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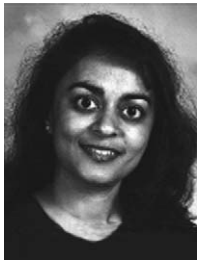
Preface

Management of the High-Risk Pregnancy



Michael O. Gardner, MD, MPH Manju Monga, MD
Guest Editors

The practice of obstetrics is, for the most part, assisting the pregnant woman and her family with a physiologic process to produce a healthy full-term infant. In fact, the *raison d'etre* of prenatal care is to identify women who have risk factors with the potential to adversely affect this expected outcome of a healthy mother and child. A particular challenge for the clinician in the prenatal period is the management of pregnancy in women who have a pre-existing medical condition. This is the focus of this issue of the *Obstetrics and Gynecology Clinics of North America*. Coexisting medical complications are becoming more common in modern practice, because women are often delaying reproduction until later in life, when these conditions become more prevalent. We have endeavored to cover a wide range of topics, from those that are commonly seen by most obstetricians to those that are rarely managed in routine practice.

Dr. Gregg reviews the current concepts of chronic hypertension, its treatment, and the development and treatment of pregnancy-induced hypertension. Drs. Conway and Griffith have provided an excellent review of the management principles involving diabetes, including diagnosis of the disease and treatment with both glyburide and insulin. Dr. Nader discusses thyroid disease and other less common endocrine conditions such as pituitary and adrenal disease in pregnancy. Hemoglobinopathies are frequently encountered by physicians caring for women from varied ethnic backgrounds. The comprehensive discussion of this topic by Drs. Rappaport, Velazquez, and Williams will be an invaluable resource for these physicians. Recently, much attention has been given to the issues of thrombophilias, both inherited and acquired. The article by Drs. Doyle and Monga on this topic is augmented by Drs. Warren and Silver's review of

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antiphospholipid antibody syndrome and lupus in pregnancy. Dr. Pschirrer has contributed a concise reference about seizure disorders in pregnancy with a contemporary review of medications that are used to treat these disorders. Asthma remains a significant cause of maternal morbidity and mortality, and a practical plan of management is outlined in the article by Drs. Doyle and Gardner. Drs. Mastrobattista and Katz discuss preconception counseling, medication use, and pregnancy management in women who have undergone organ transplantation—a steadily increasing cohort. Finally, the exhaustive review of cardiac disease by Drs. Galan and Klein provide valuable management strategies for these complicated and potentially life-threatening conditions.

It is our hope that readers will find these articles full of novel information about the physiologic aspects of these conditions as well as practical recommendations for the appropriate diagnosis and treatment of these medical complications in pregnancy.

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Hypertension in pregnancy

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The hypertensive diseases that are encountered most commonly during pregnancy include: pre-eclampsia/eclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed pre-eclampsia. At first glance, these disorders are well-defined with varied pathogeneses; however, it is important to recognize that the defining features of these conditions have varied between professional organizations and even within the same organizations (Table 1). Furthermore, when these entities are viewed within the context of a clinical management algorithm the definitions can become blurred. Thus, when exploring management options for disorders that are characterized by hypertension in pregnancy, an effort will be made to point out where the management schemes under discussion are driven by commonly held dictum, controlled or retrospective studies, or personal experience. The approaches to managing hypertensive diseases during pregnancy have a common goal of limiting maternal and fetal/neonatal morbidity. Thus, one attempts to maximize pregnancy duration without unnecessarily jeopardizing maternal or fetal well-being.

Management of the common clinical entities

Pre-eclampsia/eclampsia

The management of pre-eclampsia varies across the spectrum of the disease and across gestational ages. This creates difficulty in interpreting the literature; attempts will be made to clarify the spectrum of disease and the gestational ages studied. Prevention strategies will not be discussed; instead, management of established cases is discussed with a focus on specific areas of controversy.

