

# IX MEDICAL PROBLEMS IN PREGNANCY

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Thanks to modern medicine, many women whose fertility—or even survival—would once have been compromised by disease are able to conceive and carry a child to term. Consequently, many more pregnancies require skilled medical management than in the past.

A variety of physiologic adaptations take place over the course of pregnancy. For example, blood volume increases by as much as 50%, resulting in a mild dilutional anemia. Cardiac output rises in compensation. Placental secretion of hormones, such as placental lactogen, promotes maternal insulin resistance; glucose is shunted to the fetus, and the mother uses ketones and triglycerides to meet her metabolic needs.

To achieve favorable outcomes in pregnancy, the clinician needs to understand how pregnancy may change the management of preexisting disease (e.g., hypertension) or result in the development of new disease (e.g., preeclampsia). Because the outcome of pregnancy is often influenced by maternal status in the initial weeks, counseling and management are best done before conception. Because pregnancy is often unplanned, these considerations should be part of the medical management in any woman of reproductive age.

## Teratogens

Concerns about teratogenesis are important and warranted. The perceived risk is often greater than the actual risk, however. Female patients of reproductive age should be made aware of the teratogenic potential of the medications they are taking [see Table 1]. In patients who are planning to become pregnant, the clinician needs to discuss teratogenicity versus efficacy, because inadequately controlled disease may be dangerous for mother and fetus alike.

## Hypertensive Disorders

Hypertension in pregnancy can be difficult to classify and, on occasion, may be difficult to manage. The hypertensive disorders of pregnancy have been divided into three categories: chronic hypertension, preeclampsia, and gestational hypertension.

### CHRONIC HYPERTENSION

Chronic hypertension is defined as hypertension that predates pregnancy or is diagnosed in the first half of pregnancy. Chronic hypertension can be classified as either essential (idiopathic) or secondary. Essential hypertension accounts for 90% of all cases. Secondary hypertension may be the result of underlying renal disease, connective tissue disease, endocrine disease, genetic predisposition, or other cardiovascular disease.

### Epidemiology

From 1% to 5% of pregnancies in the United States are complicated by chronic hypertension. The incidence varies somewhat by race and age. African-American women are affected more often than women of other races. In women who are older than 30 years, the rate is about 5%, whereas in women who are 20 to 29 years of age, the rate is approximately 1%.

### Diagnosis

Ideally, chronic hypertension is diagnosed before the patient becomes pregnant. The National High Blood Pressure Working Group on High Blood Pressure in Pregnancy has established criteria for making this diagnosis [see Table 2].<sup>1</sup> This diagnosis is best made before 20 weeks' gestation, lest the disorder be confused with either early-onset preeclampsia or gestational hypertension.

Initial laboratory evaluation should include a complete blood count, determination of serum creatinine and blood urea nitrogen (BUN) levels, and urinalysis. Quantification of urinary protein excretion and calculation of creatinine clearance are also recommended to establish baseline renal function. If indicated, a complete metabolic panel may be included to screen for elevations in liver enzymes, uric acid, and hyperlipidemia.<sup>2</sup> The liver enzyme and uric acid measurements will serve as a baseline to guide later assessment for superimposed preeclampsia, in which case these values will tend to rise; hyperlipidemia may provide an indication of cardiac risk. Also, in patients older than 40 years—especially those who have had hypertension for more than 10 years—an electrocardiogram is worthwhile because of the possibility of ischemic heart disease.<sup>3</sup> In women at very high risk, prepregnancy exercise tolerance testing may also be recommended.

### Treatment

Chronic hypertension is most effectively managed before conception. Evaluation of risk status, disease severity, and medication regimens will allow the clinician to better inform

Table 1 Selected Drugs with Suspected or Known Teratogenic Potential<sup>49</sup>

Alcohol	Phenytoin
Aminopterin	Quinolones
Androgens	Retinoids and derivatives
Angiotensin-converting enzyme inhibitors	Tetracycline
Carbamazepine	Thalidomide
Cocaine	Trimethadione/ paramethadione
Lithium	Valproic acid
Methotrexate	Warfarin

Table 2 Diagnostic Criteria for Chronic Hypertension in Pregnancy

Mild: Systolic blood pressure > 139 mm Hg and Diastolic blood pressure > 89 mm Hg
Severe: Systolic blood pressure > 179 mm Hg or Diastolic blood pressure > 109 mm Hg
Onset before 20 weeks' gestation
Use of antihypertensive medication before pregnancy
Postpartum persistence of hypertension

the patient about the risks of pregnancy to herself and to the fetus. Also, uncontrolled severe hypertension at the time of conception is associated with a much higher rate of first-trimester pregnancy loss, preeclampsia, fetal growth restriction, and abruptio placentae.

