If the patient remains febrile despite the use of IV antibiotics, consider drainage of any fluid collections and possible uterine curettage.

Prompt removal of suspected or diagnostic identifiable tissue within the uterine cavity will often control the infection. Delay in initiating adequate therapy may result in preventable death. Following successful IV antibiotic therapy, the patient does not require oral antibiotic therapy upon being discharged home.

Table 89.3 Alternative regimens.

Antibiotics "first-line"	IV dose	Frequency	Other
Ampicillin/sulbactam sodium (Unasyn®)	3 g	Every 6 h	
Ticarcillin/clavulanate (Timentin®)	3.1 g	Every 6 h	
Cefoxitin (Mefoxin®)	2 g	Every 6 h	
Piperacillin/tazobactam (Zosyn®)	3.375 g	Every 6 h	
Imipenem/cilastatin (Primaxin®)	500 mg	Every 6 h	
Ceftriaxone (Rocephin®)	2 g	Every 24 h	
+ Metronidazole (Flagyl®)	500 mg	Every 8 h (IV or PO)	Avoid in breastfeeding mothers
Levofloxacin (Levaquin®)	500 mg	Every 24 h	
+ Metronidazole (Flagyl®)	500 mg	Every 8 h (IV or PO)	Avoid in breastfeeding mothers
Piperacillin/tazobactam (Zosyn®)	3.375 g	Every 6 h	
+ Doxycycline (BioTab®/Doxyx®/ Vibramycin®)	100 mg	Every 12 h	

COMPLICATIONS

Potential complications from postpartum endometritis include:

- Septic thrombophlebitis
- Pelvic peritonitis
- Sepsis/septic shock
- Development of pelvic abscesses (i.e. tubo-ovarian)
- Future infertility (i.e. from salpingitis)
- Chronic pelvic pain

FOLLOW-UP

Patients may be discharged home after they have been afebrile for 24–48 h *without* antibiotic therapy. Outpatient therapy is otherwise unnecessary. Approximately 90% of women treated with one of the above noted antibiotic regimens will note improvement in 48–72 h.

PREVENTION

The American College of Obstetricians and Gynecologists (ACOG) supports the use of prophylactic antibiotics for all cesarean sections. Prophylactic intraoperative antibiotics administered after cord clamping may include: first-generation cephalosporins (i.e., cefazolin [Ancel®] 1 g intravenous piggyback (IVPB) or clindamycin [Cleocin®] 900 mg IVPB (in the presence of a penicillin allergy). In the presence of Group B Beta-Hemolytic Streptococcus (GBBS) intrapartum antibiotics (i.e., Penicillin G 5 g intravenous (IV) load followed by 2.5 mg every 4 h until delivery) or ampicillin 2 g IV load followed by 1 g every 4 h until delivery or clindamycin (in the presence of a penicillin allergy) 900 mg IVPB every 8 h until delivery should be utilized. Use of these prophylactic measures has been shown to reduce the risk of postpartum endometritis by as much as 75%. The use of broad spectrum antibiotics or *multiple dosing* does not offer any added benefit. Limiting the use of ampicillin is recommended because of the increasing prevalence of ampicillin-resistant *E. coli*.

Note that the evidence remains inconclusive for the administration of intraoperative antibiotics for elective and/or scheduled repeat cesarean sections; however, in two recent studies conducted by Bagratee *et al.*³ and Chelmow *et al.*,⁴ prophylaxis in these settings was justified.

In a study conducted by Watts *et al.*,⁵ the presence of bacterial vaginosis in patients undergoing a cesarean section was associated with an increased risk of postpartum endometritis. To date there are no studies linking preoperative treatment of bacterial vaginosis with decreased risk of developing postpartum endometritis. Krohn *et al.*⁶ also linked vaginal colonization with GBS at the time of delivery with an 80% greater likelihood of developing postpartum endometritis.

Mycoplasmas are often isolated from the endometrium of patients with endometritis, as is *Ureaplasma urealyticum*.

Other techniques, which may be of value in reducing the risk of postpartum endometritis, include:

- Adherence to the principles of asepsis
- Gentle tissue handling
- Meticulous hemostasis
- Wound irrigation
- Intrapartum treatment of intra-amniotic infection
- Adherence to protocols for active management of labor⁷

CONCLUSIONS

Postpartum endometritis remains the most common infectious complication after delivery. Adhering to protocols for prevention as well as the ability to promptly evaluate, diagnose, and treat infected patients will help maintain the high rates of cure and reduce the risk of morbidity associated with postpartum endometritis.

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Vaginal and vulvar hematoma

Robert Resnik

INTRODUCTION

The formation of a pelvic hematoma in the puerperium is a rare but potentially life-threatening complication. The reported incidence ranges from as low as 1 in 300 to 1 in 10,000 deliveries, but if one considers only those cases that require surgical intervention, a more realistic frequency is approximately 1 in 1000 births. Early reports suggested a maternal mortality of up to 21% for vulvovaginal hematomas, although management consisting of blood transfusion, aggressive surgical intervention, and antibiotics will, in almost all cases, eliminate the risk of mortality and significant morbidity.¹

PATHOPHYSIOLOGY AND DIAGNOSIS

Puerperal hematomas usually result from birth trauma or improper hemostasis at the time of episiotomy or vaginal laceration repair, although they may also occur following an uncomplicated spontaneous vaginal delivery. Associated factors include primiparity, operative delivery, large fetal weight, prolonged second stage of labor, and vulvar varicosities. In most cases, the patient will present with exquisite perineal pain shortly following delivery, and examination in many cases will reveal an obvious vulvar hematoma. However, a paravaginal hematoma may also develop that is not obvious externally, and can only be diagnosed by vaginal examination. In this instance, it is common to have the hematoma mass occlude the vaginal canal and dissect into the ischiorectal fossa.

Hematomas can be classified into four groups, depending on their location:²

- 1 Vulvar:** bleeding is limited to the vulvar tissues, superficial to fascial planes
- 2 Vulvovaginal:** the hematoma is evident on the vulva, but extends into the paravaginal tissues
- 3 Vaginal:** the hematoma is confined to the paravaginal tissues, and is not evident on external examination
- 4 Supravaginal or subperitoneal:** the hematoma may dissect retroperitoneally forming a mass palpable above the Poupart ligament, or may develop within the broad ligament

Patients with intraligamentous hematomas present with abdominal pain, hypotension, and tachycardia consistent with blood loss, and upward and lateral deviation of the uterus in the abdomen to the side opposite the hematoma. Although perineal or rectal pain, or both, is the most common symptom, patients may present with continued vaginal bleeding, hypotension, or urinary retention.

MANAGEMENT

If the hematoma is relatively small, not enlarging, and painless, expectant management is warranted.³ In the presence of an expanding and/or painful hematoma, more aggressive treatment is necessary. Blood should be made available for transfusion, in as much as the blood loss is usually well in excess of what is visible at the time of examination, and caused by the anticipated blood loss during surgical evacuation. An initial hematocrit, as well as serial blood count monitoring, is indicated for 12–24 h following resolution of bleeding. Under adequate anesthesia and in an operating room setting, the hematoma should be opened, the clot evacuated, and any apparent bleeding sites ligated. The space should be closed with deep mattress sutures, a drain placed, and the vaginal mucosa and/or vulvar skin reapproximated without tension. In the presence of a paravaginal hematoma, the vagina should be packed tightly and a Foley catheter left in place.

If bleeding continues, or if there is reformation of the hematoma following surgical intervention, the next most effective step in management is that of angiographic embolization.^{4,5} This requires pelvic arteriography with selective catheterization of the internal iliac to identify the area of contrast extravasation, followed by embolization with small gel foam particles. This will, in almost all cases, stop the bleeding rapidly, and allow for occlusion only of the bleeding vessel. Hypogastric artery ligation is frequently ineffective for stopping pelvic hemorrhage,⁶ disrupts blood supply to a larger area than is necessary, and precludes subsequent pelvic catheterization for embolization.

Management of a hematoma within the broad ligament is dependent on its size and progression. A very large hematoma should be evacuated surgically with ligation of bleeding sites. If bleeding reoccurs, pelvic arteriography and embolization are again helpful for definitive therapy. Patients should be treated with broad-spectrum antibiotics.

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PART 7

*Clinical
reference tables*

APPENDIX A

Commonly used ultrasound measurements

Antonio Barbera

Table A-1 Predicted menstrual age (MA) in weeks from crown–rump length (CRL) measurements (cm).* (From Hadlock FP, Shah YP, Kanon DJ, Lindsey JV. Fetal crown–rump length: re-evaluation of relation to menstrual age (5–18 weeks) with high-resolution real-time US. *Radiology* 1992;182:501–5.)

CRL	MA	CRL	MA	CRL	MA	CRL	MA	CRL	MA	CRL	MA
0.2	5.7	2.2	8.9	4.2	11.1	6.2	12.6	8.2	14.2	10.2	16.1
0.3	5.9	2.3	9.0	4.3	11.2	6.3	12.7	8.3	14.2	10.3	16.2
0.4	6.1	2.4	9.1	4.4	11.2	6.4	12.8	8.4	14.3	10.4	16.3
0.5	6.2	2.5	9.2	4.5	11.3	6.5	12.8	8.5	14.4	10.5	16.4
0.6	6.4	2.6	9.4	4.6	11.4	6.6	12.9	8.6	14.5	10.6	16.5
0.7	6.6	2.7	9.5	4.7	11.5	6.7	13.0	8.7	14.6	10.7	16.6
0.8	6.7	2.8	9.6	4.8	11.6	6.8	13.1	8.8	14.7	10.8	16.7
0.9	6.9	2.9	9.7	4.9	11.7	6.9	13.1	8.9	14.8	10.9	16.8
1.0	7.2	3.0	9.9	5.0	11.7	7.0	13.2	9.0	14.9	11.0	16.9
1.1	7.2	3.1	10.0	5.1	11.8	7.1	13.3	9.1	15.0	11.1	17.0
1.2	7.4	3.2	10.1	5.2	11.9	7.2	13.4	9.2	15.1	11.2	17.1
1.3	7.5	3.3	10.2	5.3	12.0	7.3	13.4	9.3	15.2	11.3	17.2
1.4	7.7	3.4	10.3	5.4	12.0	7.4	13.5	9.4	15.3	11.4	17.3
1.5	7.9	3.5	10.4	5.5	12.1	7.5	13.6	9.5	15.3	11.5	17.4
1.6	8.0	3.6	10.5	5.6	12.2	7.6	13.7	9.6	15.4	11.6	17.5
1.7	8.1	3.7	10.6	5.7	12.3	7.7	13.8	9.7	15.5	11.7	17.6
1.8	8.3	3.8	10.7	5.8	12.3	7.8	13.8	9.8	15.6	11.8	17.7
1.9	8.4	3.9	10.8	5.9	12.4	7.9	13.9	9.9	15.7	11.9	17.8
2.0	8.6	4.0	10.9	6.0	12.5	8.0	14.0	10.0	15.9	12.0	17.9
2.1	8.7	4.1	11.0	6.1	12.6	8.1	14.1	10.1	16.0	12.1	18.0

*The 95% confidence interval is $\pm 8\%$ of the predicted age.

Table A-2 Gestational sac measurement. (From Hellman LM, Kobayashi M, Fillisti L, *et al*: Growth and development of the human fetus prior to the twentieth week of gestation. *Am J Obstet Gynecol* 1969;**103**:789.)

Mean predicted gestational sac (cm)	Gestational age (weeks)	Mean predicted gestational sac (cm)	Gestational age (weeks)
1.0	5.0	3.6	8.8
1.1	5.2	3.7	8.9
1.2	5.3	3.8	9.0
1.3	5.5	3.9	9.2
1.4	5.6	4.0	9.3
1.5	5.8	4.1	9.5
1.6	5.9	4.2	9.6
1.7	6.0	4.3	9.7
1.8	6.2	4.4	9.9
1.9	6.3	4.5	10.0
2.0	6.5	4.6	10.2
2.1	6.6	4.7	10.3
2.2	6.8	4.8	10.5
2.3	6.9	4.9	10.6
2.4	7.0	5.0	10.7
2.5	7.2	5.1	10.9
2.6	7.3	5.2	11.0
2.7	7.5	5.3	11.2
2.8	7.6	5.4	11.3
2.9	7.8	5.5	11.5
3.0	7.9	5.6	11.6
3.1	8.0	5.7	11.7
3.2	8.2	5.8	11.9
3.3	8.3	5.9	12.0
3.4	8.5	6.0	12.2
3.5	8.6		

Table A-3 Sac size versus human chorionic gonadotropin (hCG) levels for normal pregnancies ($n = 56$). (From Nyberg DA, Filly RA, Duane Filho DL, *et al.* Abnormal pregnancy: early diagnosis by US and serum chorionic gonadotropin levels. *Radiology*. 1986;158:393–6.)

Mean sac diameter (mm)	hCG level (mIU/mL)		
	Predicted*	95% Confidence limits	
		Lower	Upper
5	1,932	1,026	3,636
6	2,165	1,226	4,256
7	2,704	1,465	4,990
8	3,199	1,749	5,852
9	3,785	2,085	6,870
10	4,478	2,483	8,075
11	5,297	2,952	9,508
12	6,267	3,502	11,218
13	7,415	4,145	13,266
14	8,773	4,894	15,726
15	10,379	5,766	18,682
16	12,270	6,776	22,235
17	14,528	7,964	26,501
18	17,188	9,343	31,621
19	20,337	10,951	37,761
20	24,060	12,820	45,130
21	28,464	15,020	53,970
22	33,675	17,560	64,570
23	39,843	20,573	77,164

* $\text{Log}(\text{hCG}) = 2.92 + 0.073 (\text{MSD}); R^2 = 0.93; P < 0.001.$

Table A-4 Reference values for length of nasal bone. (Reproduced with permission from Guis E, Ville V, Vincent V, Doumerc S, Pons JC, *et al.* Ultrasound evaluation of the length of the fetal nasal bones throughout gestation. *Ultrasound Obstet Gynecol* 1995;5:304–7.)

Gestational age (weeks)	Length of nasal bone (mm)		
	-2 SD	Mean	+2 SD
14	3.3	4.2	5.0
16	3.1	5.2	7.3
18	5.0	6.3	7.6
20	5.7	7.6	9.5
22	6.0	8.2	10.4
24	6.8	9.4	12.0
26	7.2	9.7	12.3
28	7.8	10.7	13.6
30	8.3	11.3	14.4
32	8.0	11.6	15.2
34	7.5	12.3	17.0

Table A-5 Biparietal diameter (BPD) and gestational age. (Reproduced with permission from Hadlock FP, Deter RL, Harrist RB. Fetal biparietal diameter. *J Ultrasound Med* 1982;1:97.)

BPD (cm)	Menstrual age (weeks)	BPD (cm)	Menstrual age (weeks)	BPD (cm)	Menstrual age (weeks)	BPD (cm)	Menstrual age (weeks)
2.0	12.2	4.0	18.0	6.0	24.6	8.0	32.5
2.1	12.5	4.1	18.3	6.1	25.0	8.1	32.9
2.2	12.8	4.2	18.6	6.2	25.3	8.2	33.3
2.3	13.1	4.3	18.9	6.3	25.7	8.3	33.8
2.4	13.3	4.4	19.2	6.4	26.1	8.4	34.2
2.5	13.6	4.5	19.5	6.5	26.4	8.5	34.7
2.6	13.9	4.6	19.9	6.6	26.8	8.6	35.1
2.7	14.2	4.7	20.2	6.7	27.2	8.7	35.6
2.8	12.5	4.8	20.5	6.8	27.6	8.8	36.1
2.9	14.7	4.9	20.8	6.9	28.0	8.9	36.5
3.0	15.0	5.0	21.2	7.0	28.3	9.0	37.0
3.1	15.3	5.1	21.5	7.1	28.7	9.1	37.5
3.2	15.6	5.2	21.8	7.2	29.1	9.2	38.0
3.3	15.9	5.3	22.2	7.3	29.5	9.3	38.5
3.4	16.2	5.4	22.5	7.4	29.9	9.4	38.9
3.5	16.5	5.5	22.8	7.5	30.4	9.5	39.4
3.6	16.8	5.6	23.2	7.6	30.8	9.6	39.9
3.7	17.1	5.7	23.5	7.7	31.2	9.7	40.5
3.8	17.4	5.8	23.9	7.8	21.6	9.8	41.0
3.9	17.7	5.9	24.2	7.9	32.0	9.9	41.5
						10.0	42.0

Table A-6 Percentile values head circumference. (Adapted from Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. *Radiology* 1984;152:497–501.)

Menstrual age (weeks)	Head circumference (cm)				
	Percentiles				
	3rd	10th	50th	90th	97th
14.0	8.8	9.1	9.7	10.3	10.6
15.0	10.0	10.4	11.0	11.6	12.0
16.0	11.3	11.7	12.4	13.1	13.5
17.0	12.6	13.0	13.8	14.6	15.0
18.0	13.7	14.2	15.1	16.0	16.5
19.0	14.9	15.5	16.4	17.4	17.9
20.0	16.1	16.7	17.7	18.7	19.3
21.0	17.2	17.8	18.9	20.0	20.6
22.0	18.3	18.9	20.1	21.3	21.9
23.0	19.4	20.1	21.3	22.5	23.2
24.0	20.4	21.1	22.4	23.7	24.3
25.0	21.4	22.2	23.5	24.9	25.6
26.0	22.4	23.2	24.6	26.0	26.8
27.0	23.3	24.1	25.6	27.0	27.9
28.0	24.2	25.1	26.6	28.1	29.0
29.0	25.0	25.9	27.5	29.1	30.0
30.0	25.8	26.8	28.4	30.0	31.0
31.0	26.7	27.6	29.3	31.0	31.9
32.0	27.4	28.4	30.1	31.8	32.8
33.0	28.0	29.0	30.8	32.6	33.6
34.0	28.7	29.7	31.5	33.3	34.3
35.0	29.3	30.4	32.2	34.1	35.1
36.0	29.9	30.9	32.8	34.7	35.8
37.0	30.3	31.4	33.3	35.2	36.3
38.0	30.8	31.9	34.2	36.2	36.8
39.0	31.1	32.2	34.2	36.2	37.3
40.0	31.5	32.6	34.6	36.6	37.7

Table A-7 Reference values for abdominal circumference. (Adapted from Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. *Radiology* 1984;152:497–501.)

Menstrual age (weeks)	Abdominal circumference (cm)				
	Percentiles				
	3rd	10th	50th	90th	97th
14.0	6.4	6.7	7.3	7.9	8.3
15.0	7.5	7.9	8.6	9.3	9.7
16.0	8.6	9.1	9.9	10.7	11.2
17.0	9.2	10.3	11.2	12.1	12.7
18.0	10.9	11.5	12.5	13.5	14.1
19.0	11.9	12.6	13.7	14.8	15.5
20.0	13.1	13.8	15.0	16.3	17.0
21.0	14.1	14.9	16.2	17.6	18.3
22.0	15.1	16.0	17.4	18.8	19.7
23.0	16.1	17.0	18.5	20.0	20.9
24.0	17.1	18.1	19.7	21.3	22.3
25.0	18.1	19.1	20.8	22.5	23.5
26.0	19.1	20.1	21.9	23.7	24.8
27.0	20.0	21.1	23.0	24.9	26.0
28.0	20.9	22.0	24.0	26.0	27.1
29.0	21.8	23.0	25.1	27.2	28.4
30.0	22.7	23.9	26.1	28.3	29.5
31.0	23.6	24.9	27.1	29.4	30.6
32.0	24.5	25.8	28.1	30.4	31.8
33.0	25.3	26.7	29.1	31.5	32.9
34.0	26.1	27.5	30.0	32.5	33.9
35.0	26.9	28.3	30.9	33.5	34.9
36.0	27.7	29.2	31.8	34.4	35.9
37.0	28.5	30.0	32.7	35.4	37.0
38.0	29.2	30.8	33.6	36.4	38.0
39.0	29.9	31.6	34.4	37.3	38.9
40.0	30.7	32.4	35.3	38.2	39.9

Table A-8 Reference values for femur length. (Adapted from Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. *Radiology* 1984;**152**:497–501.)

Menstrual age (weeks)	Femur length (cm)				
	Percentiles				
	3rd	10th	50th	90th	97th
14.0	1.2	1.3	1.4	1.5	1.6
15.0	1.5	1.6	1.7	1.9	1.9
16.0	1.7	1.8	2.0	2.2	2.3
17.0	2.1	2.2	2.4	2.6	2.7
18.0	2.3	2.5	2.7	2.9	3.1
19.0	2.6	2.7	3.0	3.3	3.4
20.0	2.8	3.0	3.3	3.6	3.8
21.0	3.0	3.2	3.5	3.8	4.0
22.0	3.3	3.5	3.8	4.1	4.3
23.0	3.5	3.7	4.1	4.5	4.7
24.0	3.8	4.0	4.4	4.8	5.0
25.0	4.0	4.2	4.6	5.0	5.2
26.0	4.2	4.5	4.9	5.3	5.6
27.0	4.4	4.6	5.1	5.6	5.8
28.0	4.6	4.9	5.4	5.9	6.2
29.0	4.8	5.1	5.6	6.1	6.4
30.0	5.0	5.3	5.8	6.3	6.6
31.0	5.2	5.5	6.0	6.5	6.8
32.0	5.3	5.6	6.2	6.8	7.1
33.0	5.5	5.8	6.4	7.0	7.3
34.0	5.7	6.0	6.6	7.2	7.5
35.0	5.9	6.2	6.8	7.4	7.8
36.0	6.0	6.4	7.0	7.6	8.0
37.0	6.2	6.6	7.2	7.9	8.2
38.0	6.4	6.7	7.4	8.1	8.4
39.0	6.5	6.8	7.5	8.2	8.6
40.0	6.6	7.0	7.7	8.4	8.8

Table A-9 Length of fetal long bones (mm). (From Jeanty P. Fetal limb biometry (letter). *Radiology* 1983;147:602.)