Mild pre-eclampsia

Generally, mild pre-eclampsia encompasses the minimal diagnostic criteria of new-onset hypertension and proteinuria that begins after 20 weeks' gestation

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Table 1
Criteria for establishing the diagnosis of pre-eclampsia

Organization	Blood pressure values (mm Hg) and gestational age	Blood pressure nuances	Urine protein dip/24-hour collection	Edema and weight gain	
American College of Obstetrics and Gnecology [1]	Adopted the most recent criteria put forth by NHLBI/NIH (see below)		Adopted the most recent criteria put forth by NHLBI/NIH (see below)		
Canadian Hypertension Society [2]	Diastolic blood pressure $\geq$ 90	A manual cuff that is 1.5 times the circumference of the arm is recommended. Patient should be seated with cuff at level of heart. The diastolic reading is taken as the muffling sound (Korotkoff 4). Unless the value is $\geq$ 110, two determinations 4 hours apart should be used to define hypertension. The repeated blood pressure measurements should be less than 1 week apart.	1 + (30 mg/dL) or 0.3 g/24-hour Dipstick value must be interpreted within the context of other variables reported on a urinalysis (eg, pH, leukocyte esterase, specific gravity)	Not included	The term "gestational hypertension with proteinuria" is used instead of pre-eclampsia.
NHLBI/NIH [3]	With baseline value (< 20 weeks) Systolic increase of 30, or diastolic increase of 15. Without baseline values $\geq$ 140/90	High blood pressure must resolve by 42 days postpartum.	1 + (30 mg/dL) or 0.3 g/24-hour	Clinically evident or rapid increase in weight gain	Proteinuria or edema must accompany hypertension

NHLBI/NIH [4]	Normotensive at baseline (< 20 weeks) $\geq$ 140/90	The diastolic reading is taken as the disappearance of the sound (Korotkoff 5). At least two determinations should be used to define hypertension. The repeated blood pressure measurements should be less than 1 week apart.	1 + (30 mg/dL) or 0.3 g/24-hour (a 24-hour specimen is strongly recommended or at least a timed specimen with correction for creatinine excretion)	Not included	With baseline blood pressure value (<20 weeks) Systolic increase of 30 or diastolic increase of 15 warrants close observation for proteinuria and hyperuricemia (uric acid $\geq$ 6 mg/dL). No evidence of urinary tract infection. Suspect pre-eclampsia even without proteinuria if headache, blurred vision, or abdominal pain are combined with low platelet count and abnormal liver enzymes.
WHO World Health Organization [5]	Diastolic blood pressure $\geq$ 90	Patient should be in a 15–30° lateral recumbency position. The diastolic reading is taken as the muffling sound (Korotkoff 4). Unless value is $\geq$ 100, two determinations 4 hours apart should be used to define hypertension.	>0.3 g/24-hour	Not included	Diastolic blood pressure >85 should be considered abnormal

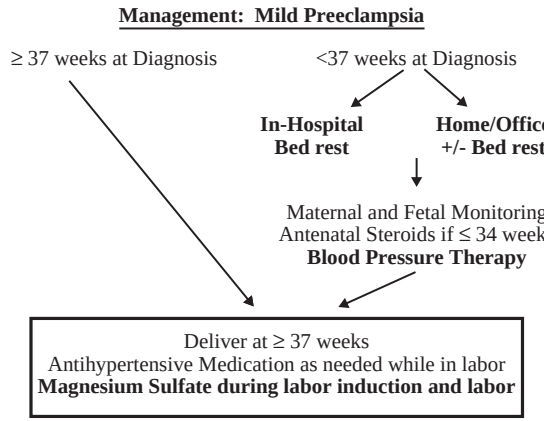

Fig. 1. A management algorithm for mild pre-eclampsia. Bold type indicates controversial management options.