The treatment of chronic hypertension during pregnancy depends to a large degree on disease severity. Mild to moderate chronic hypertension does not require pharmacotherapy, because drug treatment does not seem to improve maternal and fetal/neonatal outcomes in such cases.<sup>3,4</sup> Pharmacotherapy is indicated when systolic blood pressures persist above 179 mm Hg or when diastolic blood pressures persist above 109 mm Hg.<sup>5</sup> In so-called high-risk hypertensive patients (e.g., those with severe hypertension before pregnancy, diabetes, underlying cardiac disease, or retinopathy), treatment is recommended for diastolic pressures that persist above 90 mm Hg.<sup>6</sup> There are a number of agents from which to choose when treating chronic hypertension during pregnancy.

**$\alpha$ -Methyldopa** Long used in obstetrics,  $\alpha$ -methyldopa has an established record of efficacy and safety and is widely regarded as the agent of choice for nonacute oral antihypertensive therapy in this setting.<sup>5</sup> Dosing generally begins at 250 mg twice a day and may be increased to a maximum of 1 g four times a day.

**Beta blockers** Labetalol, a combination alpha blocker and beta blocker, is effective for managing hypertension during pregnancy and may also be used for acute blood pressure lowering when indicated. There have been reports of fetal growth restriction with labetalol, as there have been with all beta blockers, and although this is not a contraindication to the use of these agents, close surveillance of fetal growth should be done in patients who receive them.<sup>7</sup> Labetalol may be started at a dosage of 100 mg twice a day; the dosage may be increased to a maximum of 400 mg every 4 hours. The beta blockers metoprolol and atenolol have been successfully used in pregnancy, although atenolol should be used with great care in pregnant patients because of its association with fetal growth restriction.

**Nifedipine** The usual dosage of this calcium channel blocker in pregnant women is 10 to 30 mg three times a day.<sup>5</sup> It is not clear whether long-acting preparations are as effective in pregnant patients as they are in nonpregnant patients.

**Angiotensin inhibitors** The use of angiotensin-converting enzyme (ACE) inhibitors in the second and third trimester has been associated with fetal hypocalvaria, oligohydramnios, fetal renal failure, and neonatal death. It is recommended that ACE inhibitors and angiotensin receptor blockers not be used during pregnancy.<sup>8,9</sup>

#### *Maternal and Fetal Risks*

Chronic hypertension can result in adverse pregnancy outcomes for both mother and fetus. Maternal risks include superimposed preeclampsia and abruptio placentae.<sup>10</sup> Uncontrolled hypertension can also result in maternal stroke. Fetal risks include growth restriction, prematurity (usually secondary to superimposed preeclampsia in the mother), and an overall increase in the risk of fetal and neonatal death. Experts are not in agreement on how best to monitor pregnancies complicated by chronic hypertension. However, most recommend regular ultrasonographic evaluation of fetal growth as well as weekly as-

essment of the fetus using nonstress testing and biophysical profile determination. Such assessment should begin at 26 to 34 weeks, depending on the risk status of the mother and fetus.<sup>5,11</sup> Hospitalization is required for all patients in whom the control of blood pressure is difficult. Patients with chronic hypertension should be delivered by 40 weeks' gestation. Successful vaginal delivery may be expected in the majority of patients with chronic hypertension, although the rate of cesarean section is higher in this population. The long-term prognosis for mother and fetus is generally excellent, provided that maternal end-organ damage and fetal complications arising from growth restriction and prematurity can be avoided.

#### **PREECLAMPSIA**

Preeclampsia is defined as hypertension, proteinuria, and pathologic edema, occurring after the 20th week of gestation. It is a multiorgan disease that affects blood pressure, vascular permeability, vascular reactivity, coagulation, and platelet function.

#### *Epidemiology*

Preeclampsia affects approximately 5% to 7% of all pregnancies. There does not seem to be a predisposition by race, although some variants of preeclampsia may show racial predilection. Risk factors include nulliparity, extremes of maternal age (younger than 15 or older than 35 years), and obesity. Additional risk factors for preeclampsia include chronic hypertension, multiple gestation, underlying renal disease, a history of preeclampsia with a previous pregnancy, type 1 (insulin-dependent) diabetes mellitus, and carriage of the angiotensinogen gene mutation T235. Less clear associations are with thrombophilias such as factor V Leiden, the prothrombin gene mutation, and antiphospholipid antibodies.<sup>12,13</sup>

#### *Pathogenesis*

Although the etiology of preeclampsia remains unknown, disordered trophoblast invasion and endothelial cell injury appear to be central to development of clinical disease.<sup>14</sup> The cause of the injury is the subject of speculation but probably involves oxygen free radical formation, ischemia, and microthrombosis. Several strategies addressing each of these putative mechanisms have been developed in the hope of preventing this disorder, but thus far results have been disappointing.