Week No.	Humerus percentile			Ulna percentile			Radius percentile			Femur percentile			Tibia percentile			Fibula percentile		
	5	50	95	5	50	95	5	50	95	5	50	95	5	50	95	5	50	95
11	3	6	10	—	5	—	—	—	—	—	—	—	—	4	—	—	—	—
12	5	9	13	—	8	—	—	—	—	—	—	—	—	7	—	—	—	—
13	5	9	20	3	11	18	—	—	—	—	—	—	—	10	—	—	—	—
14	5	16	20	4	13	17	8	13	12	19	19	19	4	10	17	6	11	10
15	11	18	26	10	16	22	12	15	19	11	19	26	5	16	27	10	14	18
16	12	21	25	8	19	24	9	18	21	13	22	24	7	19	25	6	17	22
17	19	24	29	11	21	32	11	20	29	20	25	29	15	22	29	7	19	31
18	18	27	30	13	24	30	14	22	26	19	28	31	14	24	29	10	22	28
19	22	29	36	20	26	32	20	24	29	23	31	38	19	27	35	18	24	30
20	23	32	36	21	29	32	21	27	28	22	33	39	19	29	35	18	27	30
21	28	34	40	25	31	36	25	29	32	27	36	45	24	32	39	24	29	34
22	28	36	40	24	33	37	24	31	34	29	39	44	25	34	39	21	31	37
23	32	38	45	27	35	43	26	32	39	35	41	48	30	36	43	23	33	44
24	31	41	46	29	37	41	27	34	38	34	44	49	28	39	45	26	35	41
25	35	43	51	34	39	44	31	36	40	38	46	54	31	41	50	33	37	42
26	36	45	49	34	41	44	30	37	41	39	49	53	33	43	49	32	39	43
27	42	46	51	37	43	48	33	39	45	45	51	57	39	45	51	35	41	47
28	41	48	52	37	44	48	33	40	45	45	53	57	38	47	52	36	43	47
29	44	50	56	40	46	51	36	42	47	49	56	62	40	49	57	40	45	50
30	44	52	56	38	47	54	34	43	49	49	58	62	41	51	56	38	47	52
31	47	53	59	39	49	59	34	44	53	53	60	67	46	52	58	40	48	57
32	47	55	59	40	50	58	37	45	51	53	62	67	46	54	59	40	50	56
33	50	56	62	43	52	60	41	46	51	56	64	71	49	56	62	43	51	59
34	50	57	62	44	53	59	39	47	53	57	65	70	47	57	64	46	52	56
35	52	58	65	47	54	61	38	48	57	61	67	73	48	59	69	51	54	57
36	53	60	63	47	55	61	41	48	54	61	69	74	49	60	68	51	55	56
37	57	61	64	49	56	62	45	49	53	64	71	77	52	61	71	55	56	58
38	55	61	66	48	57	63	45	49	53	62	72	79	54	62	69	54	57	59
39	56	62	69	49	57	66	46	50	54	64	74	83	58	64	69	55	58	62
40	56	63	69	50	58	65	46	50	54	66	75	81	58	65	69	54	59	62

Table A-10 Fetal weight percentiles by gestational age. Reproduced with permission from Hadlock FP, Harrist RB, Martinez-Poyer J. *In utero* analysis of fetal growth: a sonographic weight standard. *Radiology* 1991;181:129–33. Extrapolated to 42 weeks from 40 weeks.)

Gestational age (wk)	Fetal weight percentiles (g)				
	3rd	10th	50th	90th	97th
10	26	29	35	41	44
11	34	37	45	53	56
12	43	48	58	68	73
13	54	61	73	85	92
14	69	77	93	109	117
15	87	97	117	137	147
16	109	121	146	171	183
17	135	150	181	212	227
18	166	185	223	261	280
19	204	227	273	319	342
20	247	275	331	387	415
21	298	331	399	467	500
22	357	397	478	559	599
23	424	472	568	664	712
24	500	556	670	784	840
25	586	652	785	918	984
26	681	758	913	1068	1145
27	787	876	1055	1234	1323
28	903	1005	1210	1415	1517
29	1029	1145	1379	1613	1729
30	1163	1294	1559	1824	1955
31	1306	1454	1751	2048	2196
32	1457	1621	1953	2285	2449
33	1613	1795	2162	2529	2711
34	1773	1973	2377	2781	2981
35	1936	2154	2595	3036	3254
36	2098	2335	2813	3291	3528
37	2259	2514	3028	3542	3797
38	2414	2687	3236	3785	4058
39	2563	2852	3435	4018	4307
40	2700	3004	3619	4234	4538
41	2825	3144	3787	4430	4749
42	2935	3266	3934	4602	4933

Table A-11 Estimated fetal weights. (Reprinted with permission from Shepard MJ, Richards VA, Berkowitz RL, et al. An evaluation of two equations for predicting fetal weight by ultrasound. *Am J Obstet Gynecol* 1982; **142**:47-55.)

Biparietal diameters	Abdominal circumferences																									
	15.5	16.0	16.5	17.0	17.5	18.0	18.5	19.0	19.5	20.0	20.5	21.0	21.5	22.0	22.5	23.0	23.5	24.0	24.5	25.0	25.5	26.0	26.5	27.0	27.5	28.0
3.1	224	234	244	255	267	279	291	304	318	332	346	362	378	395	412	431	450	470	491	513	536	559	584	610	638	666
3.2	231	241	251	263	274	286	299	312	326	340	355	371	388	405	423	441	461	481	502	525	548	572	597	624	651	680
3.3	237	248	259	270	282	294	307	321	335	349	365	381	397	415	433	452	472	493	514	537	560	585	611	638	666	695
3.4	244	255	266	278	290	302	316	329	344	359	374	391	408	425	444	463	483	504	526	549	573	598	624	652	680	710
3.5	251	262	274	285	298	311	324	338	353	368	384	401	418	436	455	475	495	517	539	562	587	612	638	666	695	725
3.6	259	270	281	294	306	319	333	347	362	378	394	411	429	447	466	486	507	529	552	575	600	626	653	681	710	740
3.7	266	278	290	302	315	328	342	357	372	388	404	422	440	458	478	498	519	542	565	589	614	640	667	696	725	756
3.8	274	286	298	310	324	337	352	366	382	398	415	432	451	470	490	510	532	554	578	602	628	654	682	711	741	772
3.9	282	294	306	319	333	347	361	376	392	409	426	444	462	482	502	523	545	568	592	616	642	669	697	727	757	789
4.0	290	303	315	328	342	356	371	386	403	419	437	455	474	494	514	536	558	581	606	631	657	684	713	743	773	806
4.1	299	311	324	338	352	366	381	397	413	430	448	467	486	506	527	549	572	595	620	645	672	700	729	759	790	828
4.2	308	320	333	347	361	376	392	408	424	442	460	479	498	519	540	562	585	609	634	660	688	716	743	776	807	841
4.3	317	330	343	357	371	387	402	419	436	453	472	491	511	532	554	576	600	624	649	676	703	732	762	793	825	859
4.4	326	339	353	367	382	397	413	430	447	465	484	504	524	545	567	590	614	639	665	692	719	749	779	810	843	877
4.5	335	349	363	377	393	408	425	442	459	478	497	517	538	559	581	605	629	654	680	708	736	765	796	828	861	896
4.6	345	359	373	388	404	420	436	454	472	490	510	530	551	573	596	620	644	670	696	724	753	783	814	846	880	915
4.7	355	369	384	399	415	431	448	466	484	503	523	544	565	588	611	635	660	686	713	741	770	801	832	865	899	934

Continued

4.8	366	380	395	410	426	443	460	478	497	517	537	558	580	602	626	650	676	702	730	758	788	819	851	884	919	954
4.9	376	391	406	422	438	455	473	491	510	530	551	572	594	617	641	666	692	719	747	776	806	837	870	903	938	975
5.0	387	402	418	434	451	468	486	505	524	544	565	587	610	633	657	683	709	736	765	794	824	856	889	923	959	996
5.1	399	414	430	446	463	481	499	518	538	559	580	602	625	649	674	699	726	754	783	812	843	876	909	944	980	1017
5.2	410	426	442	459	476	494	513	532	552	573	595	618	641	665	690	717	744	772	801	831	863	895	929	964	1001	1039
5.3	422	438	455	472	489	508	527	547	567	589	611	634	657	682	708	734	762	790	820	851	883	916	950	986	1023	1061
5.4	435	451	468	485	503	522	541	561	582	604	627	650	674	699	725	752	780	809	839	870	903	936	971	1007	1045	1084
5.5	447	464	481	499	517	536	556	577	598	620	643	667	691	717	743	771	799	828	859	891	924	958	993	1030	1068	1107
5.6	461	477	495	513	532	551	571	592	614	636	660	684	709	735	762	789	818	848	879	911	945	979	1015	1052	1091	1131
5.7	474	491	509	527	547	566	587	608	630	653	677	701	727	753	780	809	838	869	900	933	966	1001	1038	1075	1114	1155
5.8	488	505	524	542	562	582	603	625	647	670	695	719	745	772	800	829	858	889	921	954	989	1024	1061	1099	1139	1180
5.9	502	520	539	558	578	598	619	642	664	688	713	738	764	792	820	849	879	911	943	977	1011	1047	1085	1123	1163	1205
6.0	517	535	554	573	594	615	636	659	682	706	731	757	784	811	840	870	900	932	965	999	1035	1071	1109	1148	1189	1231
6.1	532	550	570	590	610	632	654	677	700	725	750	777	804	832	861	891	922	955	988	1023	1058	1095	1134	1173	1214	1257
6.2	547	566	586	606	627	649	672	695	719	744	770	797	824	853	882	913	945	977	1011	1046	1083	1120	1159	1199	1241	1284
6.3	563	583	603	624	645	667	690	714	738	764	790	817	845	874	904	935	967	1001	1035	1071	1107	1145	1185	1226	1268	1311
6.4	580	600	620	641	663	686	709	733	758	784	811	838	867	896	927	958	991	1025	1059	1096	1133	1171	1211	1253	1295	1339
6.5	597	617	638	659	682	705	728	753	778	805	832	860	889	919	950	982	1015	1049	1084	1121	1159	1198	1238	1280	1323	1368

Continued

Biparietal

Abdominal circumferences

diameters

	15.5	16.0	16.5	17.0	17.5	18.0	18.5	19.0	19.5	20.0	20.5	21.0	21.5	22.0	22.5	23.0	23.5	24.0	24.5	25.0	25.5	26.0	26.5	27.0	27.5	28.0
6.6	614	635	656	678	701	724	748	773	799	826	853	882	911	942	973	1006	1039	1074	1110	1147	1185	1225	1266	1308	1352	1397
6.7	632	653	675	697	720	744	769	794	820	848	876	905	935	965	997	1030	1065	1100	1136	1174	1213	1253	1294	1337	1381	1427
6.8	651	672	694	717	740	765	790	816	842	870	898	928	958	990	1022	1056	1090	1126	1163	1201	1241	1281	1323	1367	1411	1458
6.9	670	691	714	737	761	786	811	838	865	893	922	952	983	1015	1048	1082	1117	1153	1190	1229	1269	1310	1353	1397	1442	1489
7.0	689	711	734	758	782	807	833	860	888	916	946	976	1008	1040	1074	1108	1144	1181	1219	1258	1298	1340	1383	1427	1473	1521
7.1	709	732	755	779	804	830	856	883	912	941	971	1002	1033	1066	1100	1135	1171	1209	1247	1287	1328	1370	1414	1459	1505	1553
7.2	730	763	777	801	827	853	880	907	936	965	996	1027	1060	1093	1128	1163	1200	1238	1277	1317	1358	1401	1445	1491	1538	1586
7.3	751	775	799	824	850	876	904	932	961	991	1022	1054	1087	1121	1156	1192	1229	1267	1307	1348	1390	1433	1478	1524	1571	1620
7.4	773	797	822	847	874	901	928	957	987	1017	1049	1081	1114	1149	1184	1221	1259	1297	1338	1379	1421	1465	1511	1557	1605	1655
7.5	796	820	845	871	898	925	954	983	1013	1044	1076	1109	1143	1178	1214	1251	1289	1328	1369	1411	1454	1499	1544	1592	1640	1690
7.6	819	844	870	896	923	951	980	1009	1040	1072	1104	1137	1172	1207	1244	1281	1320	1360	1401	1444	1487	1533	1579	1627	1676	1727
7.7	843	868	894	921	949	977	1007	1037	1068	1100	1133	1167	1202	1238	1275	1313	1352	1393	1434	1477	1522	1567	1614	1663	1712	1764
7.8	868	894	920	947	975	1004	1034	1065	1096	1129	1162	1197	1232	1269	1306	1345	1385	1426	1468	1512	1557	1603	1650	1699	1749	1801
7.9	893	919	946	974	1003	1032	1062	1094	1126	1159	1193	1228	1264	1301	1339	1378	1418	1460	1503	1547	1592	1639	1687	1737	1787	1840
8.0	919	946	973	1002	1031	1061	1091	1123	1156	1189	1224	1259	1296	1333	1372	1412	1453	1495	1538	1583	1629	1676	1725	1775	1826	1879
8.1	946	973	1001	1030	1060	1090	1121	1153	1187	1221	1256	1292	1329	1367	1406	1446	1488	1531	1575	1620	1666	1714	1763	1814	1866	1919
8.2	974	1001	1030	1059	1089	1120	1152	1185	1218	1253	1288	1325	1363	1401	1441	1482	1524	1567	1612	1657	1704	1753	1803	1854	1906	1960

Continued

8.3	1002	1030	1059	1089	1120	1151	1183	1217	1251	1286	1322	1359	1397	1436	1477	1518	1561	1605	1650	1696	1744	1793	1843	1895	1948	2002
8.4	1032	1060	1090	1120	1151	1183	1216	1249	1284	1320	1356	1394	1433	1473	1513	1555	1599	1643	1689	1735	1784	1833	1884	1936	1990	2045
8.5	1062	1091	1121	1151	1183	1216	1249	1283	1318	1355	1392	1430	1469	1510	1551	1594	1637	1682	1728	1776	1825	1875	1926	1979	2033	2089
8.6	1093	1122	1153	1184	1216	1249	1283	1318	1354	1390	1428	1467	1507	1548	1589	1633	1677	1722	1769	1817	1866	1917	1969	2022	2077	2134
8.7	1125	1155	1186	1218	1250	1284	1318	1353	1390	1427	1465	1505	1545	1586	1629	1673	1717	1764	1811	1859	1909	1960	2013	2067	2122	2179
8.8	1157	1188	1220	1252	1285	1319	1354	1390	1427	1465	1504	1543	1584	1626	1669	1714	1759	1806	1854	1903	1953	2005	2058	2113	2169	2226
8.9	1191	1222	1254	1287	1321	1356	1391	1428	1465	1503	1543	1583	1625	1667	1711	1756	1802	1849	1897	1947	1998	2050	2104	2159	2216	2274
9.0	1226	1258	1290	1324	1358	1393	1429	1456	1504	1543	1583	1624	1666	1709	1753	1799	1845	1893	1942	1992	2044	2097	2151	2207	2264	2322
9.1	1262	1294	1327	1361	1396	1432	1468	1506	1544	1584	1624	1666	1708	1752	1797	1843	1890	1938	1988	2039	2091	2144	2199	2255	2313	2372
9.2	1299	1332	1365	1400	1435	1471	1508	1546	1586	1626	1667	1709	1752	1796	1841	1888	1936	1984	2035	2086	2139	2193	2248	2305	2363	2423
9.3	1337	1370	1404	1439	1475	1512	1550	1588	1628	1668	1710	1753	1796	1841	1887	1934	1982	2032	2083	2135	2188	2242	2298	2356	2414	2475
9.4	1376	1410	1444	1480	1516	1554	1592	1631	1671	1712	1755	1798	1842	1887	1934	1982	2030	2080	2132	2184	2238	2293	2350	2407	2467	2527
9.5	1416	1450	1486	1522	1559	1597	1635	1675	1716	1758	1800	1844	1889	1935	1982	2030	2080	2130	2182	2235	2289	2345	2402	2460	2520	2582
9.6	1457	1492	1528	1565	1602	1641	1680	1720	1762	1804	1847	1892	1937	1984	2031	2080	2130	2181	2233	2287	2342	2398	2456	2515	2575	2637
9.7	1500	1535	1572	1609	1547	1686	1726	1767	1809	1852	1895	1940	1986	2033	2082	2131	2181	2233	2286	2340	2396	2452	2510	2570	2631	2693
9.8	1544	1580	1617	1654	1693	1733	1773	1815	1857	1900	1945	1990	2037	2085	2133	2183	2234	2286	2340	2395	2451	2508	2567	2627	2688	2751
9.9	1589	1625	1663	1701	1740	1781	1822	1864	1907	1951	1996	2042	2089	2137	2186	2237	2288	2341	2395	2450	2507	2565	2624	2684	2746	2810
10.0	1635	1672	1710	1749	1789	1830	1871	1914	1958	2002	2048	2094	2142	2191	2241	2292	2344	2397	2452	2507	2564	2623	2682	2743	2806	2870

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Biparietal Abdominal circumferences

diameters	28.5	29.0	29.5	30.0	30.5	31.0	31.5	32.0	32.5	33.0	33.5	34.0	34.5	35.0	35.5	36.0	36.5	37.0	37.5	38.0	38.5	39.0	39.5	40.0
3.1	696	726	759	793	828	865	903	943	985	1029	1075	1123	1173	1225	1279	1336	1396	1458	1523	1591	1661	1735	1812	1893
3.2	710	742	774	809	844	882	921	961	1004	1048	1094	1143	1193	1246	1301	1358	1418	1481	1546	1615	1686	1761	1838	1920
3.3	725	757	790	825	861	899	938	979	1022	1067	1114	1163	1214	1267	1323	1381	1441	1504	1570	1639	1711	1786	1865	1946
3.4	740	773	806	841	878	916	956	998	1041	1087	1134	1183	1235	1289	1345	1403	1464	1528	1595	1664	1737	1812	1891	1973
3.5	756	789	823	858	896	934	975	1017	1061	1107	1154	1204	1256	1311	1367	1426	1488	1552	1619	1689	1762	1839	1918	2001
3.6	772	805	840	876	913	953	993	1036	1080	1127	1175	1226	1278	1333	1390	1450	1512	1577	1645	1715	1789	1865	1945	2029
3.7	788	822	857	893	931	971	1012	1056	1101	1147	1196	1247	1300	1356	1413	1474	1536	1602	1670	1741	1815	1893	1973	2057
3.8	805	839	874	911	950	990	1032	1076	1121	1168	1218	1269	1323	1379	1437	1498	1561	1627	1696	1768	1842	1920	2001	2086
3.9	822	856	892	930	969	1009	1052	1096	1142	1190	1240	1292	1346	1402	1461	1523	1586	1653	1722	1794	1870	1948	2030	2115
4.0	839	874	911	949	988	1029	1072	1117	1163	1212	1262	1315	1369	1426	1486	1548	1612	1679	1749	1822	1898	1977	2059	2145
4.1	857	892	929	968	1008	1049	1093	1138	1185	1234	1285	1338	1393	1451	1511	1573	1638	1706	1776	1849	1926	2005	2088	2174
4.2	875	911	948	987	1028	1070	1114	1159	1207	1256	1308	1361	1417	1475	1536	1599	1664	1733	1804	1878	1954	2035	2118	2205
4.3	893	930	968	1007	1048	1091	1135	1181	1229	1279	1331	1385	1442	1500	1562	1625	1691	1760	1832	1906	1984	2064	2148	2236
4.4	912	949	987	1027	1069	1112	1157	1204	1252	1303	1355	1410	1467	1526	1588	1652	1718	1788	1860	1935	2013	2094	2179	2267
4.5	932	969	1008	1048	1090	1134	1179	1226	1275	1326	1380	1435	1492	1552	1614	1679	1746	1816	1889	1964	2043	2125	2210	2298
4.6	951	989	1028	1069	1112	1156	1202	1249	1299	1351	1404	1460	1518	1579	1641	1706	1774	1845	1918	1994	2073	2156	2241	2330
4.7	971	1010	1049	1091	1134	1178*	1225	1273	1323	1375	1430	1486	1545	1605	1669	1734	1803	1874	1948	2024	2104	2187	2273	2363