(see Table 1). The management of this condition can be dichotomized by gestational age (Fig. 1). Patients who present with a diagnosis at or near term most often are delivered. The gestational age of 37 weeks was chosen (see Fig. 1) because this splits the difference between the recommendations by the World Health Organization (WHO) (36 weeks) [5] and those of the National Heart Lung and Blood Institute/ National Institutes of Heath (NHLBI/NIH) (≥38 weeks) [4].

A primary dichotomy in management emerges for those who present before 37 weeks' gestation. Are these patients best managed within a hospital setting or at home? Problems that are inherent in studies of this nature center on the definition, duration, and type of bedrest. Is the semirecumbent position adequate or must the head be down in a recumbent position? Is the amount of time spent in the left or right lateral decubitus position important? Most would agree that home bed rest is likely to be less stringent than hospitalized bed rest. With this in mind one must remember the intent of hospitalized bed rest—the reduction in maternal and fetal morbidities (Box 1). The belief is that morbidities can be reduced through bed rest's impact on maternal and fetal/placental physiology, or in the case of hospitalized bed rest, on improved maternal and fetal surveillance that may result in prevention of morbidity and mortality. How bed rest became the mainstay of treatment in cases of pre-eclampsia apparently is rooted in the 1950s. According to one commentary, this treatment was suggested for the nonproteinuric hypertensive patient to prevent associated morbidity in 1952 [6]. Later studies of physiology during pregnancy seem to have been extrapolated and result in today's management approach. Studies of uterine blood flow and placental transfer showed aberrancies in cases of hypertension during pregnancy [7–9]. These studies were followed by studies of exercise during pregnancy which suggested impaired placental perfusion [10–12]. Reports of improved urinary excretion of estriol (a crude measure of placental function) during bed rest followed [13,14]. These investigations seem to have resulted in the common

Box 1. Maternal and fetal/neonatal morbidities that are associated with hypertensive disease

Maternal

Abruption placenta
Central nervous system event (eg, stroke, seizure)
End organ dysfunction (eg, acute tubular necrosis)
Coagulopathy
Hypercoagulable state

Fetal/neonatal

Sequelae of prematurity
Ischemic encephalopathy
Intrauterine growth restriction

practice, wherein patients who have pre-eclampsia are prescribed bed rest; however, questions of efficacy remain. In a study that evaluated physiologic changes among women who had pre-eclampsia, a regimen of complete hospitalized bed rest was compared with one of liberal ambulation. Renal function did not improve, whereas placental function showed some suggestion of improvement with bedrest. The most important conclusion may be that complete bed rest allowed earlier detection of impending morbidity, and, thus, earlier intervention [15,16] (Table 2). In the absence of conclusive data, one investigator suggested that the correlation of the increase in hospitalized bed rest with improved ma-

Table 2
Impact of bed rest on maternal or fetal physiology

Reference	Bed rest protocol	Maternal physiology	Fetal/placental physiology	Monitoring intervention
Curet & Olson, 1979 [18]	Home bed rest 4 hours daily in left lateral decubitus, hydralazine when diastolic blood pressure is greater than 110 mm Hg			Intervention protocol was extensive; a near 50% reduction in perinatal mortality was demonstrated
Mathews et al, 1980 [15]	Hospitalized bed rest v hospitalized ambulation ad lib	No improvement in plasma urate or urea		
Mathews et al, 1982 [16]	Hospitalized bed rest v hospitalized ambulation ad lib		Nonsignificant increase in serum estriol or human placental lactogen	Possibly earlier detection of premonitory symptoms of eclampsia

ternal, fetal, and neonatal outcomes in cases of pre-eclampsia suggested a benefit [17]. This contrasts with conclusions by the Canadian Hypertension Society [2] who stated that a policy of strict bed rest is not advised for gestational hypertension with or without proteinuria (grade B recommendation). It may be that these recommendations require some consideration of the patient population and their ability to follow-up with outpatient management schemes. Some investigators argued that disease progression is not predictable and used this as a basis for hospitalized bed rest; however, there is general agreement that when disease progression (not specified) of mild pre-eclampsia has occurred, hospitalization is preferred [15].