#### *Diagnosis and Treatment*

Clinically, the onset of preeclampsia is typically marked by acute fluid retention, which presents as edema of the face or hands (as opposed to the lower-extremity edema that characteristically develops in the second and third trimesters). Diagnostic criteria for preeclampsia include blood pressure greater than 140/90 mm Hg on at least two occasions separated by at least 6 hours and proteinuria of 300 mg or more on a 24-hour urine test. Severe preeclampsia causes a variety of other clinical and laboratory abnormalities, including central nervous system dysfunction, pulmonary edema, and thrombocytopenia [see Table 3].

Once the diagnosis of preeclampsia is made, a plan for management and possible delivery is required. To date, delivery of the fetus and placenta is the only known cure for preeclampsia. Essential features of a management strategy include minimizing maternal risks of preeclampsia, particularly stroke. Additionally, the risks of prematurity must be weighed against the risks to the mother of continuing the pregnancy. In mild preeclampsia, expectant management may continue to term if

**Table 3 Diagnostic Criteria for Severe Preeclampsia\***

Blood pressure > 160 mm Hg (systolic) or > 110 mm Hg (diastolic) on two or more occasions separated by at least 6 hours while patient is at rest  
Proteinuria in the nephrotic range (> 5 g in a 24-hour specimen)  
Oliguria (output < 500 ml in 24 hours)  
Visual disturbances  
Pulmonary edema  
Epigastric or right upper quadrant pain  
Elevated transaminase levels  
Thrombocytopenia  
Fetal growth restriction

\* Presumes that criteria for preeclampsia have been met.

mother and fetus are well.<sup>5</sup> In severe preeclampsia, premature delivery is necessary, but expectant management may be considered until 32 to 34 weeks' gestation, provided that blood pressure can be controlled, liver and kidney function remain stable, and coagulation remains normal. Close surveillance in a tertiary setting is essential for the expectant management of patients with severe preeclampsia.<sup>5,15</sup>

In addition to careful control of blood pressure, liberal utilization of magnesium sulfate is recommended for preventing disease progression to eclampsia, which is defined as a tonic-clonic grand mal seizure in a patient with preeclampsia without underlying neurologic disease. Although the value of magnesium sulfate in the management of preeclampsia has been a source of controversy for decades, several recent large clinical trials have demonstrated the efficacy of this approach.<sup>16</sup>

#### *Complications*

The major complications from preeclampsia are end-organ damage in the mother and the risks associated with prematurity in the fetus. Antenatal corticosteroids are used in the management of these cases to accelerate fetal lung development and reduce the incidence of CNS bleeding and necrotizing enterocolitis. Careful control of blood pressure and judicious fluid management will minimize the risks of adverse sequelae in the mother. Maternal death from preeclampsia is most often secondary to stroke or pulmonary edema. The risk of stroke is especially high in patients with a variant of severe preeclampsia known as the HELLP syndrome, which comprises hemolysis, elevated liver enzyme levels, and low platelet counts. As with other cases of severe preeclampsia, imminent delivery is advised in cases of HELLP syndrome.

#### *Prognosis*

In general, the prognosis for women with preeclampsia is excellent. A single episode of preeclampsia does not seem to pose long-term health risks to the mother. More than one episode of preeclampsia is, however, associated with an increased risk of the development of chronic hypertension later in life. Recurrence of preeclampsia in subsequent pregnancies ranges from 15% to 65%. The earlier preeclampsia occurs in gestation, and the more severe it is, the more likely that it will recur in a subsequent pregnancy. This information may be helpful in counseling patients with respect to future pregnancy risk.

## GESTATIONAL HYPERTENSION

Gestational hypertension is defined as hypertension diagnosed in the last half of pregnancy that is not chronic hypertension and is not preeclampsia. It is probably the least problematic of the three forms of hypertension seen in pregnancy. The treatment guidelines for gestational hypertension are the same as those for chronic hypertension (see above). However, gestational hypertension is usually mild; in most cases, blood pressure does not become high enough to require treatment.

## Diabetes Mellitus

In the past, diabetes management in pregnancy focused on gestational diabetes. Until the advent of insulin therapy, most patients with type 1 (insulin-dependent) diabetes mellitus were infertile or did not live to reproductive age; until recently, onset of type 2 (non-insulin-dependent) diabetes mellitus most often occurred after a woman's reproductive years. Now, pregnancy is commonplace in women with type 1 diabetes, and type 2 diabetes is becoming epidemic in adolescents.<sup>17</sup>

### TYPE 1 DIABETES

Poorly controlled type 1 diabetes is associated with increased rates of spontaneous abortion, congenital abnormalities, and other adverse pregnancy outcomes. For that reason, preconception counseling and diagnostic screening is preferred. Optimizing glycemic control and overall health before establishment of pregnancy will improve the likelihood of a normal outcome.