Continued



4.8	992	1031	1071	1113	1156	1201	1248	1297	1348	1401	1455	1512	1571	1633	1697	1763	1832	1904	1978	2055	2136	2219	2306	2396
4.9	1013	1052	1093	1135	1179	1225	1272	1322	1373	1426	1482	1539	1599	1661	1725	1792	1861	1934	2009	2086	2167	2251	2339	2429
5.0	1034	1074	1115	1158	1203	1249	1297	1347	1399	1452	1508	1566	1626	1689	1754	1821	1891	1964	2040	2118	2200	2284	2372	2463
5.1	1056	1096	1138	1181	1226	1273	322	1372	1425	1479	1535	1594	1655	1718	1783	1851	1922	1995	2071	2150	2232	2317	2406	2498
5.2	1078	1119	1161	1205	1251	1298	1347	1398	1451	1506	1563	1622	1683	1747	1813	1882	1953	2027	2103	2183	2266	2351	2440	2532
5.3	1101	1142	1185	1229	1276	1323	1373	1425	1478	1533	1591	1651	1713	1777	1843	1913	1984	2059	2136	2216	2299	2386	2475	2568
5.4	1124	1166	1209	1254	1301	1349	1399	1452	1506	1562	1620	1680	1742	1807	1874	1944	2016	2091	2169	2250	2333	2420	2510	2604
5.5	1148	1190	1234	1279	1327	1376	1426	1479	1534	1590	1649	1710	1773	1838	1906	1976	2049	2124	2203	2284	2368	2456	2546	2640
5.6	1172	1215	1259	1305	1353	1402	1454	1507	1562	1619	1678	1740	1803	1869	1938	2008	2082	2158	2237	2319	2403	2491	2582	2677
5.7	1197	1240	1285	1332	1380	1430	1482	1535	1591	1649	1709	1770	1835	1901	1970	2041	2115	2192	2272	2354	2439	2528	2619	2714
5.8	1222	1266	1311	1358	1407	1458	1510	1564	1621	1679	1739	1802	1866	1934	2003	2075	2150	2227	2307	2390	2475	2564	2657	2752
5.9	1248	1292	1338	1386	1435	1486	1539	1594	1651	1710	1770	1834	1899	1966	2037	2109	2184	2262	2342	2426	2512	2602	2694	2790
6.0	1274	1319	1366	1414	1464	1515	1569	1624	1682	1741	1802	1866	1932	2000	2071	2144	2219	2298	2379	2463	2550	2640	2733	2829
6.1	1301	1346	1393	1442	1493	1545	1599	1655	1713	1773	1835	1899	1965	2034	2105	2179	2255	2334	2416	2500	2588	2678	2772	2869
6.2	1328	1374	1422	1471	1522	1575	1630	1686	1745	1805	1868	1932	1999	2069	2140	2215	2291	2371	2453	2538	2626	2717	2811	2909
6.3	1356	1403	1451	1501	1552	1606	1661	1718	1777	1838	1901	1967	2034	2104	2176	2251	2328	2408	2491	2577	2665	2757	2851	2949
6.4	1385	1432	1481	1531	1583	1637	1693	1751	1810	1872	1935	2001	2069	2140	2213	2288	2366	2446	2530	2616	2705	2797	2892	2991

Continued

Biparietal Abdominal circumferences

diameters	28.5	29.0	29.5	30.0	30.5	31.0	31.5	32.0	32.5	33.0	33.5	34.0	34.5	35.0	35.5	36.0	36.5	37.0	37.5	38.0	38.5	39.0	39.5	40.0
6.6	1444	1492	1542	1594	1647	1702	1759	1817	1878	1941	2006	2073	2142	2213	2287	2364	2443	2524	2609	2696	2786	2879	2975	3075
6.7	1474	1523	1574	1626	1679	1735	1792	1852	1913	1976	2042	2109	2179	2251	2326	2403	2482	2564	2649	2737	2827	2921	3018	3117
6.8	1505	1555	1606	1658	1713	1769	1827	1887	1949	2012	2078	2147	2217	2290	2365	2442	2522	2605	2690	2778	2869	2964	3061	3161
6.9	1537	1587	1639	1692	1747	1803	1862	1922	1985	2049	2116	2184	2255	2329	2404	2482	2563	2646	2732	2821	2912	3007	3104	3205
7.0	1570	1620	1672	1726	1781	1839	1898	1959	2022	2087	2154	2223	2295	2368	2444	2523	2604	2688	2774	2863	2955	3050	3149	3250
7.1	1603	1654	1706	1761	1817	1875	1934	1996	2059	2125	2193	2262	2334	2409	2485	2564	2646	2730	2817	2907	2999	3095	3193	3295
7.2	1636	1688	1741	1796	1853	1911	1971	2044	2098	2164	2232	2302	2375	2450	2527	2607	2689	2773	2861	2951	3044	3140	3239	3341
7.3	1671	1723	1777	1832	1890	1948	2009	2072	2137	2203	2272	2343	2416	2491	2569	2649	2732	2817	2905	2996	3089	3186	3285	3388
7.4	1706	1759	1813	1869	1927	1987	2048	2111	2176	2244	2313	2384	2458	2534	2612	2693	2776	2862	2950	3041	3135	3232	3332	3435
7.5	1742	1795	1850	1907	1965	2025	2087	2151	2217	2285	2354	2426	2501	2577	2656	2737	2821	2907	2996	3088	3182	3279	3380	3483
7.6	1779	1833	1888	1945	2004	2065	2127	2192	2258	2326	2397	2469	2544	2621	2700	2782	2866	2953	3042	3134	3229	3327	3428	3531
7.7	1816	1871	1927	1985	2044	2105	2168	2233	2300	2369	2440	2513	2588	2666	2746	2828	2912	3000	3090	3182	3277	3376	3477	3581
7.8	1855	1910	1966	2025	2085	2146	2210	2275	2343	2412	2484	2557	2633	2711	2792	2874	2959	3047	3137	3230	3326	3425	3526	3631
7.9	1894	1949	2006	2065	2126	2188	2252	2318	2386	2456	2528	2603	2679	2757	2838	2921	3007	3095	3186	3279	3376	3475	3576	3681
8.0	1934	1990	2048	2107	2168	2231	2296	2362	2431	2501	2574	2649	2725	2804	2886	2969	3056	3144	3235	3329	3426	3525	3627	3733
8.1	1975	2031	2089	2149	2211	2275	2340	2407	2476	2547	2620	2695	2773	2852	2934	3018	3105	3194	3286	3380	3477	3577	3679	3785
8.2	2016	2073	2132	2193	2255	2319	2385	2462	2522	2594	2667	2743	2821	2901	2983	3068	3155	3244	3336	3431	3529	3629	3732	3838

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8.3	2059	2116	2176	2237	2300	2364	2431	2499	2569	2641	2715	2791	2870	2950	3033	3118	3206	3296	3388	3483	3581	3682	3785	3891
8.4	2102	2160	2220	2282	2345	2410	2477	2546	2617	2689	2764	2841	2920	3001	3084	3169	3257	3348	3441	3536	3634	3735	3839	3945
8.5	2146	2205	2266	2328	2392	2457	2525	2594	2665	2739	2814	2891	2970	3052	3135	3221	3310	3401	3494	3590	3688	3790	3894	4000
8.6	2192	2251	2312	2375	2439	2505	2573	2643	2715	2789	2864	2942	3022	3104	3188	3274	3363	3454	3548	3644	3743	3845	3949	4056
8.7	2238	2298	2359	2423	2488	2554	2623	2693	2765	2840	2916	2994	3074	3157	3241	3328	3417	3509	3603	3700	3799	3901	4005	4113
8.8	2285	2346	2408	2472	2537	2604	2673	2744	2817	2892	2968	3047	3128	3210	3295	3383	3472	3565	3659	3756	3855	3958	4063	4170
8.9	2333	2394	2457	2521	2587	2655	2725	2796	2869	2944	3021	3101	3182	3265	3351	3438	3528	3621	3716	3813	3913	4015	4120	4228
9.0	2382	2444	2507	2572	2639	2707	2777	2849	2923	2998	3076	3155	3237	3321	3407	3495	3585	3678	3773	3871	3971	4074	4179	4287
9.1	2433	2495	2559	2624	2691	2760	2830	2903	2977	3053	3131	3211	3293	3377	3464	3552	3643	3736	3832	3930	4030	4133	4239	4347
9.2	2484	2547	2611	2677	2744	2814	2885	2958	3032	3109	3187	3268	3350	3435	3522	3611	3702	3795	3891	3989	4090	4193	4299	4408
9.3	2536	2599	2664	2731	2799	2869	2940	3014	3089	3166	3245	3326	3409	3494	3581	3670	3761	3855	3951	4050	4151	4254	4361	4469
9.4	2590	2653	2719	2786	2854	2925	2997	3070	3146	3224	3303	3384	3468	3553	3641	3738	3822	3916	4013	4111	4213	4316	4423	4532
9.5	2644	2709	2774	2842	2911	2982	3054	3129	3205	3283	3362	3444	3528	3614	3701	3791	3884	3978	4075	4174	4275	4379	4486	4595
9.6	2700	2765	2831	2899	2969	3040	3113	3188	3264	3343	3423	3505	3589	3675	3763	3854	3946	4041	4138	4237	4339	4443	4550	4659
9.7	2757	2822	2889	2958	3028	3099	3173	3248	3325	3404	3484	3567	3651	3738	3826	3917	4010	4105	4202	4302	4404	4508	4615	4724
9.8	2815	2881	2948	3017	3088	3160	3234	3309	3387	3466	3547	3630	3715	3802	3890	3981	4074	4170	4267	4367	4469	4573	4680	4790
9.9	2874	2941	3009	3078	3149	3222	3296	3372	3450	3529	3611	3694	3779	3866	3956	4047	4140	4236	4333	4433	4536	4640	4747	4857
10.0	2935	3002	3070	3140	3211	3285	3359	3436	3514	3594	3676	3759	3845	3932	4022	4113	4207	4303	4400	4501	4603	4708	4815	4924

Log (birth weight) = 1.7492 + 0.166 (BPD) + 0.046 (AC) - 2.646 (AC + BPD)/1000.

SD = ±106.0 g/kg birth weight.

Table A-12 Amniotic fluid index values in normal pregnancy. (Adapted from Moore TR, Coyle JE. The amniotic fluid index in normal human pregnancy. *Am J Obstet Gynecol* 1990;**162**:1168.)

Week	Amniotic fluid index percentile values (mm)				
	3rd	5th	50th	95th	97th
16	73	79	121	185	201
17	77	83	127	194	211
18	80	87	133	202	220
19	83	90	137	207	225
20	86	93	141	212	230
21	88	95	143	214	233
22	89	97	145	216	235
23	90	98	146	218	237
24	90	98	147	219	238
25	89	97	147	221	240
26	89	97	147	223	242
27	85	95	146	226	245
28	86	94	146	228	249
29	84	92	145	231	254
30	82	90	145	234	258
31	79	88	144	238	263
32	77	86	144	242	269
33	74	83	143	245	274
34	72	81	142	248	278
35	70	79	140	249	279
36	68	77	138	249	279
37	66	75	135	244	275
38	65	73	132	239	269
39	64	72	127	226	255
40	63	71	123	214	240
41	63	70	116	194	216
42	63	69	110	175	192

Table A-13 A nomogram of the transverse cerebellar diameter (TCD) (mm). (Reprinted with permission from Goldstein I, Reece EA, Pihu G, *et al.* Cerebellar measurements with ultrasonography in the evaluation of fetal growth and development. *Am J Obstet Gynecol.* 1987;**156**:1065–9.)

Gestational age (weeks)	Percentile		
	10th	50th	90th
15	13	14	16
16	14	16	17
17	16	17	18
18	17	18	19
19	18	19	20
20	19	20	21
21	20	21	23
22	22	23	24
23	23	24	26
24	23	26	28
25	25	27	30
26	26	28	32
27	27	30	33
28	28	31	35
29	29	33	38
30	31	35	40
31	33	38	42
32	34	39	43
33	35	40	44
34	38	41	44
35	41	42	45
36	42	43	45
37	43	45	48
38	45	48	50
39	48	52	55
40	52	55	58

Table A-14 Reference values for umbilical artery Doppler resistive index and systolic : diastolic ratio. (From Kofinas AD, Espeland MA, Penry M, Swain M, Hatjis CG. Uteroplacental Doppler flow velocity waveform indices in normal pregnancy: a statistical exercise and the development of appropriate reference values. *Am J Perinatol* 1992;9:94–101.)

Gestational age (weeks)	Percentiles					
	5th		50th		95th	
	Resistive index	Systolic : diastolic ratio	Resistive index	Systolic : diastolic ratio	Resistive index	Systolic : diastolic ratio
16	0.70	3.39	0.80	5.12	0.90	10.50
17	0.69	3.27	0.79	4.86	0.89	9.46
18	0.68	3.16	0.78	4.63	0.88	8.61
19	0.67	3.06	0.77	4.41	0.87	7.90
20	0.66	2.97	0.76	4.22	0.86	7.30
21	0.65	2.88	0.75	4.04	0.85	6.78
22	0.64	2.79	0.74	3.88	0.84	6.33
23	0.63	2.71	0.73	3.73	0.83	5.94
24	0.62	2.64	0.72	3.59	0.82	5.59
25	0.61	2.57	0.71	3.46	0.81	5.28
26	0.60	2.50	0.70	3.34	0.80	5.01
27	0.59	2.44	0.69	3.22	0.79	4.76
28	0.58	2.38	0.68	3.12	0.78	4.53
29	0.57	2.32	0.67	3.02	0.77	4.33
30	0.56	2.26	0.66	2.93	0.76	4.14
31	0.55	2.21	0.65	2.84	0.75	3.97
32	0.54	2.16	0.64	2.76	0.74	3.81
33	0.53	2.11	0.63	2.68	0.73	3.66
34	0.52	2.07	0.62	2.61	0.72	3.53
35	0.51	2.03	0.61	2.54	0.71	3.40
36	0.50	1.98	0.60	2.47	0.70	3.29
37	0.49	1.94	0.59	2.41	0.69	3.18
38	0.47	1.90	0.57	2.35	0.67	3.08
39	0.46	1.87	0.56	2.30	0.66	2.98
40	0.45	1.83	0.55	2.24	0.65	2.89
41	0.44	1.80	0.54	2.19	0.64	2.81
42	0.43	1.76	0.53	2.14	0.63	2.73

Note: Resistive index = $0.97199 - 0.01045 \times \text{gestational age}$ (SD = 0.06078);
systolic: diastolic ratio = $11(1 - \text{resistive index})$.

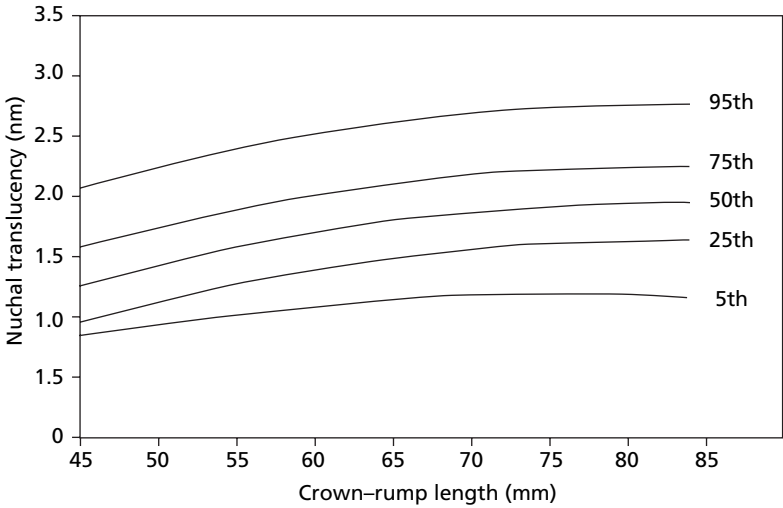


Fig. A-1 Reference range of fetal nuchal translucency and chromosomal defects. (From Nicolaides KH, Sebire NJ, Snijders RJM, eds. *The 11–14 Week Scan: The Diagnosis of Fetal Abnormalities*. New York, NY: Parthenon Publishing, 1999.)

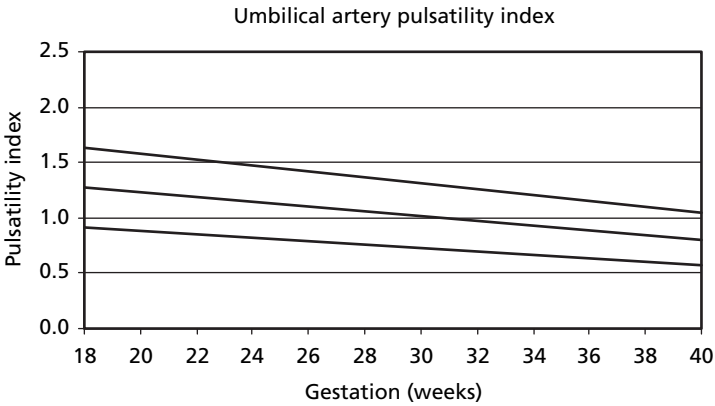


Fig. A-2 Umbilical artery pulsatility index throughout gestation. (From Ferrazzi E, Gementi P, Bellotti M, et al. Doppler velocimetry: critical analysis of umbilical, cerebral and aortic reference values. *Eur J Obstet Gynaecol* 1990;**38**:189–96.)

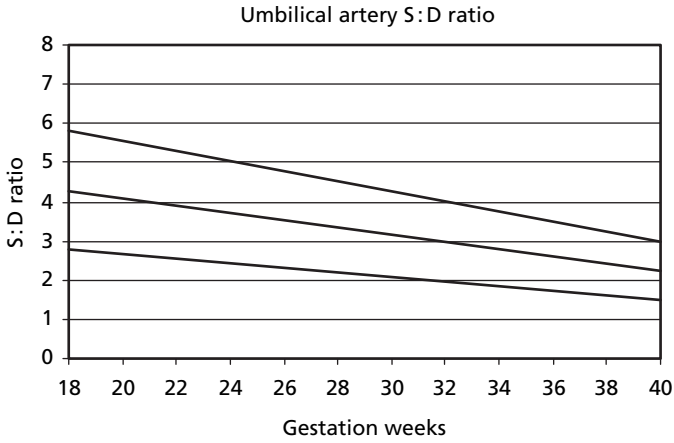


Fig. A-3 Umbilical systolic : diastolic ratio throughout gestation. (From Ferrazzi E, Gementi P, Bellotti M, *et al.* Doppler velocimetry: critical analysis of umbilical, cerebral and aortic reference values. *Eur J Obstet Gynaecol* 1990;**38**:189–96.)

APPENDIX B

Changes in laboratory values during pregnancy

Shad H. Deering

Table B-1 Pregnancy-induced changes in thyroid function.

Parameter	Non-pregnant	First trimester	Second trimester	Third trimester
T ₄ (μg/dL)	5–11	35% increase	65% increase	65% increase
Free T ₄ (ng/dL)	0.7–2.2	No change	No change	No change
TSH (μg/mL)	0.3–5.0	No change*	No change	No change
T ₃ (ng/mL)	70–200	30% increase	50–70% increase	50–70% increase
Free T ₃ (pg/mL)	200–500	No change	No change	No change

*With hyperemesis gravidarum, up to 60% of women will have a mildly decreased TSH, but normal free T₄.

Table B-2 Pregnancy-induced changes in steroid production (mg/24 h).

Steroid	Non-pregnant	Pregnant
Estradiol-17β	0.1–0.6	15–20
Estriol	0.02–0.1	50–150
Progesterone	0.1–40	250–600
Aldosterone	0.05–0.1	1.0–2.0
Cortisol	10–30	10–20
Deoxycorticosterone	0.05–0.5	1–12

Table B-3 Hormone/steroid serum levels.

	Non-pregnant	Pregnant
Prolactin (ng/mL) ¹	5–20	10–180
Cortisol (nmol/L) ²	22–450 (mean = 175)	197–1206 (mean = 581)*

*Third trimester levels.

Table B-4 Pregnancy-induced changes in pulmonary function.

Parameter	Non-pregnant	Pregnant
Residual volume (mL)	965	770
Tidal volume (mL)	485	680
Vital capacity (mL)	3260	3310
Inspiratory capacity (mL)	2625	2745
Minute ventilation (mL)	7270	10,340
Respiratory rate (L/min)	15	16
Arterial pH	7.38–4.42	7.40–7.45
P_{O_2} (mmHg)	98–100	101–104
P_{CO_2} (mmHg)	35–40	25–30
Base deficit (mEq/L)	0.0–2.0	3.0–4.0
Bicarbonate (mEq/L)	24–30	18–21

Table B-5 Pregnancy-induced changes in water-soluble nutrients.

Nutrient	Change (% decrease)
Ascorbic acid	39
Albumin	30
Amino acids	17
Biotin	49
Folate	33
Vitamin B ₆	33
Glucose	10
Iron	26
Magnesium	5
Vitamin B ₁₂	33

Table B-6 Pregnancy-induced changes in lipid metabolism.

Lipid	Non-pregnant	Pregnant
Total lipids	600	1000
Triglycerides (mg/dL)	10–150	180–260
Total cholesterol (mg/dL)	100–200	240–400
VLDL (mg/dL)	120–180	160–200
LDL (mg/dL)	120–180	160–200
HDL (mg/dL)	3–70	80–100

Table B-7 Pregnancy-induced changes in iron storage and metabolism.

Parameter	Non-pregnant	First trimester	Second trimester	Third trimester
Hemoglobin (g/dL)	10.9 ± 0.8	12.2 ± 1.3	10.9 ± 0.8	11.0 ± 0.9
Serum Iron (g/dL)	56.0 ± 31.0	106.5 ± 24.5	75.3 ± 37.8	56.0 ± 31.0
Transferrin (µg/dL)	244.6 ± 52.7	244.6 ± 52.7	336.2 ± 72.6	362.8 ± 55.4
Ferritin (µg/L)	63.0 ± 34.7	97.4 ± 39.4	22.2 ± 14.6	14.7 ± 7.7

Table B-8 Pregnancy-induced changes in calcium metabolism.