Of the two criteria that are used to define pre-eclampsia, hypertension and proteinuria, no remedy has been shown to reduce the degree of proteinuria. The opposite is true for hypertension. Because the pathogenesis of pre-eclampsia is presumed to be different from that of essential hypertension, several important questions emerge: (1) Does pharmacologic intervention control blood pressure in cases of mild pre-eclampsia? (2) Is blood pressure control important in cases of mild pre-eclampsia? and (3) If pharmacologic intervention is important, which agent works best? Questions 1 and 2 are best answered by looking at data from studies that compared pharmacologic intervention with placebo. The third question is answered best by comparing various agents. The outcome measure that is most important to question 1 is the degree of blood pressure control. For question 2, the impact of medications on maternal and fetal/neonatal morbidity is most important. The combined answers to questions 1 and 2 address the third question. Randomized trials that apply these questions to confirmed mild pre-eclampsia only have been limited in number, but do exist (Table 3). It seems that the use of antihypertensive agents reduces the occurrence of severe hypertension, but offers no immediate benefit to the fetus. Thus, blood pressure control can be achieved, but with no confirmed benefit to mother or fetus.

The timing of delivery in cases of mild pre-eclampsia can be considered within the context of disease progression. Disease progression follows no predictable pattern; therefore, the value of extending the antepartum period beyond 37 weeks' gestation is questionable. When one considers the possibility of placental abruption, placental failure, fetal death, and deterioration of maternal physiology when HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets) arises, the risk-benefit ratio seems to favor delivery at 37 weeks' gestation. Arguments have been made that suggest that the prolongation of pregnancies beyond 34 weeks' gestation may offer real advantages to the fetus [23]

Indications for delivery remote from term have been suggested (Box 2). Absent the appearance of these indications, the risk-benefit ratio favors expectant management until 37 weeks' gestation [19]. Given the current indications for the use of antenatal steroids to reduce neonatal and childhood morbidity that is caused by prematurity [1], their use is prudent in cases where expectant management is undertaken before 34 weeks' gestation.

The management of mild pre-eclampsia has long included the use of magnesium sulfate for seizure prophylaxis. The recent Magpie Trial Collabora-

Table 3
Selected randomized trials that assessed efficacy of blood pressure medications for the treatment of mild pre-eclampsia

Reference	Medication[a]/comparison	N[b]	Physiology outcomes	Maternal outcomes	Fetal/neonatal outcomes
Sibai et al, 1992 [20]	Nifedipine + hospitalized bed rest/hospitalized bed rest	100/100	Nifedipine reduced systolic and diastolic blood pressure. No change in laboratory values.	Nifedipine group had a lower rate of severe hypertension. Labor, ruptured membranes, prolongation of pregnancy, cesarean section, abruptio placenta, and HELLP syndrome had no differences. Patients going to term no difference.	Small-for-gestational-age, and abnormal fetal tracing not different
Sibai et al, 1987 [21]	Labetolol + hospitalization/ hospitalization	100/100	Labetolol group worsening creatinine clearance, platelet count	Labetolol group had a lower rate of severe hypertension	SGA was more frequent in the labetolol group. The fetal death rate, NICU admission rate, umbilical cord arterial pII $\leq$ 7.2, and frequency of abnormal fetal tracings were not different.
Sanchez-Ramos et al, 1995 [22]	Calcium (2g/d) ÷ hospitalized bed rest / placebo + hospitalized bed rest	36/39	No difference in blood pressure control, proteinuria, creatinine clearance, urinary calcium, uric acid, platelet count, or LDH	No difference in occurence of severe preeclampsia, cesarean section rate, or spontaneous labor rate	No difference in fetal heart rate abnormality, pulmonary maturity, birth weight, APGAR scores, umbilical arterial cord pH <7.16, perinatal death, birth weight, or fetal growth restriction.