Preconception evaluation in patients with type 1 diabetes should include an evaluation of renal function, an ophthalmologic examination, and, depending on age and blood pressure status, a cardiac evaluation. Screening for evidence of hyperlipidemia may also be warranted, although treatment during pregnancy is not recommended.

The need for insulin shifts during pregnancy and postpartum: typically, insulin needs decrease early in pregnancy, increase later in pregnancy (to as much as three times the non-pregnant dose), then decrease markedly after delivery. Consequently, pregnancy in women with type 1 diabetes is best managed by a clinician familiar with insulin management and the complications of pregnancy that occur with increased frequency in this group of patients.

Because neural tube defects and cardiac anomalies occur more frequently in pregnancy associated with type 1 diabetes, second-trimester ultrasonography is recommended to screen for congenital anomalies. Complications developing later in pregnancy in this population include fetal growth restriction, abruptio placentae, and preeclampsia (among others). Therefore, fetal surveillance consisting of nonstress testing and ultrasound biophysical assessment of the fetus is also recommended, beginning in the third trimester.<sup>18</sup> In patients with well-controlled diabetes, delivery at term is permitted, provided the results of fetal testing have been reassuring, the maternal condition is stable, and fetal growth has remained normal.

### TYPE 2 DIABETES

When a patient with type 2 diabetes becomes pregnant, standard practice is to treat with diet only, if possible. Patients should check their blood sugar level regularly; if fasting levels exceed 140 mg/dl, insulin therapy is indicated.

Insulin-sensitizing agents are not approved for use in pregnancy by the Food and Drug Administration. Metformin is a

pregnancy category B drug; there is a growing body of evidence that metformin is safe in pregnant women, but this evidence is still preliminary, so this drug typically is discontinued if the patient becomes pregnant. The thiazolidinediones—pioglitazone and rosiglitazone—are category C drugs. Because their safety in pregnancy has not yet been confirmed, these agents also are typically discontinued in pregnancy. Because of their efficacy, however, and because the original agent in this class, troglitazone, was found to be safe in pregnancy, some endocrinologists use thiazolidinediones during pregnancy in selected cases.

ACE inhibitors are widely used in patients with type 2 diabetes to treat hypertension and maintain renal function. Because of their teratogenic effects, however, these agents are contraindicated in pregnancy [see Angiotensin Inhibitors, above]. When pregnancy is planned, withdrawal of ACE-inhibitor treatment can be arranged before conception. With unplanned pregnancy, the ACE inhibitor should be stopped as soon as pregnancy is confirmed. The patient can be reassured that the adverse effects of ACE inhibitors are seen with their use later in pregnancy.

Poorly controlled type 2 diabetes places the fetus at risk for macrosomia; consequently, the likelihood of delivery by cesarean section is increased. Birth injury and metabolic disturbances may also afflict the macrosomic newborn. Unfortunately, avoidance of macrosomia is frequently an elusive goal. Careful and regular evaluation of fetal size and growth will help minimize complications caused by macrosomia.

Prematurity is another complication of diabetes, because early delivery is sometimes necessitated by deteriorating maternal or fetal condition or superimposition of another disease process, such as severe preeclampsia. After adjusting for congenital anomalies, prematurity is the leading cause of death among infants of diabetic mothers. Maternal prognosis tends to be more favorable if pregnancy was negotiated without complication. Pregnancy in diabetic patients with renal disease may have long-term adverse effects on renal function, although the data are inconclusive. In diabetic patients with hypertension, blood pressure should be more aggressively controlled to protect renal function as much as possible.

#### GESTATIONAL DIABETES

In otherwise normoglycemic pregnant women, gestational diabetes is usually diagnosed in the second or early third trimester of pregnancy. The diagnosis of gestational diabetes may be a marker for increased risk of developing type 2 diabetes later in life.<sup>19</sup>

The diagnosis of gestational diabetes is most often made on the basis of a two-step screening procedure. There is controversy as to whether universal screening is superior to screening on the basis of risk factors, but universal screening appears to be the predominant practice at this time.<sup>20</sup>

Universal screening for gestational diabetes is performed at 24 to 28 weeks' gestation. In patients considered to be at very high risk or in whom glucose intolerance is suspected, screening may be carried out earlier in the pregnancy.

Screening for gestational diabetes utilizes a glucose challenge test, which consists of giving an oral 50 g glucose load and obtaining a blood glucose determination at 60 minutes. A value of less than 140 mg/dl (7.8 mmol/L) is considered normal.<sup>19</sup> A value exceeding 140 mg/dl warrants a 3-hour glucose tolerance test with 100 g oral glucose [see Table 4].<sup>21,22</sup> Two abnor-

**Table 4 Normal Results for 3-Hour Glucose Tolerance Testing**

<i>Time</i>	<i>Normal Maximum Values</i>
Pretest (fasting)	105 mg/dl (5.8 mmol/L)
1 hr	190 mg/dl (10.5 mmol/L)
2 hr	165 mg/dl (9.1 mmol/L)
3 hr	145 mg/dl (8.0 mmol/L)

mal values on the 3-hour glucose tolerance test constitute a diagnosis of gestational diabetes.