Parameter	Non-pregnant	First trimester	Second trimester	Third trimester
1,25-dihydroxy vitamin D (pg/mL)	51	94	118	117
25-Hydroxy vitamin D (ng/mL)	14	16	18	16
Intact parathyroid hormone (ng/mL)	25	13	16	14
Ionized calcium (mg/dL)	5.2	4.9	5.1	5.3
Total calcium (mg/dL)	10.3	9.2	9.3	9.6

Table B-9 Pregnancy-induced changes in coagulation parameters.

Parameter	Change during pregnancy
Platelet count	No change*
Fibrinogen	Increases by 50%
Erythrocyte sedimentation rate (ESR)	Increases
Protein S	Decreases
Protein C	No change
PT (prothrombin time)	No change†
PTT (partial thromboplastin time)	No change†
Antithrombin III	No change
Factors I, VII, VIII, IX, X	Increase
Factors II, V, XII	No change
Factors XI, XIII	Decrease

*The platelet count actually decreases over the course of pregnancy, but should remain in the normal range, with the mean level in the third trimester being $278 \pm 75 \text{ } \mu\text{g/mm}^3$.³

†The PT and PTT actually decrease slightly, but remain within the normal non-pregnant range.

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- 1 Biswas S, Rodeck CH. Plasma prolactin levels during pregnancy. *Br J Obstet Gynaecol* 1976;**83**:683–7.
- 2 Noltén WE, Lindheimer MD, Rueckert PA, Oparil S, Ehrlich EN. Diurnal patterns and regulation of cortisol secretion in pregnancy. *J Clin Endocrinol Metab* 1980;**51**:466–72.
- 3 Pitkin RM, Witte DL. Platelet and leukocyte counts in pregnancy. *JAMA* 1979;**242**:2696–8.

APPENDIX C

Evaluation of fetal defects and maternal disease

Lynn L. Simpson

Table C-1 Risk of karyotypic abnormalities related to maternal age at delivery. (From Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. *JAMA* 1983;**249**:2034.)

Maternal age (years)	Incidence of trisomy 21		Incidence of any abnormality	
	Livebirth	Amniocentesis	Livebirth	Amniocentesis
20	1/1734	1/1231	1/526	
25	1/1250	1/887	1/476	
30	1/965	1/685	1/385	
31	1/915	1/650	1/385	
32	1/794	1/563	1/322	
33	1/639	1/452	1/286	
34	1/496	1/352	1/238	
35	1/386	1/274	1/192	1/83
36	1/300	1/213	1/156	1/76
37	1/234	1/166	1/127	1/67
38	1/182	1/129	1/102	1/58
39	1/141	1/100	1/83	1/49
40	1/100	1/78	1/66	1/40
41	1/86	1/61	1/53	1/32
42	1/66	1/47	1/42	1/26
43	1/52	1/37	1/33	1/21
44	1/40	1/29	1/26	1/19
45	1/31	1/22	1/21	1/15
46	1/24	1/17	1/16	1/12
47	1/19	1/13	1/13	1/20
48	1/15	1/10	1/10	1/18
49	1/11	1/8	1/8	1/16

Table C-2 Frequency of chromosome aberrations in newborns. (Modified from a summary of six surveys (Hook and Hamerton 1977) including 56,952 newborns.)

Aberration	Incidence	
Numerical		
<i>Sex chromosomes</i>		
47,XXX	1/1000	MB
47,XXY	1/1000	MB
Other (males)	1/1350	MB
45,X	1/10,000	FB
47,XXX	1/1000	FB
Other (female)	1/2700	FB
Autosomes		
<i>Trisomies*</i>		
No. 13–15 (group D)	1/20,000	LB
No. 16–18 (group E)	1/8000	LB
No. 21–22 (group G)	1/800	LB
<i>Other</i>	1/50,000	LB
Structural		
<i>Balanced</i>		
Robertsonian		
t(Dq;Dq)	1/1500	LB
t(Dq;Gq)	1/5000	LB
Reciprocal translocations and insertional inversions	1/7000	LB
<i>Unbalanced</i>		
Robertsonian	1/14,000	LB
Reciprocal and insertional	1/8000	LB
Inversions	1/50,000	LB
Deletions	1/10,000	LB
Supernumeraries	1/5000	LB
Other	1/8000	LB
Total	1/160	LB

FB, female births; LB, livebirths; MB, male births.

*Because most surveys did not use banding techniques, individual chromosomes within a group could not always be differentiated. However, group D trisomies are generally no. 13, group E no. 18, and group G no. 21.

Table C-3 Available prenatal diagnosis for common disorders. (Modified from Jenkins TM, Wapner RJ. Prenatal diagnosis of congenital disorders. In: Creasy RK, Resnik R, Iams JD, eds. *Maternal–Fetal Medicine*, 5th edn. Philadelphia, PA: Saunders, 2004: 260.)

Disorder	Mode of inheritance	Molecular diagnosis
α_1 -Antitrypsin deficiency	AR	Determine PiZZ allele
α -Thalassemia	AR	α Hemoglobin gene mutation
Adult polycystic kidney	AD	PKD1 and PKD2 gene mutations
β -Thalassemia	AR	β Hemoglobin gene mutation
Congenital adrenal hyperplasia	AR	CYP21A2 gene mutations and deletions
Cystic fibrosis	AR	CFTR gene mutation
Duchenne–Becker muscular dystrophy	XLR	Dystrophin gene mutation
Fragile X syndrome	XLR	CGG repeat number
Hemoglobinopathy (SS, SC)	AR	β -Chain gene mutation
Hemophilia A	XLR	Factor VIII gene inversion and mutations
Huntington disease	AD	CAG repeat number
Marfan syndrome	AD	Fibrilin (FBN-1) gene mutation
Myotonic dystrophy	AD	CTG expansion in the DMPK gene
Neurofibromatosis type 1	AD	NF1 gene mutation
Phenylketonuria	AR	Common mutations
Tay–Sachs disease	AR	Enzyme absence and gene mutation

AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive.

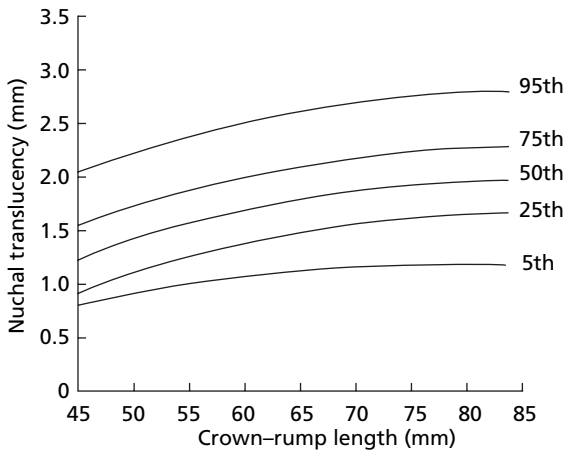


Fig. C-1 Nuchal translucency measurements between 11 and 14 weeks' gestation. Nuchal translucency >95th percentile associated with risk of trisomy 21. (From Nicolaides KH, Sebire NJ, Snijders RJM. *The 11–14 Week Scan*. New York, NY: Parthenon, 1999.)

Table C-4 Prevalence of major cardiac defects by nuchal translucency thickness in chromosomally normal fetuses. (From Hyatt J, Perdu M, Sharland G, *et al.* Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks of gestation: population based cohort study. *BMJ* 1999;**318**:81.)

Nuchal translucency	n	Major cardiac defects	Prevalence per 1000
<95th percentile	27,332	22	0.8
≥95th percentile–3.4 mm	1507	8	5.3
3.5–4.4 mm	208	6	28.9
4.5–5.4 mm	66	6	90.0
≥5.5 mm	41	8	195.1
Total	29,154	50	1.7

Table C-5 Increased risk for neural tube defect (NTD).

Sibling with NTD	2%
Parent with NTD	2%
Sibling with spinal dysraphism	4%
Sibling with multiple vertebral anomalies	2%
Cousin with NTD	0.5%
Sibling with communicating hydrocephalus	1%
Elevated maternal serum alpha-fetoprotein	10%

Table C-6 White's classification of diabetes during pregnancy.

Class	Definition
A	Abnormal glucose tolerance test
B	Onset after age 20 and duration less than 10 years
C	Onset at age 10–20 years or duration of 10–20 years
D	Onset before age 10 or duration of 20 or more years; benign retinopathy
F	Renal disease
H	Coronary artery disease
R	Proliferative retinopathy
T	Renal transplant

Table C-7 Diagnostic criteria for 100-g 3-h oral glucose tolerance test. No data from clinical trials to determine which values are superior for diagnosis. (Modified from Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diab Care* 2000;**23**:S4.)

Time (h)	Carpenter/Coustan values* Glucose level (mg/dL)	O'Sullivan/Mahan values* Glucose level (mg/dL)
Fasting	95	105
1	180	190
2	155	165
3	140	145

*If two or more of the glucose levels are equal to or higher than the values listed, gestational diabetes is diagnosed.

Table C-8 Drugs associated with congenital malformations in humans. (Modified from Andres RL. Effects of therapeutic, diagnostic, and environmental agents and exposure to social and illicit drugs. In: Creasy RK, Resnik R, Iams JD, eds. *Maternal-Fetal Medicine*, 5th edn. Philadelphia, PA: Saunders, 2004: 282.)

Drug	Potential defect	Comments
ACE inhibitors	Renal dysgenesis, oligohydramnios, IUGR, and skull ossifications defects. Neonatal renal failure	Risk increases with use in second and third trimester
Alcohol	Prenatal and postnatal growth restriction, CNS abnormalities (microcephaly and mental retardation), and craniofacial dysmorphism (fetal alcohol syndrome). Renal, cardiac, and other major malformations	Risk not limited to first trimester. Late pregnancy use associated with IUGR and developmental delay. Incidence of defects >30% among "heavy drinkers"
Aminopterin and methotrexate	SAB, craniofacial dysmorphism, limb defects, NTD, craniosynostosis, and IUGR	Folic acid antagonists. Anomalies in 30% of liveborn fetuses
Androgens and norprogesterones	Masculinization of external female genitalia	Labioscrotal fusion can occur with exposure < 9 weeks. Cliteromegaly possible at any gestational age

Continued

Drug	Potential defect	Comments
Carbamazepine	NTD, craniofacial abnormalities, nail hypoplasia, IUGR, and developmental delay	Risks of NTD 1–2%
Diethylstilbestrol	Clear cell adenocarcinoma of the vagina, vaginal adenosis, abnormalities of the cervix and uterus, testicular abnormalities, and male/female infertility	Risk of carcinoma rare. Exposure in first trimester = 50% vaginal adenosis
Isotretinoin	CNS defects, abnormal ears, thymic abnormalities, cardiac defects, and fetal death	As many as 50% of exposed are affected
Lithium	Cardiac defects (Ebstein anomaly)	Greatest risk (1%) in first trimester
Penicillamine	Cutis laxa	Seen with chronic use
Phenytoin	Craniofacial dysmorphism, IUGR, nail hypoplasia, microcephaly, and developmental delay	Full syndrome in 10%. As many as 30% exhibit some manifestations
Streptomycin	Hearing loss, eighth nerve damage	
Tetracycline	Discoloration of deciduous teeth and enamel hypoplasia	Risk only in second and third trimester
Thalidomide	Limb reduction defects, ear and cardiac abnormalities	Critical period 38–50 days postconception. 20% of exposed are affected
Trimethadione	Developmental delay, V-shaped eyebrows, oral clefts, and craniofacial abnormalities	80% rate of abnormalities associated with first trimester exposure
Valproic acid	NTD, minor facial defects	Risk of NTD 1%
Warfarin	Nasal hypoplasia, stippled epiphyses, and CNS abnormalities	Greatest risk from 6–9 weeks; 15–25% affected

ACE, angiotensin-converting enzyme; CNS, central nervous system; IUGR, intrauterine growth restriction; NTD, neural tube defect; SAB, spontaneous abortion.

Table C-9 Food and Drug Administration categories for drug labeling. The Food and Drug Administration has established five categories of drugs based on their potential for causing birth defects in infants born to women who use the drugs during pregnancy. By law, the label must set forth all available information on teratogenicity.

Category A	Well-controlled human studies have not disclosed any fetal risk. Possibility of fetal harm appears to be remote
Category B	Animal studies have not disclosed any fetal risk, or have suggested some risk not confirmed in controlled studies in women, or there are not adequate studies in women
Category C	Animal studies have revealed adverse fetal effects; there are no adequate controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus
Category D	Evidence of human fetal risk, but benefits may outweigh risk (e.g. life-threatening illness, no safer effective drug). Patient should be warned of risk
Category X	Fetal abnormalities in animal and human studies; risk of the drug not outweighed by benefit. <i>Contraindicated in pregnancy</i>

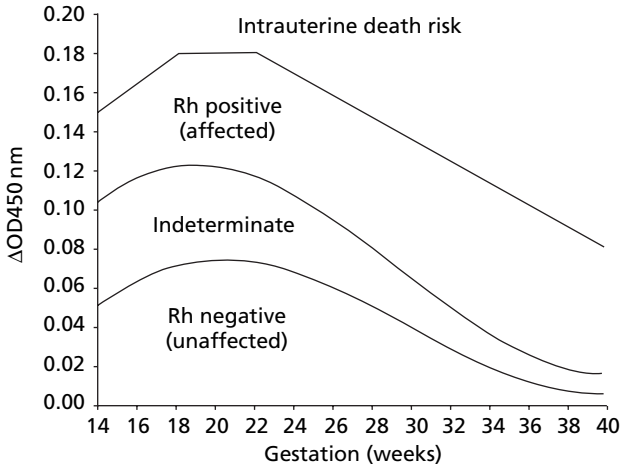


Fig. C-2 Amniotic fluid $\Delta OD_{450\text{ nm}}$ management zones. (From Queenan JT, Tomai TP, Ural SH, *et al.* Deviation in amniotic fluid optical density at a wavelength of 450 nm in Rh-immunized pregnancies from 14 to 40 weeks' gestation: a proposal for clinical management. *Am J Obstet Gynecol* 1993;**168**:1370.)

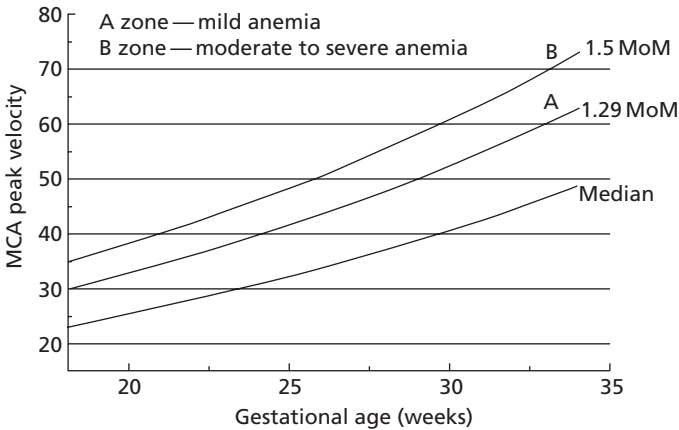


Fig. C-3 Middle cerebral artery (MCA) Doppler peak velocities. Peak MCA Doppler velocity $> 1.5\text{ MoM}$ for gestational age predictive of fetal anemia. (From Moise KJ. Modern management of Rhesus alloimmunization in pregnancy. *Obstet Gynecol* 2002;**100**:600.)

Table C-10 Hemolytic disease resulting from irregular antibodies. (Modified from Weinstein L. Irregular antibodies causing hemolytic disease of the newborn: a continuing problem. *Clin Obstet Gynecol* 1982;25:321.)

Blood group system	Antigen	Severity of hemolytic disease	Blood group system	Antigen	Severity of hemolytic disease
Rh subtype	C	+ to +++	Lutheran	Lua	+
	Cw	+ to +++		Lub	+
	c	+ to +++	Diego	Dia	+ to +++
	E	+ to +++		Dib	+ to +++
	e	+ to +++		P	P
Lewis	Lea	-		PPIPk (Tja)	+ to +++
	Leb	-			
I	I	-	Xg	Xga	+
Kell	K	+ to +++	Public antigens	Yta	+ to ++
	k	+		Ytb	+
	Ko	+		Lap	+
	Kpa	+		Ena	+ to +++
	Kpb	+		Ge	+
	Jsa	+		Jra	+
	Jsb	+		Coa	+ to +++
				Coab	+
Duffy	Fya	+ to +++	Private antigens	Batty	+
	Fyb	-		Becker	+
	Fy3	+		Berrens	+
Kidd	Jka	+ to +++		Biles	+ to ++
	Jkb	+ to +++		Evans	+
	Jk3	+		Gonzales	+
MNSs	M	+ to +++		Good	+ to +++
	N	-		Heibel	+ to ++
	S	+ to +++		Hunt	+
	s	+ to +++		Jobbins	+
	U	+ to +++		Radin	+ to ++
	Mia	++		Rm	+
	Mta	++		Ven	+
	Vw	+		Wrighta	+ to +++
	Mur	+		Wrightb	+
	Hil	+		Zd	+ to ++
	Hut	+			

-, Not a proven cause of hemolytic disease of the newborn, no change in management.

+, Mild, expectant management with no further diagnostic testing or intervention until delivery.

++, Moderate, serial evaluations with middle cerebral Dopplers or amniotic fluid Δ OD450.

+++, Severe, serial evaluations with middle cerebral Dopplers or AF Δ OD450.

Table C-11 Fetal blood sampling.

Test	Tube type	Minimum amount (mL)
Complete blood count, differential, reticulocyte count	Purple	0.3
Type and cross	Dry Bullet (Salmon)	0.5
Direct/indirect Coombs	Dry Bullet (Salmon)	0.5
Total IgM	Red	0.5
Toxoplasma and CMV IgM	Red	0.5
Rubella IgM	Red	0.5
Parvovirus IgG and IgM	Red	1.0
CMV blood culture	Red	1.0
Bilirubin (total and direct)	Red	0.5
Total protein and albumin	Red	0.5
Chem-7	Red	0.5
Chem-20	Red	1.0
Kleihauer–Betke stain	Purple	0.5
Prothrombin time/partial thromboplastin time	Blue	1.8
Clotting factor level	Blue (on ice)	1.8
Venous blood gas	Heparinized TB	0.3
Arterial blood gas	Heparinized TB	0.3
Chromosomes	Green	1.0
FISH	Green	1.0
Cystic fibrosis DNA testing	Green	3–4
Polymerase chain reaction	Purple/green	0.5

CMV, cytomegalovirus; FISH, fluorescence *in situ* hybridization; Ig, immunoglobulin; TB, tuberculin syringe.

APPENDIX D

The newborn: reference charts and tables

Adam Rosenberg

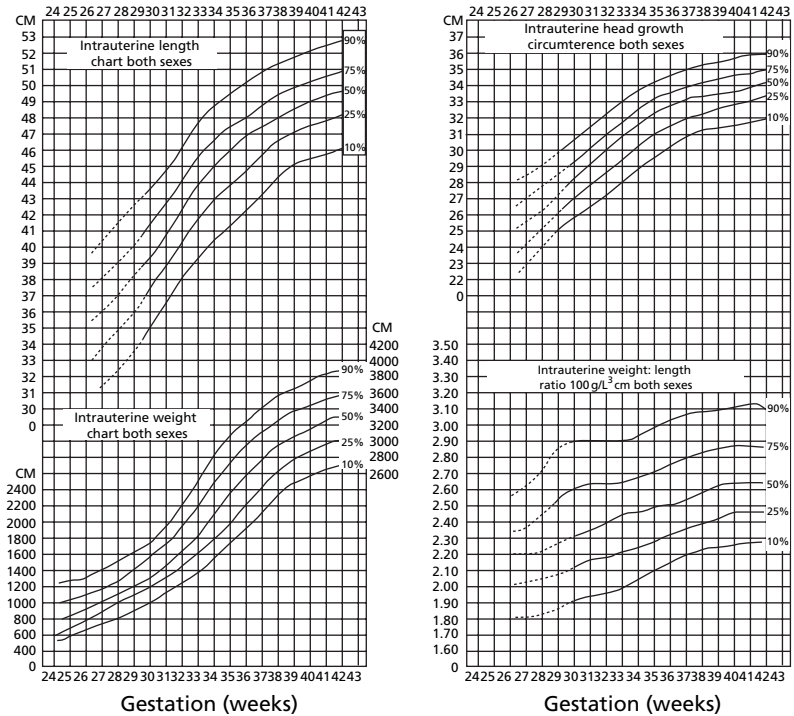


Fig. D-1 Intrauterine growth curves for weight, length, and head circumference for singleton births in Colorado. (Reproduced with permission from Lubchenco LO, *et al.* Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26–42 weeks. *Pediatrics* 1966;37:403.)

Table D-1 Relative timing and developmental pathology of certain malformations. (Adapted from Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 5th edn. Philadelphia, PA: WB Saunders, 1997.)