Abbreviations: APGAR, Newborn assessment score proposed by Virginia Apgar; LDH, lactate dehydrogenase; NICU, neonatal intensive care unit; SGA, small for gestational age.

[a] Medication dosage varied unless a dose is specifically stated.

[b] Denotes number of patients in each treatment group.

Box 2. Criteria used to establish severe pre-eclampsia

Severe blood pressure elevation*
Elevated liver function studies*
Low platelet count (100,000)*
Eclampsia
Persistent maternal headache
Scotomata/blurred vision
Proteinuria ($\geq$ 5g/24 h) and at least 34 weeks' gestation*
Nonreassuring tests of fetal well-being
Oligohydramnios
Fetal growth restriction
Placental abruption

* This might lend itself to temporizing measures in an effort to improve neonatal outcomes; however, individualized care within a tertiary care center is indicated [19].

tive Group Study [24] demonstrated the superior efficacy of magnesium sulfate compared with placebo in preventing eclampsia (50% reduction); however, patients who had mild disease or severe disease were not analyzed separately. About 25% of participants had severe pre-eclampsia at the time of enrollment. Although magnesium sulfate's use in cases of severe pre-eclampsia is difficult to dispute as an effective means of preventing eclampsia, its use in cases of mild disease deserves scrutiny [25]. A study that was designed to have the power to answer the question of magnesium sulfate's usefulness in preventing mild pre-eclampsia from progressing to eclampsia has not been published. At least one smaller randomized placebo-controlled trial suggested that under carefully monitored circumstances, magnesium sulfate may not be needed in cases of mild disease [26].

When the diagnosis of mild preeclampsia is made at 37 weeks' gestation or longer, delivery offers the greatest maternal and fetal/neonatal benefit with the least risk. Hospitalized observation should be considered optional in all patient populations. Pregnancies should be monitored carefully for disease progression or fetal deterioration, independent of the monitoring location. Use of strict bed rest, pharmacologic intervention for blood pressure control, and magnesium sulfate as prophylaxis for seizures remain unproven management options in mild pre-eclampsia.

Severe pre-eclampsia

The primary aim in managing severe pre-eclampsia is the immediate elimination of the disease phenotype. Among the criteria that are used to establish severe disease, several may be temporized in cases where the pregnancy is far from term (Box 2). Just exactly how remote from term efforts should be made to prolong

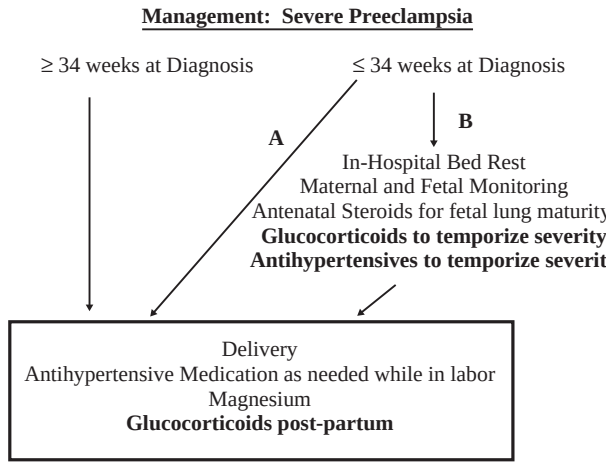

Fig. 2. A management algorithm for mild pre-eclampsia. Bold type indicates controversial management options. For patients who are diagnosed at or before 34 weeks' gestation, option A or B can be considered.

pregnancy is not scientifically addressed. Clearly, discussions with the patient that address specific risks to her health and her fetus/neonate are appropriate.