Treatment of gestational diabetes is with diet, if possible. Maintenance of fasting blood glucose levels below 105 mg/dl and of 2-hour postprandial levels below 120 mg/dl is ideal.<sup>23</sup> If fasting blood glucose levels exceed 140 mg/dl, insulin therapy is indicated.

In general, no special evaluation of other organ systems is required for diet-controlled gestational diabetic patients. Performance of these evaluations before pregnancy will allow the best opportunity for thorough follow-up and will allow for optimal counseling of the patient with respect to risks of pregnancy.

Fetal surveillance in gestational diabetic patients is somewhat less clearly defined than it is for patients with type 1 diabetes.<sup>19</sup> In diet-controlled gestational diabetes, fetal surveillance may not be needed, although initiation of nonstress testing at 38 weeks is commonly done. If other risk factors exist, however—such as hypertension, macrosomia, preeclampsia, or growth restriction—then fetal testing should be done. If evidence of fetal distress is detected, consideration should be given to initiating delivery.

The prognosis for patients with gestational diabetes is, in general, excellent. Because of the increased risk of developing type 2 diabetes later in life, it is particularly important for these patients to avoid obesity and maintain a regimen of regular exercise. Although postpartum follow-up testing for diabetes has been advocated, long-term studies to confirm the benefits of this approach have not been reported.<sup>19</sup> However, such testing may be indicated on the basis of other risk factors (e.g., obesity or ethnicity).

#### Thyroid Disease

Thyroid disease can be present before pregnancy, or it can manifest itself during pregnancy.<sup>24</sup> In either case, the disease must be distinguished from the changes in the thyroid and its function that normally occur during pregnancy.

In women who live in iodine-deficient areas, the thyroid enlarges in size during pregnancy.<sup>25</sup> In all pregnant women, thyroxine-binding globulin levels increase as a result of increased estrogen levels; consequently, blood levels of total triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) rise. Levels of free T<sub>4</sub> and thyroid-stimulating hormone (TSH) remain in the normal range, although free T<sub>4</sub> levels increase transiently in the first trimester and then drop to low-normal values.<sup>25</sup>

Hypothyroidism in pregnancy is associated with hypertension and premature labor.<sup>26</sup> Some children born to women whose TSH level was mildly elevated during pregnancy have been found to have lower scores on tests of neuropsychological development.<sup>27</sup>

The goal of treatment is to maintain TSH in the normal range, which may require a higher dose of T<sub>4</sub> than before preg-

nancy. In one study, the mean replacement dose needed to maintain TSH in the normal range rose from 100 µg before pregnancy to 150 µg during pregnancy.<sup>28</sup>

Hyperthyroidism occurs in 0.2% of pregnancies. Diagnosis of mild cases can be complicated by the fact that many of the physiologic changes of pregnancy mimic the milder manifestations of the disease. Mild to moderate hyperthyroidism in pregnancy generally poses little risk, but severe disease can cause spontaneous abortion or premature labor, and thyroid storm can be fatal.

Management of hyperthyroidism during pregnancy is typically most difficult in the first trimester and easiest in the third trimester. The treatment of choice is propylthiouracil, which should be given in the lowest dose possible to maintain the free T<sub>4</sub> level in the high-normal range. Propylthiouracil crosses the placenta, but to a lesser degree than methimazole, and is associated with a lower incidence of fetal aplasia cutis than is methimazole. Aplasia cutis is a localized failure of skin development, often occurring on the scalp. Instead of skin and hair, there is a thin, translucent membrane that can become ulcerated and covered by granulation tissue. Supplemental treatment with beta blockers and potassium iodide may be indicated in refractory cases. Use of radioactive iodine (for either scanning or treatment) is absolutely contraindicated during pregnancy because of its effects on the fetal thyroid.

### Thromboembolism

Thromboembolism is the leading cause of maternal mortality in the United States.<sup>29</sup> The major elements of thrombosis are described by the classic triad of Virchow, which comprises stasis, local injury or trauma to the vessel wall, and hypercoagulability. Both hypercoagulability and a tendency toward stasis (especially in late pregnancy, as the expanding uterus compromises venous return from the lower extremities) are part of the normal physiologic changes of pregnancy. The risk of thromboembolism is further increased in patients who have an underlying predisposition to development of a thromboembolic event [see *V:XIV Thrombotic Disorders*]. The most commonly identified inherited predisposition to thromboembolism is resistance to activated protein C, or the so-called factor V Leiden mutation.<sup>30</sup> Far less commonly implicated are disorders of protein C, protein S, antithrombin III, and plasminogen; the prothrombin gene (*G20210A*) mutation is also implicated. Antiphospholipid antibody syndrome and methylenetetrahydrofolate reductase (*C677T*) deficiency have also been associated with increased risk of thromboembolism. Dislodgement of a thrombus resulting in thromboembolism (usually pulmonary) often produces no symptoms. Symptomatic thromboembolism is a medical emergency.