System	Malformation	Embryology	Timing	Comment
Central nervous system	Anencephaly	Closure of anterior neural tube	26 days	Subsequent degeneration of forebrain
	Meningomyelocele	Closure of posterior neural tube	28 days	80% lumbosacral
Face	Cleft lip	Closure of lip	36 days	42% with cleft palate
	Cleft maxillary palate	Fusion of maxillary palatal shelves	10 weeks	
	Branchial sinus and/or cyst	Resolution of branchial cleft	8 weeks	Preauricular ; anterior to the sternocleidomastoid
Gastrointestinal	Esophageal atresia/tracheoesophageal fistula	Lateral septation of foregut into trachea and foregut	30 days	
	Anal atresia with fistula	Lateral septation of cloaca into rectum and urogenital sinus	6 weeks	
	Duodenal atresia	Recanalization of duodenum	7–8 weeks	
	Malrotation	Rotation of intestinal loop	10 weeks	
	Omphalocele	Return of midgut from yolk sac to abdomen	10 weeks	
	Meckel diverticulum	Obliteration of vitelline duct	10 weeks	May contain gastric or pancreatic tissue
	Diaphragmatic hernia	Closure of pleuroperitoneal canal	6 weeks	Associated with lung hypoplasia
Genitourinary	Bladder exstrophy	Migration of infraumbilical mesenchyme	30 days	Associated mullerian and wolffian duct defects
	Hypospadias Cryptorchidism	Fusion of urethral folds Descent of teste into scrotum	12 weeks 7–9 months	
Cardiac	Transposition of great vessels	Directional development of bulbus cordis septum	34 days	
	Ventricular septal defect	Closure of ventricular septum	6 weeks	
Limb	Aplasia of radius	Genesis of radial bone	38 days	
	Syndactyly, severe	Separation of digital rays	6 weeks	

Table D-2 Types of genetic abnormalities. (Adapted from Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 5th edn. Philadelphia, PA: WB Saunders, 1997.)

Gene dosage effects	Chromosomal maldistribution	Aneuploidy Trisomies 21, 18, 13 etc
	Chromosomal rearrangements	Translocations, fragility, duplications, deletions, submicroscopic deletions
Major mutant genes	Autosomal dominant	Over 6000 individually rare disorders
	Autosomal recessive	
	X-linked	
	Mitochondrial	
Multifactorial inheritance	Major and minor genes determining susceptibility interacting with the environment	Common isolated malformations, schizophrenia, coronary artery disease, hypertension, diabetes



Fig. D-2 Mortality rates reported by gestational age in 2001. Population consists of 32,339 infants from 408 centers worldwide reporting data on births < 1500 g to the Vermont Oxford Network. (Reproduced with permission from the Vermont Oxford Network, 2002.)

Mortality by birthweight
Vermont Oxford Network 2001

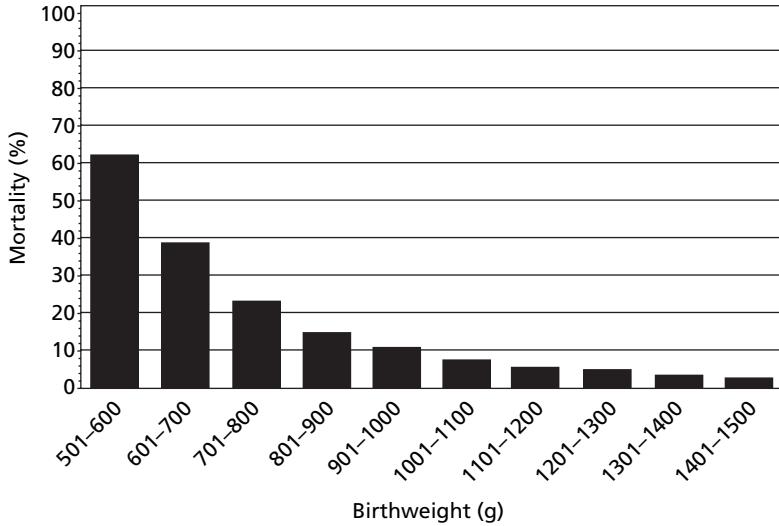


Fig. D-3 Mortality rates before discharge by 100-g birth weight subgroups in 2001. Population consists of 32,339 infants from 408 centers worldwide reporting data on births < 1500 g to the Vermont Oxford Network. (Reproduced with permission from the Vermont Oxford Network, 2002.)

Table D-3 Assessment of gestational age using the Ballard examination. The examination evaluates physical and neurologic characteristics of the infant. (Reproduced with permission from Ballard JL *et al.* New Ballard score, expanded to include extremely premature infants. *J Pediatr* 1991;**119**:417.)

Neuromuscular maturity								
Neuromuscular maturity sign	Score							Record score here
	-1	0	1	2	3	4	5	
Posture								
Square window (wrist)								
Arm recoil								
Popliteal angle								
Scarf sign								
Heel to ear								
Total neuromuscular maturity score								
Physical maturity								
Physical maturity sign	Score							Record score here
	-1	0	1	2	3	4	5	
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling &/or rash; few veins	Cracking pale areas rare veins	Parchment, deep cracking no vessels	Leathery, cracked, wrinkled	
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald		
Plantar suriace	Heel toe 40-50mm; -1 <140mm: -2	>50 mm: no crease	Faint red marks	Anterior transverse crease only	Creases anterior two-thirds	Creases over entire sole		
Breast	Imperceptible	Barely perceptible	Flat areola; no bud	Stippled areola; 1- to 2-mm bud	Raised areola; 3- to 4-mm bud	Full areola; 5- to 10-mm bud		
Eye/Ear	Lids fused loosely: -1 tightly: -2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna; soft but ready recoil	Formed and firm instant recoil	Thick cartilage; ear stiff		
Genitals (male)	Scrotum flat, smooth	Scrotum empty; faint rugae	Testes in upper canal; rare rugae	Testes descending; few rugae	Testes down; good rugae	Testes pendulous; deep rugae		
Genitals (female)	Clitoris prominent and labia flat	Prominent clitoris and small labia minora	Prominent clitoris and enlarging minora	Majora and minora equally prominent	Majora large; minora small	Majora cover clitoris and minora		
Total physical maturity score								

Maturity	Score	-10	-5	0	5	10	15	20	25	30	35	40	45	50
Rating	Weeks	20	22	24	26	28	30	32	34	36	38	40	42	44

Table D-4 Incidence of common complications in preterm infants. Recalculated based on cumulative data reported to the Vermont Oxford Neonatal Network. This represents information on 32,339 infants reported from 408 centers with a birthweight <1500 g. Severe IVH is a grade 3 or 4 intraventricular hemorrhage and severe ROP is retinopathy of prematurity at prethreshold or threshold for treatment. (Reproduced with permission, Vermont Oxford Network, 2002.)

Complication	501–700 g	701–900 g	901–1100 g	1101–1300 g	1301–1500 g
Respiratory distress syndrome (%)	93	90	79	67	52
Mechanical ventilation (%)	90	89	79	62	47
Late onset sepsis/meningitis (%)	23	18	11	7	5
Patent ductus arteriosus (%)	52	52	39	27	17
Necrotizing enterocolitis (%)	9	9	7	4	2
Severe IVH (%)	24	16	9	6	3
Periventricular leukomalacia (%)	5	5	3	2	2
Severe ROP (%)	36	20	7	1	1
Chronic lung disease (%)	79	53	32	19	11

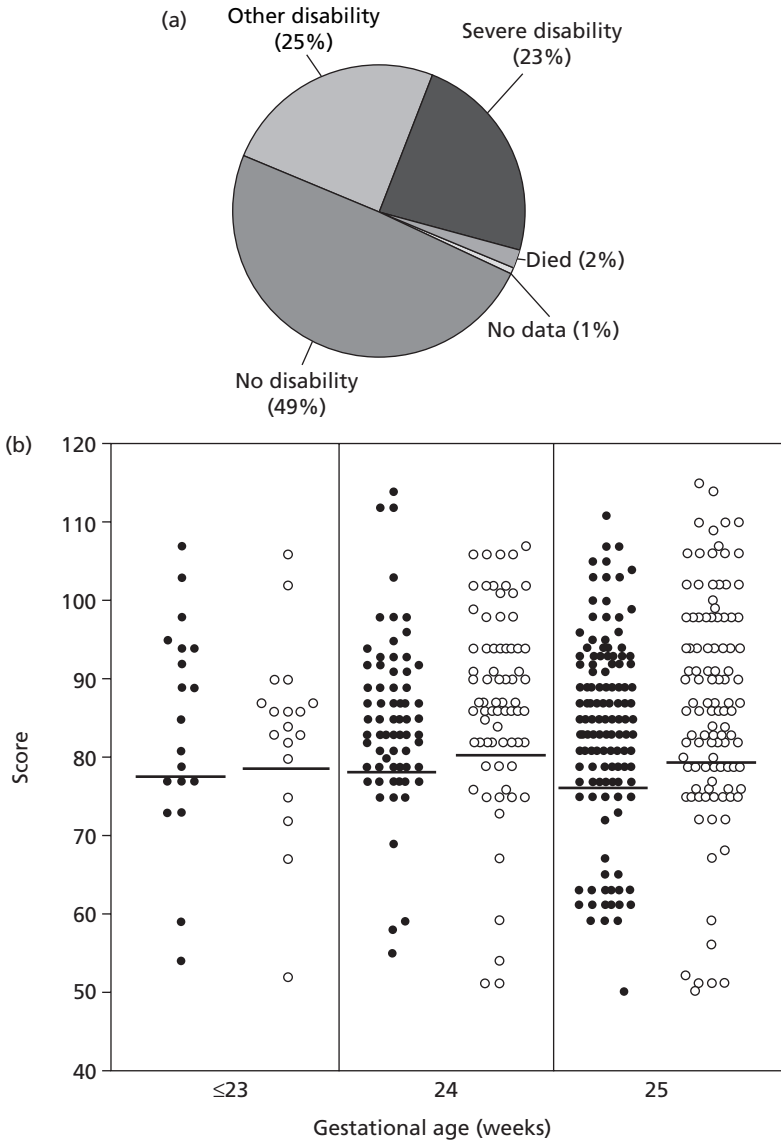


Fig. D-4 Neurodevelopmental outcome in infants born at 23–25 weeks gestation. (a) Disability includes cerebral palsy, cognitive and behavioral disorders. The incidence of neurodevelopmental handicap is less at higher gestational ages with infants of 28–32 weeks gestational age at birth experiencing a < 10% rate of severe disability. (b) Represents scores on the Bayley scales of infant development at 30 months for 23–25 weeks' gestational age survivors. The open circles are scores on the psychomotor portion and the closed circles scores on the mental portion of the test. The mean score for a normal term population is 100; the means here are 1 standard deviation below that level. Thirty month Bayley scores correlate well with school age outcome. (Reproduced with permission from Wood NS, *et al.* Neurologic and developmental disability after extremely preterm birth. *N Engl J Med* 2000;343:378.)

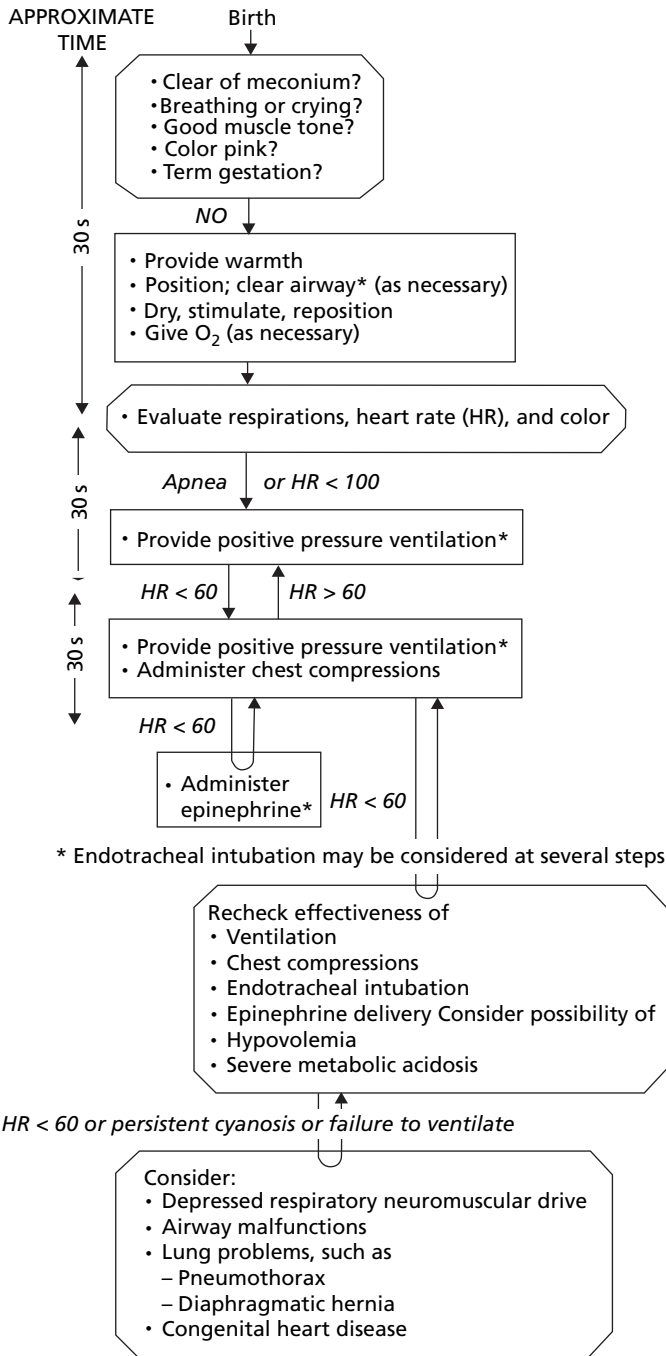


Fig. D-5 Neonatal resuscitation program schema for delivery room management of the newborn. (Reproduced with permission from the American Heart Association, American Academy of Pediatrics. *Neonatal Resuscitation Textbook*, 4th edn, 2000.)

Table D-5 Traumatic birth injury in the newborn.

Type of injury	Examples
Soft-tissue injuries	Abrasions, bruising, fat necrosis, lacerations
Extracranial bleeding	Cephalohematoma, subgaleal bleed
Intracranial bleeding	Subarachnoid, epidural, subdural, cerebral, cerebellar
Nerve injuries	Facial, cervical nerve roots (brachial plexus palsies, phrenic), Horner syndrome, recurrent laryngeal
Spinal cord injuries	Epidural hemorrhage of the cervical cord
Fractures	Clavicle, humerus, femur, skull
Dislocations	
Torticollis (sternocleidomastoid bleeding)	
Eye injuries	Subconjunctival and retinal hemorrhages
Solid organ injury	Liver, spleen

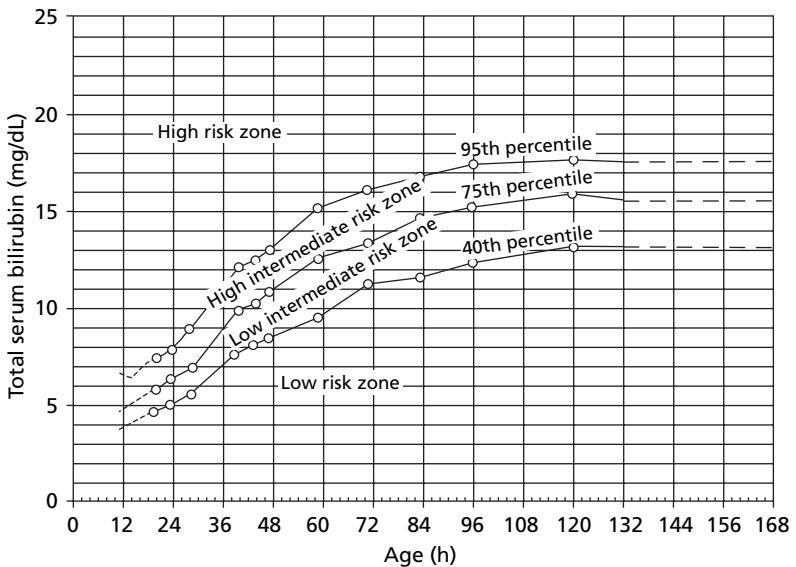


Fig. D-6 Risk designation of term and near term newborns based on their hour specific bilirubin values. Infants with a total serum bilirubin greater than the 95th percentile for age in hours have a 40% risk of developing subsequent significant hyperbilirubinemia. (Reproduced with permission from Bhutani VK, *et al.* Predictive ability of a predischarge hour-specific serum bilirubin test for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics* 1999;**103**:6.)

Table D-6 Guidelines for successful breastfeeding. (Reproduced with permission from Gabrielski L. *Lactation Support Services*. The Childrens Hospital, Denver, 1999.)

	First 8 h	8-24 h	Day 2	Day 3	Day 4	Day 5	Day 6 onward
Milk supply	You may be able to express a few drops of milk	Wake up your baby.	Milk should come in between the second and fourth days			Milk should be in. Breasts may be firm or leak milk	Breasts should feel softer after feedings
Baby's activity	Baby is usually wideawake in the first hour of life. Put baby to breast within 30 minutes after birth	Babies may not wake up on their own to feed	Baby should be more cooperative and less sleepy	Look for early feeding cues such as rooting and hands to face		Breasts may be firm or leak milk	Baby should appear satisfied after feedings
Feeding routine	Baby may go into a deep sleep 2-4 hours after birth	Feed your baby every 1-4 hours or as often as wanted—at least 8-12 times a day	Use chart to write down time of each feeding			May go one longer interval (up to 5 h between feeds) in a 24-h period	

Continued



Breast feeding	Baby will wake up and be alert and responsive for several more hours after initial deep sleep	As long as mother is comfortable, nurse at both breasts as long as baby is actively sucking	Try to nurse both sides each feeding, aiming at 10 min per side. Expect some nipple tenderness	Consider hand expressing or pumping a few drops of milk to soften the nipple if the breast is too firm for the baby to latch on	Nurse a minimum of 10–30 min per side every feed for the first few weeks of life Once milk supply is well established, allow baby to finish the first breast before offering the second	Mom's nipple tenderness is improving or is gone
Baby's urine output	Baby must have a minimum of one wet diaper in first 24 h	Baby must have at least one wet diaper every 8–11 h	Baby must see an increase in wet diapers (up to 4–6) in 24 h	You should see an increase in wet diapers (up to 4–6) in 24 h	Baby's urine should be light yellow Baby should have 6–8 wet diapers per day of colorless or light yellow urine	The number of stools may decrease gradually after 4–6 weeks of life
Baby's stool	Baby should have a black–green (meconium) stool	Baby may have a second very dark (meconium) stool	Baby's stools should be in transition from black–green to yellow.	Baby's stools should be in transition from black–green to yellow.	Baby should have 3 or 4 yellow, seedy stools a day	

Medications cited

Catalin S. Buhimschi and Carl P. Weiner

It is very important for the clinician to become familiar with all aspects of drugs that they prescribe. The purpose of this Appendix is to provide a quick resource of drugs commonly used for pregnant and lactating women. The information provided in this appendix is very concise, user friendly, and will allow rapid access to the drug-related questions mentioned in this text.