The management of severe pre-eclampsia includes delivery when the gestational age is at least 34 weeks (Fig. 2). The comfort level with continuing a pregnancy when the gestational age is less than 34 weeks can vary from purely expectant management to a range of interventions. Traditionally, proteinuria of at least 5 g/24 hours had signified the need for immediate delivery [1]. Historically, any of the criteria for severe disease were considered grounds for delivery when the pregnancy was far from term; however, data from several studies question this intervention in cases where proteinuria is the only criterion that is present [27–30]. Expectant management seems to be an acceptable approach and can lead to improved neonatal outcomes in cases of severe pre-eclampsia that are defined solely by proteinuria ($\geq$ 5g/24 h). Newer recommendations are for patients who have severe pre-eclampsia to be managed in tertiary care centers or in consultation with personnel who are experienced in the management of this condition [31,32].

The use of antihypertensive medications to treat blood pressure as part of an expectant management approach has been considered. Current evidence suggests that there is a place for this when the gestational age is less than 34 weeks. When patients who had severe disease at 28 to 32 weeks' gestation were randomized to immediate delivery or bed rest with antihypertensive therapy (labetolol or nifedipine as needed), the group that was managed expectantly achieved a gestational age benefit of nearly 2 weeks. This translated into a greater birthweight, the need for a lower level and fewer days of neonatal care, and reduced rates of respiratory distress syndrome and necrotizing enterocolitis. Small-for-gestational-age fetuses were more common in the group that was managed with

Table 4
Corticosteroid use for HELLP syndrome

Author (year)	Study type	N^s/N^c	medication	Inclusion criteria	Exclusion criteria	Outcomes[a]
Magann et al, 1994 [41]	PRmC	12/13	Antepartum Dex 10 mg IV q 12 h through delivery	Class 2/3 HELLP 24–37 wks' gestation	Platelet count <50,000. Fetal compromise.	Improved urine output, platelet counts, LDII, and AST. Delivery interval increased (41 v 15 hrs) from enrollment.
Magann et al, 1994 [41]	PRmC	20/20	Immediately postpartum IV Dex 10 mg q 12 h (2 dosages) then 5 mg at 24 and 36 hours postpartum	Class 2/3 HELLP	Platelet count <50,000. Chorioamnionitis.	Improvements in MAP by 16 h, urine output by 16 h, platelet count by 24 h, LDII and AST decreased by 36 hours.
Martin et al, 1997 [44]	R	43/237	Immediately postpartum IV Dex 10 mg q 12 h (2 dosages) then 10 mg or 5 mg at 24 and 36 hours postpartum or longer (variations were at physician discretion)	Class 2/3 HELLP	Platelet count <50,000	Reduced need for apresoline in the puerperium (2 fold decrease) and less antihypertensive use in postpartum for study patients. Fewer transfusions of PRBCs and FFP in study group. Invasive monitoring, mechanical ventilation, and hospital stays were lower in the study group. Uric acid, urine protein, and CPK were worse in study group. Platelet counts and LDH showed more rapid improvements No improvements in other laboratory tests.

Tompkins & Thiagarajah, 1999 [45]	P	52/0	Antepartum IM Betamethasone 12 mg q 24 hours (2 dosages) 12 mg q 12 hours (2 dosages) or IM Dex 6 mg q 6 h (4 doses) or variable (N = 10)	HELLP (ACOG 1996) [1] 24–36 wks' gestation	Improved platelet count, AST, ALT, and alkaline phosphatase for all study groups combined.
O'Brien et al, 2000 [46]	R	11 (high dosage)/ 15 (low dosage)/ 11 control	Antepartum high dosage: Dex IV 10 mg q 6 h (2 dosages) then 6 mg q6 h (2–4 doses) low dose: Betamethasone IM 12mg q 12 hours (2 dosages) or Dex 6 mg q 6 h (4 dosages)	HELLP (Sibai et al, 1986 [47] < 34 wks' gestation	Time to delivery was increased in high-dosage group with more patients remaining undelivered 48 hours from start of treatment. Any steroid group demonstrated improved AST, LDH, and platelet count. Highest platelet count in the high-dosage group. Rebound thrombocytopenia was observed more often in low-dosage group (80%) compared with high-dosage group (60%).