### DIAGNOSIS

The most common symptom of pulmonary thromboembolism is dyspnea. However, dyspnea is common in normal pregnancy, because as the uterus grows, it forces the diaphragm higher into the chest cavity, reducing the residual volume of the lungs and resulting in an increased respiratory rate. Therefore, careful clinical assessment is essential. The laboratory and radiologic evaluation for pulmonary embolism in pregnancy is essentially identical to that of the nonpregnant patient [see *I:XVIII Venous Thromboembolism*]. The standard tests in pregnancy are screening for deep vein thrombosis with Doppler ultrasound of

the lower extremities and follow-up spiral chest CT if the screening test is positive or if there is a high clinical suspicion of pulmonary embolism (the CT beams are sufficiently focused that shielding of the uterus is unnecessary, although shielding does no harm).

### TREATMENT

The management of thromboembolism in the pregnant patient is essentially the same as that in the nonpregnant patient. Aggressive treatment is essential. In general, treatment with either unfractionated or low-molecular-weight heparin is acceptable. A number of administration protocols are available for either approach.<sup>31</sup> Warfarin is generally avoided, because it is teratogenic in the first trimester and can interfere with fetal and neonatal coagulation, owing to the fact that it freely crosses the placenta. Therapy is continued for the duration of pregnancy, with conversion to warfarin in the postpartum period; warfarin is not contraindicated in breast-feeding women. Cessation of heparin just before delivery is preferred, if scheduled delivery is possible.

### COMPLICATIONS AND PROGNOSIS

Vascular insufficiency and death are the major complications of thromboembolic disease. Cardiovascular collapse from pulmonary embolism is the most common cause of death. Recurrent thromboembolism requiring surgical intervention with filter placement in the inferior vena cava is also a complication, especially for younger women, in whom the long-term consequences of filter placement may be less understood.

Thorough evaluation for underlying disorders (genetic or acquired) is essential to better assess long-term prognosis. However, if such evaluations are negative and the clot resolves completely, the prognosis is excellent. Support of the pregnancy through the critical phase of thromboembolism is essential, and premature delivery may be required because of maternal instability or a deteriorating fetal status secondary to poor maternal oxygenation.

### Valvular Heart Disease

Valvular heart disease is the most common cardiac problem complicating pregnancy. Preconception counseling and management is based on whether the valvular heart disease is congenital or acquired. Congenital cardiac disease in the mother, with the exception of a few known mendelian disorders that affect the heart, is thought to be genetically multifactorial. Therefore, there is an increased risk of the fetus being affected (2% to 5%); genetic counseling and screening for such patients is appropriate. Fetal echocardiography is an effective tool and will usually identify major cardiac anomalies prenatally, allowing appropriate delivery preparations to be arranged.

Acquired heart disease can pose specific risks for the mother with respect to her ability to tolerate a pregnancy. One study showed a marked increase in maternal morbidity—including congestive heart failure and arrhythmias—but only rare mortality; higher morbidity and unfavorable fetal outcome were seen mostly in patients with moderate or severe mitral or aortic stenosis.<sup>32</sup>

### MITRAL STENOSIS

Mitral stenosis is the valvular lesion most likely to result in maternal decompensation and death during pregnancy. Long-standing mitral stenosis may lead to pulmonary hypertension,

which may cause sudden death, especially if pregnancy is complicated by sudden hypovolemia, as might occur with intrapartum or postpartum hemorrhage. Persistent tachycardia, which may develop in patients with severe mitral stenosis, can lead to inadequate ventricular filling times and consequent rate-related congestive heart failure.

In severe cases of mitral stenosis, balloon valvulotomy may be accomplished during pregnancy. Otherwise, management focuses on labor and delivery.

If pulmonary hypertension has been identified, labor and delivery is best carried out in a setting in which intensive care services and pulmonary artery catheterization are available. In general, vaginal delivery is less hemodynamically stressful than cesarean section. During labor, careful attention must be paid to management of pain and fluid volume to minimize fluctuations in blood pressure and heart rate.

#### MITRAL REGURGITATION AND AORTIC REGURGITATION

The decreased systemic vascular resistance that occurs in normal pregnancy tends to minimize the effects of mitral and aortic regurgitation, so these lesions are generally well tolerated during pregnancy. Mitral valve prolapse, unless severe or accompanied by other disturbances of cardiac rhythm, is generally well tolerated during pregnancy.