Generic name	Type	Trade name®	Class	Dose
Acetaminophen	Analgesic, antipyretic	Tylenol	Pregnancy: B Lactation: S	Pain and/or fever: 650–1000 mg PO/PR q 4–6 h; max 4 g/day
Aciclovir	Antivirals	Zovirax	Pregnancy: B Lactation: S	Genital herpes, recurrent: 200 mg PO 5×/day ×10 days Genital herpes, suppressive: 400 mg PO b.i.d. for up to a year, or during pregnancy, from 36 weeks onward; with HIV, 400–800 mg PO 2–3×/day, or 5–10 mg/kg IV q 8 h ×5–10 days

Continued

Generic name	Type	Trade name	Class	Dose
				Varicella, acute: 800 mg PO q.i.d. ×5 days Herpes zoster: 800 mg PO 5×/day ×7–10 days Ocular herpes: 3% ointment 5×/day ×7–10 days
Adalimumab	Antitumor necrosis factor α	Humira	Pregnancy: B Lactation: U	Rheumatoid arthritis: SC 40 mg every other week
Albuterol	Adrenergic agonists; Bronchodilators	Proventil	Pregnancy: C Lactation: S	Bronchospasm: 1–2 puffs metered dose inhaler q 4–6 h, max 12 puffs/day or 2–4 mg PO t.i.d./q.i.d. Exercise- induced asthma: 2 puffs metered dose inhaler ×1 given 15–30 min before exercise
Amantadine	Antiviral, extrapyramidal movement disorder	Contenton	Pregnancy: C Lactation: U	Influenza A: Treatment: 200 mg/day PO until 24–48 h after symptoms resolve

Continued

Generic name	Type	Trade name	Class	Dose
Amfebutamone	Antidepressants; SSRI	Zyban; Wellbutrin	Pregnancy: B Lactation: S (likely)	<p>Prophylaxis: 200 mg/day PO beginning immediately after exposure and continuing at least 10 days</p> <p>Extrapyramidal reactions: 100 mg/day PO to t.i.d. (max 300 mg/day)</p> <p>Parkinsonism: begin 100 mg/day PO, increase to b.i.d. after 1 week, max 400 mg/day; reduce to 100 mg/day if taking other antiparkinsonism drugs</p> <p>Depression: 100 mg PO t.i.d.; max dose 150 mg PO t.i.d.</p> <p>Smoking cessation: 150–300 mg PO b.i.d.; patient quits smoking after 5–7 days of treatment; 2nd dose should not be later than 6 pm and at least 8 h after 1st dose</p>

Continued

Generic name	Type	Trade name	Class	Dose
Aminophylline	Antiasthmatics, Bronchodilators; Xanthine derivatives	Aminophylline	Pregnancy: C Lactation: U	Bronchospasm: 0.3–0.8 mg/kg/h IV preceded by a variety of recommended loading doses (0.3–6 mg/kg over 12 h IV); alternatively 10–16 mg/kg/day PO
Amoxicillin/ clavulanate	Antibiotics; Penicillins	Augmentin	Pregnancy: B Lactation: S	Bacterial infection: 250–500 mg PO t.i.d., or 500–750 mg PO b.i.d. NOTE: Combined with either clarithromycin and lansoprazole/omeprazole Gonorrhea uncomplicated: 3 g PO ×1 <i>Chlamydia trachomatis:</i> 500 mg PO t.i.d. ×7 days Endocarditis prophylaxis: 2 g PO ×1, 0.5–1 h prior to the procedure <i>H. pylori</i> infection: 1 g PO b.i.d. ×10–14 days

Continued

Generic name	Type	Trade name	Class	Dose
				NOTE: Serum levels should be periodically monitored and maintained at 10–20 µg/mL
Ampicillin	Antibiotics; Penicillins	Unasyn	Pregnancy: B Lactation: S	Bacterial infection: 1.5–3 g IV/IM q 6 h; max 8 g/day NOTE: Coupling to the beta-lactamase inhibitor, sulbactam enhances the spectrum of coverage
Anakinra	Anti-interleukin one	Kineret	Pregnancy: B Lactation: U	Rheumatoid arthritis: 100 mg SC every other week
Atenolol	Antiadrenergics; Beta-blockers	Alinor	Pregnancy: B Lactation: NS	Hypertension: 50 mg/day PO; increase to 100 mg/day after 7 days MI: begin 5 mg IV over 5 min ×2 (10 min apart), then 50 mg PO q 12 h ×7 days, then 100 mg/day Angina: 50 mg/day PO, max 200 mg/day

Continued

Generic name	Type	Trade name	Class	Dose
Atropine	Anesthesia, adjunct; Antiarrhythmics; Antidotes; Cycloplegics; Mydriatics; Ophthalmics	Atropen	Pregnancy: C Lactation: U	<p>Symptomatic bradycardia: 0.5–1 mg IV q 3–5 min p.r.n., max 2 mg</p> <p>NOTE: May be combined with either difenoxin, diphenoxylate, or hyoscyamine, scopolamine and phenobarbital (Donnatal)</p> <p>Organophosphate poisoning: 1–2 mg IM/IV q 20–30 min until muscarinic symptoms resolve</p> <p>Adjunct to anesthesia: 0.4 mg IM/SC 30–60 min preoperatively to dry oral secretions before expected difficult airway management. Also given with anticholinesterase (atropine plus neostigmine when reversing neuromuscular paralysis at the end of surgery)</p>

Continued

Generic name	Type	Trade name	Class	Dose
Azathioprine	Immunosuppressants	Imuran	Pregnancy: D Lactation: U	<p>Transplant rejection: begin 3–5 mg/kg/day PO/IV; maintenance 1–3 mg/kg/day transplant protocols vary</p> <p>Crohn disease and ulcerative colitis: begin 50 mg/day PO increasing to 150–250 mg/day PO; max 2.5 mg/kg/day</p> <p>Rheumatoid arthritis: begin 1 mg/kg/day PO; increase 0.5 mg/kg/day after 6–8 weeks; max 2.5 mg/kg/day</p>
Azithromycin	Antibiotics; Macrolides	Aruzilina; Zithromax	Pregnancy: B Lactation: S (likely)	<p>Bacterial infection: 500 mg PO load ×1, then 250 mg/day PO ×6 days</p> <p>Chlamydia or chancroid: 1 g PO ×1</p> <p>Uncomplicated gonorrhea: 2 g PO ×1 (or 1 g) PO ×1 plus fluoroquinolone or ceftriaxone or cefixime</p>

Continued

Generic name	Type	Trade name	Class	Dose
				<p>PID: 500 mg/day IV \times2 days, then 250 mg/day PO \times6 days</p> <p>Community-acquired pneumonia: 500 mg/day IV \times2–5 days, then 500 mg/day PO for a total 7–10 days</p>
Beclometasone	Corticosteroids	Beclovent	Pregnancy: C Lactation: U	<p>Asthma: 4–16 inhalations/day</p> <p>NOTE: Each metered inhalation delivers 42 μg aerosolized drug</p> <p>Rhinitis: 1–2 inhalations/day in each nostril; max 336 μg/day</p> <p>Nasal polyp prophylaxis: 1–2 inhalations/day in each nostril; max 336 μg/day</p>
Betamethasone	Corticosteroids	Celestone	Pregnancy: C Lactation: U	<p>Prevention of RDS in preterm neonates in women with preterm labor <34 weeks: 12.5 mg IM \times2 doses 24 h apart</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Bursitis/ tendonitis: 1 mL into the tendon sheath or joint combined with a local anesthetic agent Rheumatoid arthritis or osteoarthritis: 0.5–2 mL into the joint
Bromocriptine	Antiparkinson agents; Dopaminergics; Ergot alkaloids and derivatives	Parlodel	Pregnancy: B Lactation: NS	Parkinson disease: 10–40 mg/day PO Amenorrhea: 5–7.5 mg/h PO Acromegaly: 20–30 mg/q.h.s. PO
Budesonide	Corticosteroids; Corticosteroids, inhalation	Budocort	Pregnancy: C Lactation: S (likely)	Asthma: 0.5–1 mg/day inhalation Rhinitis: metered dose 50 µg/puff inhalation
Bupivacaine	Anesthetics, local	Bupivacaine HCl; Marcaine	Pregnancy: C Lactation: S	Local anesthesia: varies, max 2 mg/kg, 400 mg/day; onset 2–10 min, duration 3–6 h

Continued

Generic name	Type	Trade name	Class	Dose
				Conduction anesthesia: varies, recommend consulting a specialty text
Butorfanol	Analgesics, narcotic agonist- antagonist	Stadol		Pain: 0.5–2 mg IV q 3–4 h p.r.n. pain; begin 1 mg IV or 2 mg IM Preoperative sedation: 2 mg IV before induction Epidural anesthesia: consult a specialty text
Carbamazepine	Anticonvulsants	Tegretol	Pregnancy: C Lactation: S (likely)	Seizure disorder: 400–600 mg PO b.i.d. (or 12–25 mg/kg/day); max 600 mg PO b.i.d. Trigeminal neuralgia: 200–400 mg PO b.i.d.
Carboprost tromethamine	Abortifacients; Oxytocics; Prostaglandins; Stimulants, uterine contractility	Hemabate	Pregnancy: C Lactation: U	Pregnancy termination: begin 100 µg IM test dose, then 250 µg IM q 90–120 min; max 12 mg total or use no longer than 2 days

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Uterine atony: 250 µg IM ×1, may repeat q 15–90 min; max 2 mg</p> <p>Bacterial endocarditis: 1 g IV/IM 30 min before procedure</p>
Cefotaxime	Antibiotics; Cephalosporins, 3rd-generation	Claforan; Zetaxim	Pregnancy: B Lactation: S	<p>Bacterial infection: 1–2 g IM/IV q 8 h</p> <p>NOTE: Renal dosing</p> <p>Gonorrhea: 1 g IM ×1</p> <p>Surgical prophylaxis: 1 g IV/IM 30–90 min preoperatively</p>
Cephalexin	Antibiotics; Cephalosporins, 1st-generation	Biocef; Carnosporin	Pregnancy: B Lactation: S	<p>Bacterial infection: 250 mg –1 g PO q 6 h</p>
Cetirizine	Allergy; Antihistamines	Alltec; Zyrtec	Pregnancy: B Lactation: U	<p>Allergic rhinitis: 5–10 mg/day PO; max 10 mg/day</p> <p>Urticaria: 5–10 mg/day PO; max 10 mg/day</p>

Continued

Generic name	Type	Trade name	Class	Dose
Chlorpromazine	Antiemetics; antivertigo; Antipsychotics; Phenothiazines; Tranquilizers	Thorazine	Pregnancy: C Lactation: S (likely)	<p>Psychosis: 200–800 mg/day IM; divide dose t.i.d./q.i.d.</p> <p>NOTE: See Imipenem</p> <p>Nausea: 10–25 mg PO q 4–6 h</p> <p>Hiccups: 25–50 mg PO t.i.d./q.i.d.; if no response PO, may be given IM/IV</p> <p>Tetanus: 25–50 mg IM/IV q 6–8 h</p> <p>Porphyria (acute): 25–50 mg IM t.i.d./q.i.d.</p>
Clarithromycin	Antibiotics; Macrolides	Biaxin	Pregnancy: C Lactation: U	<p>Bacterial infection: 250–500 mg PO b.i.d.</p> <p><i>Mycoplasma avium</i> cellulare infection: 15 mg/kg/day PO; dose divided q 12 h</p> <p><i>Coxiella burnetii</i> (Q fever) during pregnancy: 250–500 mg PO b.i.d.</p>

Continued

Generic name	Type	Trade name	Class	Dose
Clavulanate	Anti-infectives		Pregnancy: B Lactation: S	Clavulanate: is combined with penicillin, amoxicillin, and ticarcillin to broaden their antibacterial spectrum to include certain Gram-negative bacteria NOTE: See penicillin, amoxicillin, and ticarcillin
Clindamycin	Antibiotics; Dermatologics; Lincosamides	Cleocin	Pregnancy: B Lactation: S	Bacterial infections: 150–450 mg PO q.i.d. ×7–14 days; max 4.8 g/day; alternatively, 300–900 mg IV q 6–12 h Bacterial vaginosis: 1 applicator PV q.h.s. ×3–7 days Acne vulgaris: apply 1% gel topically b.i.d.
Clomiphene citrate	Hormones; Stimulants, ovarian	Clomid	Pregnancy: X Lactation: U	Ovulation induction: 50 mg/day PO for 5 days (menstrual cycle days 5–10); max 100 mg/day PO

Continued

Generic name	Type	Trade name	Class	Dose
Cromolyn	Antiasthmatics; Mast cell stabilizers; Ophthalmics	Cromoglicic acid; Cromogloz	Pregnancy: B Lactation: S	<p>Mastocytosis: 200 mg PO q.i.d.</p> <p>Food allergy: 200 mg PO q.i.d.</p> <p>Inflammatory bowel disease: 200 mg PO q.i.d.</p> <p>Asthma and exercise-induced asthma (chronic treatment): 20 mg NEB q.i.d.</p> <p>Allergic rhinitis: 1 puff per nostril b.i.d./t.i.d. (5.2 mg/spray)</p> <p>Allergic conjunctivitis, vernal keratitis: 1 gtt OS/OD 4–6/day</p>
Cyclophosphamide	Antineoplastics, alkylating agent; Antirheumatics	Cytokan	Pregnancy: D Lactation: NS	<p>Chemotherapy: varies depending on tumor and protocol</p> <p>Mycosis fungoides: 2–3 mg/kg/day PO</p> <p>Rheumatoid arthritis: 1.5–3 mg/kg/day PO</p> <p>NOTE: Hydration is essential</p>

Continued

Generic name	Type	Trade name	Class	Dose
Cyclosporine	Immunosuppressants	Ciclosporin	Pregnancy: D Lactation: S (likely)	Prevention of transplant rejection: 5–10 mg/kg/day PO in two divided doses; 5–6 mg/kg IV 4–12 h before surgery
Danazol	Hormones, other gynecologic	Danocrine	Pregnancy: D Lactation: S (likely)	Endometriosis: begin 200–400 mg PO b.i.d. depending on severity; continue for 3–6 month trial Fibrocystic breast disease: 50–200 mg PO b.i.d. for 2–6 months, then adjust dose Hereditary angioedema: 200 mg PO t.i.d. until response, then half dose for 1–3 months
Dapsone	Antimycobacterials	Danocrine	Pregnancy: C Lactation: S (likely)	<i>Pneumocystis carinii</i> pneumonia: 100 mg/day PO; usually given with trimethoprim (20 mg/kg/day ×3 weeks)

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Dermatitis herpetiformis: begin 50 mg/day PO, increase to 300 mg/day as needed</p> <p>Malaria suppression: 100 mg/week PO, give with pyrimethamine 12.5 mg/week PO</p> <p>Leprosy prophylaxis: 100 mg/day PO ×2–4 months</p> <p>Leprosy treatment: 50 mg/day PO</p>
Dexamethasone	Corotason; Curson	Corotason	Pregnancy: C Lactation: U	<p>Prevention of RDS in preterm neonates: 6 mg IM q 12 h × 4 doses</p> <p>Cerebral edema: 10 mg IV, then 4 mg IM q 6 h</p> <p>Adrenal insufficiency: 0.03–0.15 mg/kg/day PO/IV/IM</p> <p>Inflammatory states: 0.75–9 mg PO/IV/IM</p> <p>Inflammatory ocular: 1–2 gtt q 1–6 h</p>

Continued

Generic name	Type	Trade name	Class	Dose
Diazepam	Anxiolytics; Benzodiazepines; Muscle relaxants	Tranquil; Valitran; Valium	Pregnancy: C Lactation: U	<p>Congenital adrenal hyperplasia: 0.5 mg/day and 2 mg/day PO</p> <p>Allergic reactions: 0.75–9 mg/day PO</p> <p>Shock: 1–6 mg/kg IV q 2–6 h p.r.n.</p> <p>Diagnostic test for Cushing disease: 2.0 mg dexamethasone PO q 6 h for 48 h; 24-h urine collection required to calculate 17-hydroxycorticosteroid production IV</p> <p>Postoperative N/V: 4–5 mg</p>
				<p>Anxiety: 2–10 mg IV/IM t.i.d./q.i.d.</p>
				<p>Alcohol withdrawal: 5 mg PO t.i.d./q.i.d. p.r.n.</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Seizure disorder: 2–10 mg PO b.i.d./q.i.d. Status epilepticus: 5–10 mg IV q 10–15 min Muscle spasm: 2–10 mg PO b.i.d./q.i.d.
Dicloxacillin	Antibiotics; Penicillins	Dycill; Dynapen	Pregnancy: B Lactation: S	Skin infection: 125–500 mg PO q 6 h, 1 h before or after a meal Osteomyelitis: 250–500 mg PO q 6 h, before or after a meal Mastitis: 250– 500 mg PO q 6 h, before or after a meal
Dimenhydrinate	Anticholinergics; Antiemetics; Antivertigo	Amosyt; Biodramina	Pregnancy: B Lactation: S	Motion sickness: 50–100 mg PO/IM/IV q 4–6 h; begin at least 30 min before anticipated activity, max 400 mg/day Migraine: 50–100 mg PO

Continued

Generic name	Type	Trade name	Class	Dose
Dinoprostone	Oxytocics; Prostaglandins	Cervidil; Prepidil; Prostin E2	Pregnancy: C Lactation: S	Cervical ripening: 0.5 mg gel PV endocervical, may repeat q 6 h × 2; alternatively, 10 mg insert PV into the posterior fornix (remain supine 2 h), remove with onset of labor or uterine tachysystole
Diphenhydramine	Antihistamines	Amidryl	Pregnancy: B Lactation: S	Antihistaminic: 25–50 mg PO/IV/IM q 6 h p.r.n. Anaphylaxis: 1–1.25 mg/kg PO/IV/IM q 4–6 h; max 300 mg/day Dystonic reactions: 25–50 mg PO t.i.d./q.i.d.; max 300 mg/day Sedation: 25–50 mg PO q.i.d. p.r.n. Insomnia: 50 mg PO q.h.s. Motion sickness: 25–50 mg PO q 4–6 h p.r.n.; max 300 mg/day

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Generic name	Type	Trade name	Class	Dose
Dopamine	Adrenergic agonists; Inotropes	Intropin	Pregnancy: C Lactation: NS	<p>Adjunct for shock: 1–50 µg/kg/min IV; max 20–50 µg/kg/min</p> <ul style="list-style-type: none"> • 2–5 µg/kg/min primarily dopaminergic receptor effects, but may exhibit a pressor effect • 5–10 µg/kg/min primarily beta-adrenergic effects with inotropy and chronotropy • > 10 µg/kg/min primarily alpha-adrenergic effects with peripheral vasoconstriction <p>Refractory CHF: 1–3 µg/kg/min IV</p>
Doxycycline	Antibiotics; Tetracyclines	Doxy; Doxy-100	Pregnancy: D Lactation: NS	<p>Gonorrhea, uncomplicated: 100 mg PO b.i.d. ×7 days</p> <p>Chlamydia: 100 mg PO b.i.d. ×7 days</p> <p>PID: 100 mg PO b.i.d. ×10–14 days with another agent such as ceftriaxone 250 mg IM</p>

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Malaria: 100 mg/day PO beginning 1–2 days before departure and continuing through 4 weeks after exposure</p> <p>Lyme disease: 100 mg PO b.i.d. ×14–21 days (28 days if associated with arthritis)</p> <p>Anthrax: 100 mg IV/PO q 12 h; postexposure, 100 mg PO q 12 h for 60 days or until disease excluded</p>
Doxylamine	Antihistamines	Nyquil	Pregnancy: B Lactation: S	<p>Allergies: 12.5–25 mg PO q 4–6 h; p.r.n.</p>
Droperidol	Anesthetics, adjunct; Antivertigo; Anxiolytics; Sedatives	Inapsine	Pregnancy: C Lactation: S	<p>Nausea and vomiting (perioperative): 0.625–1.25 mg IM/IV q 3–4 h p.r.n.</p>
Efavirenz	Antivirals; Non-nucleoside reverse transcriptase inhibitors	Sustiva	Pregnancy: C Lactation: NS	<p>HIV infection: 600 mg/day PO</p>

Continued

Generic name	Type	Trade name	Class	Dose
Enoxaparin	Anticoagulants; Low molecular weight heparins	Lovenox	Pregnancy: B Lactation: S (likely)	<p>Prophylaxis DVT: begin at 20–40 mg/day SC</p> <p>NOTE: Consult a specialty text such as High Risk Pregnancy: Management Options</p> <p>Antiphospholipid syndrome: begin at 20–40 mg/day SC</p> <p>Cesarean section: at least 40 mg/day SC until patient is active</p> <p>Treatment of acute thrombosis: 1–1.5 mg/kg SC q 12 h</p>
Ephedrine	Adrenergic agonists; Bronchodilators; Decongestants, nasal	Ephedrine	Pregnancy: C Lactation: S	Decongestant: 25–50 mg PO q 6 h (max 150 mg/day)
Epinephrine	Adrenergic agonists; Bronchodilators; Inotropes; Ophthalmics; Pressors	Adrenalin Chloride	Pregnancy: C Lactation: S	Severe asthma: 0.1–0.5 mg SC q 10–15 min

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Anaphylaxis: 0.1–0.5 mg SC q 10–15 min (or 0.1–0.25 mg IV over 5–10 min)</p> <p>Cardiac arrest: 0.5–1 mg IV q 3–5 min p.r.n. (or 1 mg via ET tube, 0.1–1 mg intracardiac); may follow with 1– 4 µg/min constant infusion</p>
Erythromycin	Antibiotics; Dermatologics; Macrolides; Ophthalmics	Akne-Mycin; C-Solve-2	Pregnancy: B Lactation: S	<p>Bacterial infection: 250–500 mg PO q 6–12 h</p> <p>Preterm PROM: 250 mg PO q.i.d. ×10 days</p>
Etanercept	Antitumor necrosis factor α	Enbrel	Pregnancy: B Lactation: U	Rheumatoid arthritis: 40 mg SC every other week
Famciclovir	Antivirals	Famvir	Pregnancy: B Lactation: U	<p>Genital herpes (1st episode): 250 mg PO t.i.d. ×7 days</p> <p>Genital herpes (recurrent): 125 mg PO b.i.d. ×5 days</p> <p>Genital herpes (prophylaxis): 250 mg PO b.i.d.</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Herpes zoster: 500 mg PO t.i.d. ×7 days
Fentanyl	Analgesics, narcotic; Anesthetics, general	Fentanyl Oralet	Pregnancy: C Lactation: S	Preoperative analgesia: 50–100 µg IV 30–60 min prior to surgery Anesthesia, adjunct: 2–50 µg/kg IV depending on needs Labor epidural anesthesia: approximately 25 µg intrathecal; 40–50 µg epidural: usually followed by a dose of 20–30 µg/h mixed in solution of dilute local anesthetics (consult a specialty text) Labor analgesia (IV): begin 50 µg IV, thereafter 25 µg q 20–30 min p.r.n. Postoperative pain relief: 50–100 µg IV q 1–2 h p.r.n.