#### AORTIC STENOSIS

In general, aortic stenosis is well tolerated during pregnancy. Moderate to severe cases may be managed with limitation of activity. As with mitral stenosis, balloon valvuloplasty may be accomplished during pregnancy, if necessary.

#### ARTIFICIAL HEART VALVES

Women with mechanical heart valves are advised to avoid pregnancy, but management of pregnancy in these patients is certainly possible. Attention to coagulation status and cardiac function is essential. Although warfarin is the usual anticoagulant of choice for patients with mechanical heart valves, its use during pregnancy is probably not justified, because of the risks it poses to the fetus.<sup>31,33,34</sup> Heparin anticoagulation is generally preferred, with brief discontinuance during labor and delivery, rapid reinstitution postpartum, and conversion back to warfarin as soon as possible. Anticoagulation aside, pregnancy in women with cadaveric or porcine replacement valves who have normal cardiac function and are otherwise in good health may be managed according to routine obstetric protocol.

### Cardiomyopathy

In rare cases, idiopathic dilated cardiomyopathy may develop late in pregnancy or in the early postpartum months [see

1:XIV *Cardiomyopathies*]. Patients present with dyspnea and other manifestations of heart failure. Treatment is largely the same as that for heart failure. Outcomes range from spontaneous resolution to death; heart transplant may be lifesaving in severe cases.

### Infections

#### BACTERIAL INFECTIONS

##### *Urinary Tract Infection*

After bacterial vaginosis, urinary tract infections are the most common bacterial infections in pregnant women. Screening for asymptomatic bacteriuria should be done at the initial prenatal visit in all pregnant women. Asymptomatic bacteriuria is more common during pregnancy; if left untreated, it may progress to symptomatic urinary tract infection. It is estimated that 75% of cases of pyelonephritis in pregnancy are the result of untreated asymptomatic bacteriuria. Pyelonephritis in pregnancy is associated with an increased risk of preterm delivery.

##### *Group B Streptococcus*

Carriage of group B *Streptococcus* (GBS) at the time of vaginal delivery places the newborn at increased risk for developing acute GBS disease. To minimize this potentially devastating outcome, intrapartum treatment is given to patients at high risk for GBS [see Table 5]. All other women are screened at 35 to 37 weeks' gestation and treated if GBS is found. Penicillin G is the drug of choice for maternal intrapartum treatment. Ampicillin may also be used. Clindamycin is recommended in penicillin-allergic patients.<sup>35</sup>

#### VIRAL INFECTIONS

##### *HIV*

One of the success stories of the past decade has been the ability to reduce vertical transmission of HIV from 25% to less than 1%. These results have been accomplished by increasing our understanding about viral load; utilizing antiviral therapies, particularly intrapartum zidovudine (AZT); and more liberally utilizing cesarean section before the onset of labor.<sup>36</sup> All women should be offered HIV screening as part of prenatal care; in many states, such screening is required. Management of these cases in consultation with an infectious disease specialist will further optimize outcome. There is no evidence that pregnancy significantly alters the course of HIV disease, nor is there evidence that well-managed HIV disease significantly alters the course of pregnancy. Breast-feeding is not recommended in HIV-positive women.

##### *Cytomegalovirus*

Cytomegalovirus (CMV) is the most common cause of congenital viral infection in the United States.<sup>37</sup> Approximately 50% to 90% of women of childbearing age will already have developed antibodies to CMV; reactivation of infection is fortunately a very rare cause of congenital infection. Most cases of congenital CMV are secondary to primary maternal infection during pregnancy. There is no established effective therapy for fetal CMV, and it is not currently possible to predict which exposed fetuses will sustain significant sequelae from in utero infection.

Although screening for antibodies to CMV is not recommended as part of routine prenatal care, primary CMV infec-

**Table 5 Obstetric Risk Factors for Early-Onset Neonatal Group B *Streptococcus* (GBS) Infection**

GBS bacteriuria during pregnancy  
Previous delivery of infant with GBS infection  
Gestational age < 37 weeks at time of labor onset  
Membrane rupture > 18 hours  
Intrapartum temperature  $\geq 38^{\circ}\text{C}$  (100.4° F)

tion should be suspected in pregnant patients who develop a mononucleosis-like syndrome with high fever, fatigue, malaise, myalgias, headache, and splenomegaly. The diagnosis of CMV should be aggressively pursued in such cases, to permit appropriate counseling and presentation of options for further diagnosis and management.<sup>38</sup>

### *Herpes Simplex Virus*

Herpes simplex virus (HSV) may be acquired before or during pregnancy. Recurrent genital herpes infection poses risks to the newborn. To prevent transmission of HSV during the birth process, cesarean section is recommended if there is evidence of active disease or if there is a strong suggestion of a preactivation prodrome, either at the time of presentation in labor or near the expected date of delivery. Use of acyclovir during the last 4 weeks of gestation in women who developed their primary infection during pregnancy may reduce the risk of clinical recurrence, but whether this practice confers protection of the neonate has not been established.<sup>39</sup> Disseminated neonatal herpes infection is often fatal, and many survivors have serious neurologic sequelae.