Continued

Generic name	Type	Trade name	Class	Dose
Flunisolide	Corticosteroids, inhalation	AeroBid; Nasalide; Nasarel	Pregnancy: C Lactation: U	Asthma prophylaxis: 2 puffs INH bid (approx 50 µg per puff) Allergic rhinitis: 2 sprays/nostril b.i.d./t.i.d.
Fluticasone	Corticosteroids, inhalation; Corticosteroids, topical; Dermatologics	Cutivate; Flonase	Pregnancy: C Lactation: S	Asthma prophylaxis: begin 88 µg b.i.d. if on bronchodilator alone; max 880 µg b.i.d., taper to lowest effective dose
Formoterol	Adrenergic agonists; Bronchodilators	Foradil Aerolizer	Pregnancy: C Lactation: U	Asthma prophylaxis: 12 µg INH (inhalation) q 12 h Treatment of exercise-induced asthma: 12 µg INH 15–30 min prior to exercise; may repeat q 12 h p.r.n., max 24 µg/day COPD maintenance: 12 µg INH q 12 h; max 24 µg/day

Continued

Generic name	Type	Trade name	Class	Dose
Furosemide	Diuretics, loop, thiazide diuretics	Lasix	Pregnancy: C Lactation: S (likely)	<p>Pulmonary edema: begin at 40 mg IV \times1 slowly, assess response; may increase to 80 mg IV q 1 h p.r.n.</p> <p>Peripheral edema: 20–80 mg/day PO to b.i.d.; max 600 mg/day</p> <p>Hypertension: 40 mg PO b.i.d.; max 600 mg/day</p> <p>Hypercalcemia: 80–100 mg IV q 1–2 h, or 120 mg/day PO</p>
Foscarnet	Antivirals	Foscavir	Pregnancy: C Lactation: U	<p>Aciclovir-resistant HSV: 40 mg/kg IV given over 1 h q 8 h for 2–3 weeks</p> <p>CMV retinitis, AIDS: begin at 60 mg/kg IV given over 1 h q 8 h; administer maintenance dose \times2–3 weeks</p>
Gentamicin	Aminoglycosides; Antibiotics; Dermatologics; Ophthalmics; Otics	Garamycin; Genoptic	Pregnancy: C Lactation: S	<p>Bacterial infection: 1–3 mg/kg/day in 3 divided doses to achieve a peak 5–10 μg/mL and trough <2 μg/mL</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Endocarditis prophylaxis: 1.5 mg/kg IV 30–60 min prior to the procedure
Glyburide	Hypoglycemics; Sulfonylureas	DiaBeta; Micronase	Pregnancy: B Lactation: U	Diabetes mellitus, type 2: begin 2.5–5 mg PO with first main meal of the day; usual maintenance dose 2.5–5.0 mg/day; max 20 mg/day (micronized) 1.5–3.0 mg/day; usual maintenance dose 0.75–1.25 mg/day)
Haloperidol	Antipsychotics	Haldol	Pregnancy: B Lactation: U	Psychosis: 0.5–5 mg PO b.i.d./t.i.d.; max 100 mg/day; or 2.5 mg IV/IM q 4–8 h Tourette syndrome: begin 0.5–1.5 mg PO t.i.d., increase 2 mg/day p.r.n.; typically 9 mg/day Acute psychosis: 0.5–50 mg IV (slow, at 5 mg/min)

Continued

Generic name	Type	Trade name	Class	Dose
Heparin	Anticoagulants	Heparin Flush; Heparin Lok- Pak	Pregnancy: B Lactation: S	<p>Thromboembolic disease:</p> <ul style="list-style-type: none"> • Treatment: 80 U/kg IV \times1, then 18 U/kg/h IV to achieve an aPTT 1.5–2\times baseline • Prophylaxis: 5000 U SC b.i.d. 1st trimester, 7500 U SC b.i.d. 2nd trimester, 10,000 U SC b.i.d. 3rd trimester <p>NOTE: Keep aPTT 1.5–2.5 times control</p> <p>Antiphospholipid syndrome: 81 mg/day PO aspirin plus 5000 U SC b.i.d. 1st trimester, 7500 U SC b.i.d. 2nd trimester, 10,000 U b.i.d. 3rd trimester</p> <p style="text-align: right;"><i>Continued</i></p>

Generic name	Type	Trade name	Class	Dose
Hydralazine	Antihypertensives; Vasodilators	Apresoline; Apresrex	Pregnancy: C Lactation: S	<p>Hypertension (moderate to severe): begin 10–50 mg PO q.i.d. ×2–4 days, then 25 mg PO q.i.d. ×1 week; max 100 mg PO q.i.d.; alternatively, 5–40 mg IV/IM q 4–6 h; for chronic use, switch to PO ASAP</p> <p>CHF: begin 50–75 mg PO ×1, then 50–150 mg PO q.i.d.; max 3000 mg/day</p>
Hydroxychloroquine	Antimalarials; Antiprotozoals; Antirheumatics; Immunomodulators	Plaquenil	Pregnancy: C Lactation: S	<p>SLE: 400 mg/day PO b.i.d.</p> <p>Malaria: Treatment: begin 800 mg PO b.i.d. ×1, followed 6–8 h later by 400 mg PO, then 400 mg/day PO ×2 Prophylaxis: begin 400 mg/week PO ×2 weeks prior to exposure, continue 4–6 weeks after exposure</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Rheumatoid arthritis: begin 400–600 mg/day PO \times 4–12 weeks, then 200–400 mg PO q.i.d.
Hydroxyzine	Antiemetics; Antihistamines, H1; Antivertigo; Anxiolytics; Hypnotics; Sedatives	Atarax; Atazina	Pregnancy: C Lactation: U	Anxiety: 50–100 mg PO/M q 6 h p.r.n.; max 600 mg/day Pruritus: 25–100 mg PO q 6–8 h p.r.n. Nausea, vomiting: 25–100 mg IM q 4–6 h p.r.n.; max 600 mg/day Sedation adjunct: 25–100 mg IM \times 1 Insomnia: 50–100 mg PO q.h.s.
Imipenem	Antibiotics; Carbapenems	Primaxin	Pregnancy: C Lactation: S	Serious bacterial infection: 250–1000 mg IM/IV q 12 h; max 50 mg/kg/day or 4000 mg/day

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Generic name	Type	Trade name	Class	Dose
Indomethacin	Analgesics, non-narcotic; Antiarthritics; NSAID; Anti-inflammatory	Indocin	Pregnancy: B Lactation: S	Dysmenorrhea: 25 mg PO t.i.d./q.i.d. Mild to moderate pain: 25–50 mg PO t.i.d. p.r.n. Osteoarthritis or rheumatoid arthritis: begin 25 mg PO b.i.d./t.i.d., or 50 mg p.r.n. q.i.d., increase by 25–50 mg q 7 days; max 200 mg/day Tocolysis: 50 mg PR or PO load, then 25 mg PO/PR q 6 h × 2 days
Infliximab	Anti-inflammatory; Antirheumatics; Inflammatory bowel disease; Tumor necrosis factor modulators	Remicade	Pregnancy: C Lactation: S (likely)	Crohn disease, moderate to severe: 5 mg/kg IV ×1 Crohn disease, fistulizing: 5 mg/kg IV ×1 for weeks 0, 2, 6

Continued

Generic name	Type	Trade name	Class	Dose
				Rheumatoid arthritis: begin 3 mg/kg IV \times 1 for weeks 0, 2, 6; may increase dose to 10 mg/kg or increase dose up to 10 mg/kg
Insulin, recombinant human	Antidiabetic agents; Hypoglycemics	Humulin R, L, N and U	Pregnancy: B Lactation: S	<p>Diabetes mellitus. SC:</p> <p>R(egular): 0.5–1 U/kg/day SC in 3–4 divided doses: give 30–60 min q.a.c., onset 0.5 h, peak 2–4 h, duration 6–8 h</p> <p>L(ente): give 30 min before meal or q.h.s., onset 1–3 h, peak 8–12 h, duration 18–24 h</p> <p>N(PH): give 30–60 min before breakfast, onset 1–2 h, peak 6–12 h, duration 18–24 h</p> <p>U(ltralente): 0.5–1 U/kg/day SC in 1–2 divided doses: give 30–60 min before meal; onset 4–8 h, peak 16–18 h, duration >36 h</p>

Generic name	Type	Trade name	Class	Dose
				Diabetic ketoacidosis: begin 0.1 U/kg IV bolus of R, then 0.1 U/kg/h infusion; decrease infusion rate when glucose <275 mg/dL
Interferon- α 2a	Antineoplastics, interferon; Antivirals, interferon; Immunomodulators	Roferon A	Pregnancy: C Lactation: U	Chronic hepatitis C with compensated liver disease: 3 million U/day SC/IM 3 \times /week for 52 weeks AIDS-associated Kaposi sarcoma: begin 36 million U/day SC/IM \times 10–12 weeks, then 3 \times /week Hairy cell leukaemia: begin 3 million U/day \times 16–24 weeks, then 3 \times /week
Ipratropium bromide	Anticholinergics; Bronchodilators	Atrovent; Disne-Asmol	Pregnancy: B Lactation: S	Bronchospasm: 2–3 puffs INH t.i.d./q.i.d.; alternatively 500 μ g NEB q 6–8 h Rhinitis: 2 sprays/nostril b.i.d./t.i.d. (0.03%)

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Rhinorrhea associated with cold: 2 sprays/nostril t.i.d./q.i.d. (0.06%)</p> <p>NOTE: Available in bronchial and nasal (0.03 and 0.06%) inhalers</p>
Labetalol	Adrenergic antagonists; Alpha- and beta-blocker; Antihypertensives	Coreton; Normadate	Pregnancy: C Lactation: S	<p>Hypertension: begin 100 mg PO b.i.d., increase 100 mg b.i.d. q 2–3 weeks; max 2.4 g/day</p> <p>Acute hypertension: if diastolic BP > 105 mmHg, administer incremental dosing of 5–10 mg IV, with a cumulative dose of 40–80 mg IV over 20 min; max 300 mg IV</p>
Lamotrigine	Anticonvulsants	Lamictal	Pregnancy: C Lactation: S (likely)	<p>Seizures: begin 50 mg/day, then increase up to 50–250 mg PO b.i.d.; max 500 mg/day</p>

Continued

Generic name	Type	Trade name	Class	Dose
Leflunomide	Antirheumatics; Immunomodulators	Arava	Pregnancy: X Lactation: U	Rheumatoid arthritis: begin 100 mg/day PO $\times 3$ days, then 10–20 mg/day PO
Levofloxacin	Antibiotics; Quinolones	Cravit; Lesacin	Pregnancy: C Lactation: U	Bacterial infections: 250–500 mg/day PO/IV
Lidocaine	Anesthetics, local; Anesthetics, topical	Alphacaine; Leostesin	Pregnancy: B Lactation: S	Ventricular arrhythmia: begin 1–1.5 mg/kg IV; may repeat bolus in 5 min, then begin infusion 1–4 mg/min IV; max 300 mg $\times 1$ h Local anesthesia: infiltrate IM/SC; max 300 mg Postherpetic neuralgia: apply topically q 12 h
Magnesium sulfate	Anticonvulsants; Electrolyte replacements; Tocolytics	Tis U Sol	Pregnancy: A Lactation: U	Ventricular arrhythmia: 3–20 mg/min IV continuous IV $\times 6$ –48 h

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Eclampsia, prevention and treatment: begin 4 g IV \times1 over 30 min; then 2 g/h IV maintenance rate for at least 24 h postpartum, or during diuresis $>$200 mL/h; alternatively, 10 g IM loading dose followed by 5 g IM q 4 h until at least 24 h postpartum</p> <p>NOTE: Renal dosing; measure serum Mg every 4–6 h if infusion $>$2 g/h or oliguria or maternal symptoms of toxicity; maintain between 4–7 mEq/L (4.8–8.4 mg/dL)</p> <p>Tocolysis: begin 6 g IV \times1 over 30 min, then 2–4 g/h IV \times48 h</p> <p>Hypomagnesemia 1 g IM q 4–6 h; alternative 5 g mixed in 1 L NS IV over 3 h</p>

Continued

Generic name	Type	Trade name	Class	Dose
Meclizine	Antiemetics; Antihistamines, H1; Antivertigo	Ancolan; Antivert	Pregnancy: B Lactation: S	Nausea, vomiting and dizziness resulting from motion sickness: 25–50 mg/day PO 1 h before travel; repeat q 24 h
Medroxyprogesterone	Antineoplastics, hormone; Contraceptives; Hormones	Amen; Aragest	Pregnancy: X Lactation: S	Amennorrhea: 5–10 mg/day PO ×5 on days 16–21 of the cycle or q month Dysfunctional uterine bleeding: 5–10 mg/day PO ×5 on days 16–21 of the cycle or q month Hormone replacement: 5–10 mg/day PO ×12–14 day Contraception: 150 mg IM q 3 months
Meperidine	Analgesics, narcotic; Anesthetics, adjunct	Demerol; Doloneurin	Pregnancy: B Lactation: S	Pain: 50–150 mg PO/SC/IM q 3–4 h; IM preferred over SC/IV NOTE: 75 mg parenteral meperidine = 10 mg parenteral morphine

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Preoperative sedation: 50–100 mg SC/IM \times1, 30–60 min before surgery</p> <p>Obstetric analgesia: 50–100 mg SC/IM/IV q 3–4 h</p>
Methacholine	Cholinergics; Diagnostics, non-radioactive	Provocholine	Pregnancy: C Lactation: S	<p>Diagnosis of bronchial hyperreactivity: 5 breaths (neb); measure FEV₁ at baseline and after 5 breaths</p> <p>NOTE: Diagnostic purpose only. Methacholine inhalation challenge should be performed only under the supervision of a physician trained in and thoroughly familiar with all aspects of the technique.</p>
Methimazole	Antithyroid agents; Hormones	Antitroide-GW; Favistan	Pregnancy: D Lactation: S (likely)	<p>Hyperthyroidism: begin 5–20 mg PO q 8 h, then 5–15 mg/day PO</p>

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Generic name	Type	Trade name	Class	Dose
Methotrexate	Antineoplastics, antimetabolite; Antirheumatics	Abitrexate; Emtexate	Pregnancy: X Lactation: NS (likely)	<p>Ectopic pregnancy: 50 mg/m² IM \times1; may be repeated in 1 week if hCG rising</p> <p>Trophoblastic disease: 15–30 mg/day PO/IM \times5 days; repeat \times3–5 at $>$1 week intervals; administer with 1 mg/day folic acid PO or 5 mg/week leukovorin</p> <p>Rheumatoid arthritis: 7.5–25 mg/week PO/IM/SC; alternatively 2.5–7.5 mg PO q 12 h 3\times/week; max 30 mg/week</p> <p>Psoriasis: 10–25 mg/week PO/IM/SC; alternatively 2.5–7.5 mg PO q 12 h 3\times/week; max 30 mg/week</p> <p>Mycosis fungoides: 5–50 mg/week PO/IV; alternatively 15–37.5 mg PO 2\times/week</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Chemotherapy: numerous dosing schedules depending on disease, response, and concomitant therapy
Methyldopa	Adrenergic antagonists, central; Antihypertensives	Aldomet; Alfametildopa	Pregnancy: B Lactation: S	Hypertension: 250–500 mg PO b.i.d.; begin 250 mg PO b.i.d. and adjust q 2 days; max 3 g/day; alternative 250–500 mg IV q 6 h ×4, then PO
Methylergonovine	Ergot alkaloids; Oxytocics; Uterine stimulants	Methergine	Pregnancy: C Lactation: S	Postpartum bleeding: Emergent: 0.2 mg IM q 2–4 h; max 5 doses Non-emergent: 0.2–0.4 mg PO q 6–12 h; max duration 7 days
Methylprednisolone	Corticosteroids	Medlone; Medrol	Pregnancy: C Lactation: S	Inflammatory disorders: 2–60 mg/day PO Congenital adrenal hyperplasia: 2–60 mg/day PO Rheumatic disorders, adjunctive treatment: 2–60 mg/day PO

Continued

Generic name	Type	Trade name	Class	Dose
				Collagen vascular diseases: 2–60 mg/day PO Allergy: 2–60 mg/day PO Respiratory diseases: 2–60 mg/day PO Hematologic disorders: 2–60 mg/day PO Multiple sclerosis: acute exacerbations 200 mg/day PO ×7 days, then 80 mg/day PO ×1 month NOTE: 4 mg methylprednisolone = 5 mg prednisolone
Metoclopramide	Antiemetics; Antivertigo; Gastrointestinals	Reglan	Pregnancy: B Lactation: S	Nausea, vomiting: 5–10 mg PO/IM/IV q 6–8 h Nausea, vomiting (chemo): 1–2 mg/kg IV/PO q 2–4 h GERD: 5–15 mg PO/IV/IM q.a.c., q.h.s.

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Generic name	Type	Trade name	Class	Dose
				Gastroparesis (diabetes): 10 mg IV/PO q.a.c., q.h.s.
Metronidazole	Antibiotics; Antiprotozoals; Dermatologics	Flagyl	Pregnancy: B Lactation: S	Bacterial infections: 500 mg PO q 6–8 h ×7–14 days; alternative 15 mg/kg/IV ×1 followed by 7.5 mg/kg IV q 5 h; max 1 g/dose Amebic abscess: 500–750 mg PO t.i.d. ×5–10 days Bacterial vaginosis: 2 g PO ×1, alternative 500 mg PO b.i.d. ×7 days Giardiasis: 250 mg PO t.i.d. ×5–7 days; alternative 2 g/ day PO ×3 days C. difficile colitis: 500 mg PO t.i.d. ×7–14 days; alternative 250 mg PO q.i.d. ×7–14 days Rosacea: topical gel application b.i.d. ×9 weeks

Continued

Generic name	Type	Trade name	Class	Dose
				Vaginal trichomoniasis: 2 g PO \times 1; alternative 500 mg PO b.i.d. \times 7 days, 1 g PO b.i.d. \times 1 day (partner treatment is critical)
Misoprostol	Abortifacients; Gastrointestinals; Oxytocics; Prostaglandins; Stimulants, uterine	Cytotec	Pregnancy: X Lactation: U	NSAID-induced gastric ulcers: 100–200 μ g PO q.i.d. Constipation: 600–2400 μ g/day PO b.i.d./q.i.d. Cervical ripening: 25 μ g vaginally q 3–6 h; wait at least 4 h before initiating oxytocin; max 50 μ g/dose Abortion: 400 μ g PO \times 1; may repeat q 4–6 h
Montelukast	Antileukotriene	Singulair	Pregnancy: B Lactation: NS	Asthma: 10.4 mg/day PO

Continued

Generic name	Type	Trade name	Class	Dose
Morphine	Analgesics, narcotic	Avinza; Kadian	Pregnancy: C Lactation: S	Pain: 2.5–10 mg IV slowly over 5–15 min; alternative 5–20 mg IM/SC or 10–30 mg PO q 4 h Postcesarean section analgesia: intrathecal 100–250 µg, epidural 2–5 mg
Nalbuphine	Analeptics; Narcotic agonist-antagonists	Nubain	Pregnancy: B Lactation: S	Pain: 10 mg IV/IM/SC q 3–6 h p.r.n.; max 20 mg/dose or 160 mg/day Anesthesia (adjunct): 0.25–0.5 mg/kg p.r.n.; begin 0.3–3 mg/kg IV
Naloxone	Antidotes; Narcotic agonist-antagonists	Narcan	Pregnancy: B Lactation: S	Opiate overdose: 0.4–2 mg SC/IV/IM q 2–3 min; if no response by 10 min, the diagnosis should be questioned Postoperative opiate reversal: 0.1–0.2 mg IV q 2–3 min p.r.n.

Continued

Generic name	Type	Trade name	Class	Dose
Nevirapine	Antivirals; Non-nucleoside reverse transcriptase inhibitors	Viramune	Pregnancy: C Lactation: NS	HIV infection: 200 mg/day PO \times 14 days; continue treatment with 200 mg PO b.i.d. in combination with nucleoside antiretrovirals NOTE: Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with nevirapine
Nicardipine	Antiarrhythmics; Antihypertensives; Calcium-channel blockers	Cardene	Pregnancy: C Lactation: U	Hypertension: 20–40 mg PO t.i.d.; max 40 mg PO t.i.d. Angina: begin 20 mg PO t.i.d.; max 40 mg PO t.i.d. Acute hypertension: 5 mg/h, increase 2.5 mg/h q 5–15 min p.r.n., titrate down to effect

Continued

Generic name	Type	Trade name	Class	Dose
Nifedipine	Antiarrhythmics; Antihypertensives; Calcium- channel blockers	Adalat; Procardia XL	Pregnancy: C Lactation: S (likely)	Hypertension: begin 10 mg PO t.i.d., titer to effect; max 180 mg/day Prinzmetal angina: begin 10 mg PO t.i.d., titer to effect; max 180 mg/day Angina variant: begin 10 mg PO t.i.d., titer to effect; max 180 mg/day
Nitrofurantoin	Antibiotics; Nitrofurans	Macrochantin; Macrobid	Pregnancy: B Lactation: S (likely)	Urinary tract infection: 100 mg PO b.i.d.; alternative 50– 100 mg PO q.i.d. Urinary tract infection suppression: 50– 100 mg PO q.h.s.
Nitroglycerin	Vasodilators	Nitro-Dur; Nitrolingual	Pregnancy: C Lactation: U	Angina, acute: 0.3–0.6 mg SL q 5 min; max 3 doses within 15 min Angina, prophylaxis: 0.3–0.6 mg SL ×1; take 5–10 min before strenuous activity

Continued

Generic name	Type	Trade name	Class	Dose
				NOTE: Available in 2% cream, tablets, aerosol spray, parenteral or patch formats; store tablets in original glass container
Ondansetron	Antiemetics; Serotonin receptor antagonists	Zofran	Pregnancy: B Lactation: U	Severe nausea and vomiting: Postoperative: 4 mg IM/IV \times 1; prechemotherapy: 24 mg PO or 32 mg IV 30 min before initiating chemotherapy Radiation therapy: begin 8 mg PO 1–2 h before radiation, continue q 8 h \times 2 days
Oseltamivir	Antivirals	Tamiflu	Pregnancy: C Lactation: U	Influenza A/B Prophylaxis: 75 mg/day PO; initiate at outbreak Treatment: 75 mg PO b.i.d. \times 5 days beginning within 48 h symptoms
Oxcarbazepine	Anticonvulsants	Trileptal	Pregnancy: C Lactation: S (likely)	Seizure disorder: begin at 300 mg PO b.i.d., increasing by 300 mg/day q 3 days; max 2400 mg/day

Continued

Generic name	Type	Trade name	Class	Dose
Oxytocin	Hormones/ hormone modifiers; Oxytocics; Stimulants, uterine	Pitocin; Syntocinon; Xitocin	Pregnancy: X Lactation: S (likely)	Labor induction: 1–2 mIU/min IV; double q 20– 30 min until 8 mIU/min, then increase by 1– 2 mIU/min; max 200 mIU/min Postpartum bleeding: 10– 40 IU/L at a rate titrated to control bleeding Lactation aid: 1–2 sprays per nostril 2–3 min before feeding or pumping during the 1st week after delivery
Pancuronium	Neuromuscular blockers, non- depolarizing	Pavulon	Pregnancy: C Lactation: U	Paralysis: 0.04– 0.1 mg/kg IV Paralysis, fetal: 0.03 mg/kg fetal IM or IV into the umbilical vein
Peniclovir	Antivirals; Dermatologics	Denavir	Pregnancy: B Lactation: S (likely)	Herpes labialis: apply q 2 h ×4 days
Penicillamine	Antirheumatics; Cystine depleting agents	Cuprimine; Depen; Mercaptyl	Pregnancy: D Lactation: U	Wilson disease: 250–500 mg PO t.i.d./q.i.d. 30 min before meals

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Cystinuria: 250–1000 mg PO q.i.d. 30 min before meals</p> <p>Rheumatoid arthritis (unresponsive to conventional agents): 250 mg PO b.i.d./t.i.d. 30 min before meals; requires 3–6 months for max effect</p> <p>Heavy-metal poisoning: 125–600 mg PO t.i.d. 30 min before meals</p>
Penicillin G	Antibiotics; Penicillins	Bicillin LA; Pen-Di-Ben; Permapen	Pregnancy: B Lactation: S	<p>Systemic infection (moderate to severe): 4 million units IM/IV q 4 h</p> <p>Anthrax: 4 million units IV q 4 h as part of a multidrug regimen ×60 days for oral, GI or inhalational; 4 million units IV q 4 h ×7–10 days for cutaneous, then switch to PO for 60 days</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Neurosyphilis: 18–24 million units/days IV × 10–14 days
Perphenazine	Antiemetics; Antipsychotics; Antivertigo; Phenothiazines	Trilifan; Trilafon	Pregnancy: C Lactation: U	Psychosis: 8–16 mg PO b.i.d./q.i.d.; max 64 mg/day Severe nausea and vomiting: begin 5 mg IM/PO (avoid IV); max 24 mg/day
Phenobarbital	Anticonvulsants; Barbiturates; Preanesthetics; Sedatives/hypnotics	Barbita; Dormiral; Luminal Sodium	Pregnancy: D Lactation: S (likely)	Seizure disorder: load with 15–20 mg/kg IV, then 60 mg PO b.i.d./t.i.d. Status epilepticus: 10–20 mg/kg IV ×1; may repeat if necessary Sedation: 10–40 mg PO/IM/IV t.i.d.
Phenytoin	Anticonvulsants; Hydantoins	Dilantin; Hydantol	Pregnancy: D Lactation: S	Seizure disorder: load with 400 mg, 300 mg, and 300 mg PO 2–4 h apart, then 300–400 mg/day PO (or divided b.i.d.), alternatively, 10–20 mg/kg; IV ×1, then 4–6 mg/kg/day IV

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Status epilepticus: 15–20 mg/kg IV q 30 min p.r.n.; max 1500 mg/day</p>
Piperacillin	Antibiotics; Penicillins	Pipracil	Pregnancy: B Lactation: S	<p>Bacterial infections (<i>Pseudomonas, intra-abdominal or sepsis</i>): 3–4 g IV/IM q 4–6 h × 3–10 days</p> <p>Postgynecologic or cesarean prophylaxis: 2 g IV 30 min preoperatively or at umbilical cord clamping, then q 4–6 h ×2</p> <p>Gonorrhea, uncomplicated: 1 g probenecid PO 30 min before 2 g IM ×1</p> <p>NOTE: Renal dosing; may be combined with the beta-lactamase inhibitor tazobactam (Tazosyn; Zosyn)</p>

Continued

Generic name	Type	Trade name	Class	Dose
Piperacillin-tazobactam	Antibiotics; Penicillins	Tazosyn; Zosyn	Pregnancy: B Lactation: S (likely)	<p>Bacterial infections (<i>Pseudomonas</i>, intra-abdominal, or sepsis): 3.375 g IV q 6 h ×3–10 days</p> <p>Postpartum endomyometritis or pelvic inflammatory disease: 3.375 g IV q 6 h ×3–10 days</p> <p>Community-acquired pneumonia: 3.375 g IV q 6 h ×3–10 days</p>
Prednisone	Corticosteroids	Adasone, Deltasone	Pregnancy: B Lactation: S	<p>Inflammatory disorders: 5–60 mg/day PO</p> <p>Relapsing multiple sclerosis: begin 200 mg/day PO × 1 week, then 80 mg PO q.o.d. ×1 month</p> <p>Pneumocystic pneumonia: begin 40 mg PO b.i.d. ×5 days, then 40 mg/day ×5 days, then 20 mg/day</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Adrenal insufficiency: 4–5 mg/m ² /day PO
Primidone	Anticonvulsants	Midone; Mylepsin	Pregnancy: B Lactation: NS	Seizure disorder: begin 100–125 mg PO q.h.s. ×3 day, 100–125 mg PO b.i.d. ×3 days, then 250 mg PO t.i.d./q.i.d.; max 2 g/day Essential tremor: begin 12.5–25 mg PO q.h.s., increase 12.5–25 mg/day/week; max 750 mg/day
Probenecid	Antigouts; Uricosurics	Benemid; Panuric	Pregnancy: B Lactation: S	Adjunct to penicillin therapy: 500 mg PO q.i.d. Gout: begin 250 mg PO b.i.d. ×7 days; max 2–3 g/day
Procaine	Anesthetics, local	Novocain	Pregnancy: C Lactation: S (likely)	Local and regional anesthesia: dose varies; max 10 mg/kg

Continued

Generic name	Type	Trade name	Class	Dose
Prochlorperazine	Antiemetics; Antipsychotics; Antivertigo; Phenothiazines	Compazine; Cotranzine	Pregnancy: C Lactation: U	Nausea, vomiting: 5–10 mg PO/IM t.i.d./q.i.d., or 25 mg PR b.i.d., or 5–10 mg IV over 2 min; max 40 mg/day Psychosis: 5–10 mg PO t.i.d./q.i.d.; max 150 mg/day
Progesterone	Contraceptives; Hormones; Progestins	Gesterol 50; Lutolin-S	Pregnancy: D Lactation: S	Amenorrhea: 400 mg/day PO ×10 days Hormone replacement: 200 mg PO given each day with estrogen Infertility, progesterone deficiency: 1 applicator 8% PV/day; continue through 10–12 weeks of pregnancy Infertility, ovarian failure: 1 applicator 8% PV b.i.d. Secondary amenorrhea: 1 applicator 4% PV q.o.d.

Continued

Generic name	Type	Trade name	Class	Dose
				NOTE: Available in tablet, parenteral or vaginal cream (Crinone, 4% = 45 mg/applicator) forms
Promethazine	Antiemetics; Antihistamines; Phenothiazines	Phenergan; Phenerzine	Pregnancy: D Lactation: S	<p>Nausea, vomiting: 12.5–25 mg PO/PR/IM q 4–6 h p.r.n.</p> <p>Motion sickness: 25 mg PO b.i.d.</p> <p>Sedation: 25–50 mg PO/PR/IM q 4–6 h p.r.n.</p> <p>Allergic rhinitis: 12.5–25 mg PO q 6 h, or 25 mg PO q.h.s.</p> <p>NOTE: May be combined with codeine</p>
Propranolol	Adrenergic antagonists; Antiarrhythmics, class II; Beta-blockers	Inderal	Pregnancy: C Lactation: S	<p>Hypertension: begin 40 mg PO b.i.d., increasing q 3–7 days; max 640 mg/day</p> <p>Migraine headache prophylaxis: begin 20 mg/day PO; increase gradually to 40–60 mg PO q.i.d.</p>

Continued

Generic name	Type	Trade name	Class	Dose
				<p>SVT: begin 1–3 mg IV at 1 mg/min; may repeat 2 min later; if control, then 10–30 mg PO t.i.d./q.i.d. beginning 4 h later</p> <p>Angina: 80–120 mg PO b.i.d.; may increase q 7–10 days</p>
Propylthiouracil	Antithyroid agents; Hormone modifiers; Hormones	PTU	Pregnancy: D Lactation: S	<p>Hyperthyroidism (Graves disease): begin 100–125 mg PO t.i.d.; 200–300 mg PO q.i.d. if thyroid storm</p>
Protamine	Antidotes; Bleeding disorders	Protamine	Pregnancy: C Lactation: S (likely)	<p>Heparin reversal: 1–1.5 mg IV per 100 U heparin estimated to remain in the body; if 0–30 min from last dose, give 1–1.5 mg/100 U, if 30–60 min give 0.5–0.75 mg/100 U, if > 2 h, give 0.25–0.375 mg per 100 U</p>

Continued

Generic name	Type	Trade name	Class	Dose
Pyrimethamine	Antiprotozoals	Daraprim; Eraprelina	Pregnancy: C Lactation: S (likely)	<p>Malaria;</p> <ul style="list-style-type: none"> • Treatment: 50 mg/day PO ×2 weeks in combination with sulfadiazine and quinine; use in chloroquine-resistant areas • Prophylaxis: 25 mg/week PO for 10 weeks after exposure; use in chloroquine-resistant areas <p>Toxoplasmosis: begin 50–75 mg/day PO ×1–3 weeks, then 25–50 mg/day PO ×4–5 weeks in combination with sulfadoxine and folinic acid</p> <p>Toxoplasmosis with HIV: begin 200 mg PO ×1, then 50–100 mg/day PO ×4–8 weeks, then maintenance</p> <p>Isosporiasis: 50–75 mg/day PO</p>
Ranitidine	Antihistamines, H ₂ ; Ant ulcer; Gastrointestinals	Ranitiget; Zantac	Pregnancy: B Lactation: S (likely)	<p>Duodenal or gastric ulcer: 150 mg PO b.i.d.</p>

Continued

Generic name	Type	Trade name	Class	Dose
				Erosive esophagitis: 150 mg PO q.i.d. GERD: 150 mg PO b.i.d. Dyspepsia: 75 mg/day PO b.i.d.
Ribavirin	Antivirals	Rebetol; Viramid	Pregnancy: X Lactation: U	Chronic hepatitis C: 400 mg PO q AM and 600 mg q PM if < 75 kg; 600 mg PO b.i.d. if > 74.9 kg
Ritodrine	Adrenergic agonists; Beta-agonists; Tocolytics	Yutopar	Pregnancy: B Lactation: S	Preterm labor: begin 0.05 mg/min, increase by 0.05 mg/min q 10 min (unless maternal heart rate > 130 b/min) until contractions stop; continue that dose for 12 h after contractions end; max 0.35 mg/min
Ropivacaine	Anaesthetic, local	Naropin	Pregnancy: B Lactation: S (likely)	Epidural analgesia: 2 mg/mL continuous infusion
Salmeterol	Adrenergic agonists; Beta-agonists; Bronchodilators	Serevent; Serevent Diskus Diskus	Pregnancy: C Lactation: S	Asthma prophylaxis: 2 puffs INH q 12 h

Generic name	Type	Trade name	Class	Dose
				<p>Exercise-induced asthma: 2 puffs INH ×1</p> <p>COPD: 2 puffs INH q 12 h</p>
Scopolamine	Anesthetics, adjunct; Anticholinergics; Antiemetics; Cycloplegics; Gastrointestinals; Motion sickness; Mydriatics; Ophthalmics; Vertigo	Scopoderm; Isopto Hyoscine	Pregnancy: C Lactation: S	<p>Motion sickness: 1 patch behind the ear 4 h prior to need; may replace in 3 days</p> <p>Obstetric amnesia or preoperative sedation: 0.32–0.65 mg SC/IM Intraoperative amnesia: 0.4 mg IV</p>
Spiramycin	Antibacterial, Antiprotozoal	Rovamycine	Pregnancy: B Lactation: S (likely)	<p>Toxoplasmosis: 1–2 g (3–6 million International Units [IU]) PO b.i.d. or 500 mg IV q 8 h Alternative regimen: 500 mg–1 g (1.5–3 million IU) t.i.d.</p> <p>Severe infections: 2–2.5 g (6–7.5 7 million IU) b.i.d.</p>

Continued

Generic name	Type	Trade name	Class	Dose
				NOTE: Not available in the USA
Sufentanil	Analgesics, narcotic; Anesthesia, general	Sufenta	Pregnancy: C Lactation: S	<p>General anesthesia: begin 2–8 µg/kg IV when used with inhalational anesthetics; up to 30 µg/kg when used with amnestic and oxygen alone: titrate additional smaller doses to desired effect</p> <p>Epidural during labor: several regimens including 10–15 µg sufentanil plus 10 mL 0.125% bupivacaine</p> <p>Intrathecal during labor: several regimens including 5–7.5 µg with or without bupivacaine</p>
Sulfadiazine	Antibiotics; Sulfonamides	Microsulfon	Pregnancy: C Lactation: S (likely)	<p>Toxoplasmosis: 2–8 g/day PO in 3–4 divided doses ×4 weeks plus pyrimethamine 25 mg/day</p>

Continued

Generic name	Type	Trade name	Class	Dose
Sulindac	Analgesics, non-narcotic; NSAID	Antribid	Pregnancy: C Lactation: S	<p>Osteoarthritis or rheumatoid arthritis: 150–200 mg PO b.i.d.; max 400 mg/day</p> <p>Anti-inflammatory: 200 mg PO b.i.d. ×7–14 days; max 400 mg/day</p> <p>Ankylosing spondylitis: 150–200 mg PO b.i.d.; max 400 mg/day</p> <p>Acute gout: 150–200 mg PO b.i.d.; max 400 mg/day</p>
Terbutaline	Adrenergic agonists; Beta-agonists; Bronchodilators	Brethaire; Brethancer	Pregnancy: B Lactation: S	<p>Asthma: 5 mg PO q 6 h p.r.n.; max 15 mg/day; or, 2 puffs INH q 4–6 h; or 0.25 mg SC q 15–30 min ×2</p> <p>Tocolysis: 0.25 mg SC q 30 min; max 1 mg/4 h; or, 2.5–10 µg/min IV, max 30 µg/min</p>
Tetracycline	Antibiotics; Dermatologics; Ophthalmics; Tetracyclines	Telmycin; Tetocyn	Pregnancy: D Lactation: S	<p>Bacterial infection: 1–2 g/day divided b.i.d./q.i.d. at least 1 h before or 2 h after meals</p>

Continued

Generic name	Type	Trade name	Class	Dose
				<p>Chlamydia infection: 500 mg PO q.i.d. at least 1 h before or 2 h after meals ×7 days</p> <p>Acne vulgaris: 250–500 mg PO q.i.d. at least 1 h before or 2 h after meals</p>
Thalidomide	Dermatologics; Immunomodulators	Thalomid	Pregnancy: X Lactation: U	<p>Restricted access in USA: call 1-888-423-5436 for information</p> <p>Erythema nodosum leprosum: begin 100–300 mg PO ×2 weeks or until symptoms improve, then decrease by 50 mg/day q 2–4 weeks</p> <p>HIV wasting: 100–300 mg PO q.h.s.</p> <p>Aphthous ulcer: 200 mg/day PO</p>

Continued

Generic name	Type	Trade name	Class	Dose
Theophylline	Bronchodilators; Xanthine derivatives	Theo-Dur	Pregnancy: C Lactation: S (likely)	<p>Chronic asthma: begin 300 mg/day PO in divided doses b.i.d./t.i.d. ×3 days, then 400 mg/day ×3 days, then 600 mg/day if tolerated</p> <p>COPD (maintenance): begin 300 mg/day PO in divided doses b.i.d./t.i.d. ×3 days, then 400 mg/day ×3 days, then 600 mg/day if tolerated</p> <p>NOTE: Therapeutic level 10–20 µg/ mL; exists in multiple formats with varying release rates. Dosing quoted for theophylline only</p>
Ticarcillin	Antibiotics; Penicillins	Ticar; Timentin	Pregnancy: B Lactation: S	<p>Bacterial infection: 3–4 g IV/IM q 4–6 h, or 200–300 mg/kg IV div q 4–6 h; max 24 g/day</p>

Continued

Generic name	Type	Trade name	Class	Dose
Topiramate	Anticonvulsants	Topamax	Pregnancy: C Lactation: S	Seizures, adjunct therapy: 25–50 mg/day PO, increase 25–50 mg/week; usual dose 400 mg/day in divided doses
Triamcinolone	Corticosteroids	Aristcort	Pregnancy: C Lactation: S	Adrenal insufficiency: 4–12 mg/day PO Inflammatory disorders: 4–48 mg/day PO in divided doses Chronic asthma: 2 puffs INH t.i.d./q.i.d., rinse mouth after use; max 16 puffs/day Allergic rhinitis: 1–2 sprays/nostril/day; max 2 sprays/nostril/day; discontinue after 3 weeks if no improvement Steroid-responsive dermatitis: apply sparingly to affected area b.i.d./q.i.d.
Trimethadione	Anticonvulsants	Tridione	Pregnancy: D Lactation: U	Seizure disorder (petit mal): 300 mg t.i.d.

Continued

Generic name	Type	Trade name	Class	Dose
Trimethobenzamide	Anticholinergics; Antiemetics; Antivertigo	Arrestin; Benzacot	Pregnancy: C Lactation: U	Nausea/ vomiting: 300 mg PO t.i.d./q.i.d., or 200 mg PR/IM t.i.d./q.i.d.
Trimethoprim	Antibiotics; Folate antagonists	Bactin	Pregnancy: C Lactation: S	UTI: 100 mg PO q 12 h ×10 days UTI prophylaxis: 100 mg PO q.h.s. ×6–24 weeks Traveler's diarrhea: 200 mg PO b.i.d. ×5 days <i>Pneumocystis carinii</i> pneumonia treatment: 20 mg/kg/day PO in divided doses
Sulfamethoxazole	Bacteriostatic; inhibits dihydropteroate synthesis	Gamazole; Gantanol	Pregnancy: C Lactation: U	Bacterial infection: begin 2 g PO ×1, then 1 g PO b.i.d.
Valacyclovir	Antivirals	Valtrex	Pregnancy: B Lactation: S	Genital herpes: • Primary: 1000 mg PO.i.d. ×10 days • Recurrent: 500 mg PO b.i.d. ×3 days • Prophylaxis: 1000 mg/day PO Herpes zoster: 1000 mg PO t.i.d. ×7 days

Continued

Generic name	Type	Trade name	Class	Dose
Valproate	Anticonvulsants	Depacon; Epival	Pregnancy: D Lactation: S	Seizures: 10–15 mg/kg/day IV in divided doses t.i.d., increase by 5–10 mg/kg/day q 7 days to achieve therapeutic trough of 50–100 µg/mL; max 60 mg/kg/day
Vancomycin	Antibiotics; Glycopeptides	Balcorin; Edicin	Pregnancy: B Lactation: S	Bacterial infections: 500 mg IV q 6 h; peak 25–40 µg/mL, trough 5–10 µg/mL Endocarditis prophylaxis: 1 g slow IV over 1 h
Warfarin	Anticoagulants; Thrombolytics	Coumarin	Pregnancy: X Lactation: S	Acute therapy of thromboembolic disease: begin 2.5 mg, increase gradual over 2–4 days to achieve desired INR Prosthetic cardiac valves or atrial fibrillation: 2.5–10 mg/day PO, INR should be maintained between 2.5–3.0 depending on the valve type

Continued

Generic name	Type	Trade name	Class	Dose
Zafirlukast	Antiasthmatics; Leukotriene antagonists	Accolate	Pregnancy: B Lactation: S (likely)	Asthma prophylaxis: 20 mg PO 1 h before or 2 h after meals b.i.d.
Zanamivir	Antivirals	Relenza	Pregnancy: C Lactation: U	Uncomplicated influenza: begin within 48 h of symptoms, 10 mg INH q 2–4 h ×2, then 12 h ×5 days
Zidovudine	Antivirals; Nucleoside reverse transcriptase inhibitors	Aviral; AZT; Retrovir; Retrovis	Pregnancy: C Lactation: U	HIV during pregnancy: begin 100 mg PO 5×/day after 14 weeks until onset of labor; in intrapartum period: 2 mg/kg IV over 1 h, then 1 mg/kg/h until cord clamping HIV in non-pregnant women: 300 mg PO q 12 h, or 1 mg/kg IV q 4 h
Zileuton	Antiasthmatics; Leukotriene antagonists	Zyflo	Pregnancy: C Lactation: U	Asthma: 600 mg PO q.i.d.; max 2400 mg/day

Continued

Generic name	Type	Trade name	Class	Dose
Zonisamide	Anticonvulsants	Zonegran	Pregnancy: C Lactation: U	Partial seizures: begin 100 mg/day PO, increasing q 2 weeks or greater for control; max dose 600 mg/day in divided doses if necessary

SUGGESTED READING

Carl P Weiner, Catalin S. Buhimschi. *Drugs for Pregnant and Lactating Women*. Philadelphia, PA: Elsevier, 2004.

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