### *Parvovirus*

Infection during pregnancy with human parvovirus B19 rarely results in fetal hydrops secondary to cardiac failure from the profound anemia that develops from fetal erythroid aplasia. Determination of maternal immune status may be indicated if the patient has been exposed to a child with erythema infectiosum (fifth disease), which is caused by parvovirus B19. Close fetal surveillance with ultrasound may be warranted if the pregnancy is in the second or third trimester. Occasionally, intervention and intrauterine transfusion are required. Fortunately, most cases do not require this level of intervention.

## PARASITIC INFECTION

### *Toxoplasmosis*

In the United States, nearly 70% of women of childbearing age are susceptible to infection with toxoplasmosis.<sup>40</sup> Unfortunately, acute toxoplasmosis in immunocompetent persons is difficult to detect because most cases are asymptomatic. In symptomatic patients, the most common manifestation is cervical lymphadenopathy; a minority of symptomatic patients have generalized lymphadenopathy, sometimes accompanied by a flulike syndrome.

Most cases of primary toxoplasmosis are contracted through the ingestion of undercooked meat, but contact with contaminated feces, particularly cat feces, has also been identified as a source of infection. Congenital toxoplasmosis may be diagnosed via amniocentesis or cordocentesis, though the latter test is definitive. If pregnancy termination is not possible or is not desired, intravascular fetal treatment (provided by a specialist in obstetric infection or infectious disease) may reduce the risk of severe neonatal infection. Routine prenatal screening is not recommended.<sup>37</sup>

## Asthma

Asthma may improve, worsen, or remain stable during pregnancy. Well-controlled asthma appears to have no adverse effects on pregnancy outcome, but poorly controlled asthma is associated with a variety of adverse effects on both mother and

fetus.<sup>41</sup> The goal of therapy is prevention of hypoxia. In general, pregnant patients are candidates for the same therapy as non-pregnant patients [see 14:II *Asthma*]. Beta agonists, theophylline derivatives, glucocorticoids, and cromolyn may all be used as needed. There are insufficient data on the safety and efficacy of leukotriene antagonists to support their use during pregnancy.

Management should include patient education and utilization of at-home peak expiratory flow rate monitoring. Because asthma has implications for both mother and fetus, more liberal use of in-hospital evaluation and management may be warranted.

## Alcohol and Tobacco Use

It has been estimated that 15% of cases of low birth weight may be attributed to cigarette smoking.<sup>42</sup> Adverse antepartum effects of smoking include uteroplacental insufficiency and preterm delivery. Although it is unclear whether smoking increases the risk of preterm labor, prematurity is increased secondary to increases in placenta previa, abruptio placentae, and preterm premature rupture of membranes. Smoking has also been associated with intrauterine fetal demise<sup>43</sup> and increased risks of placenta previa, abruptio placentae, impaired cognitive development, and sudden infant death syndrome. Smoking cessation during pregnancy is possible and should be encouraged. Nicotine replacement therapy is commonly prescribed as an aid to smoking cessation in pregnant women.<sup>44</sup> Large-scale trials of the safety and efficacy of nicotine replacement therapy in pregnancy have not been done; nicotine is a category D drug, but of course smoking delivers not only nicotine but a variety of other documented reproductive toxins as well.<sup>45</sup> Adjunctive use of bupropion for smoking cessation during pregnancy has not been well studied, but safety studies of bupropion use in pregnancy have shown no risk in humans (category B).

Alcohol is a known teratogen. Despite this fact and the determination that there is no safe lower limit of alcohol consumption during pregnancy, drinking in pregnant women increased between 1991 and 1995 in the United States.<sup>46,47</sup> Data on the effects of alcohol use during pregnancy have been inconsistent with respect to specific risks, such as spontaneous miscarriage, and neurobehavioral disorders, such as attention deficit disorder. More conclusive is the association of maternal alcohol use with the development of fetal alcohol syndrome (FAS). Manifestations of FAS include growth deficiency (intrauterine and postnatal), low intelligence, fine-motor dysfunction, and a range of craniofacial, skeletal, cardiac, and other abnormalities. There is evidence that the risk of fetal alcohol syndrome increases as alcohol consumption increases. Mild to moderate alcohol use may not result in the complete syndrome but may result in infants being born with varying degrees of affliction, or so-called fetal alcohol effects. The effects of alcohol use limited to the first trimester are less well characterized.<sup>48</sup>

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