P = prospective, R= retrospective, R= Randomized, B – blinded, C= controlled, PI = placebo N^s/N^c Refers to number of patients enrolled in study or group control group. ** Dexamethasone.

Abbreviations: ACOG, American College of Obstetrics and Gynecology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, controlled; CPK, creatine kinase; Dex, dexamethasone; FFP, fresh frozen plasma; IM, intramuscularly; MAP, mean arterial pressure; N^c, number of patients in control group; N^s, number of patients in study group; P, prospective; PRBCs, packed red blood cells; R, retrospective; Rm, randomized.

[a] Significantly different outcomes are noted.

bed rest and antihypertensive medications. Patients in this group had a low rate of uncontrolled hypertension and only 6% required delivery for this indication [28]. An earlier retrospective study from the same institution used the antihypertensive agents, aldomet and hydralazine, in a conservative management scheme at earlier gestational ages (18–27 weeks). No improvement in outcomes was seen [33]. With advances in neonatology and efforts to improve fetal lung maturity, the findings of the latter study may be different today. Another study found that between the gestational ages of 28 and 34 weeks, expectant management after administration of steroids for fetal lung maturity resulted in prolongation of pregnancy (2 versus 7 days), no increase in maternal complications, and a decrease in neonatal complications. Prazosin was used for antihypertensive management and steroids were administered weekly in the group that was managed expectantly. The early delivery group received the same care as the Prazosin treated group (magnesium sulfate, two doses of betamethasone, and as needed hydralazine for blood pressure control in the first 48 hours after admission. Under a careful monitoring regimen, delivery was needed before randomization for 34% of those that qualified for the study, because of complications. Of those who were managed expectantly, 17 of 18 developed complications before reaching 34 weeks' gestation, the study's endpoint [34].

The HELLP syndrome was characterized by several investigative groups in the mid to late 1970s [35,36] and early 1980s [37–40]. The management of severe pre-eclampsia that is characterized by the HELLP syndrome met with controversy since its description. Again, the controversy centered around whether to deliver immediately or to attempt to prolong the pregnancy. An interesting observation was made by one group that treated HELLP syndrome with steroids to improve fetal lung maturity. The platelet count improved in 13 patients who were managed conservatively and 5 patients demonstrated improved platelet count and liver function studies. Steroid administration was believed to be responsible for these improvements [40]. In view of the potential benefits of steroid administration and the absence of any serious detrimental effects, it is hard to argue against using steroids for patients who have the HELLP syndrome if they are used within the parameters studied (Table 4). Potential goals of this therapy include postponing delivery of the extremely preterm gestation to achieve viability, improve maternal platelet count for operative delivery, improve fetal and neonatal organ performance (not well documented), and facilitate maternal transport [41]. The justification for postpartum corticosteroid administration for patients who had HELLP syndrome was largely economic (shorter time to recovery and earlier discharge) [42]. In a review of maternal mortality that is associated with HELLP syndrome, no maternal deaths were observed in women who were treated with corticosteroids [43].

The benefit of prolonging gestation beyond 34 weeks in cases of severe pre-eclampsia (severity determined by any criteria) is not supported in the literature. Expectant management of severe pre-eclampsia before 32 to 34 weeks' gestation and defined solely by proteinuria ($\geq$ 5g/24 h) is justified in an effort to prolong gestation. There is limited data available to support the use of antihypertensive

therapy to prolong gestation in cases of severe pre-eclampsia that present before 32 weeks' gestation. Steroid use (celestone, betamethasone or dexamethasone) at lower doses to improve fetal lung maturity before 34 weeks' gestation currently is recommended [1]; however, the use of higher dosage regimens for specific purposes and under a specific protocol may find favor with some investigators.

Chronic hypertension

The diagnosis of chronic hypertension during pregnancy is made whenever a patient is known to have hypertension (140 mm Hg systolic 90 mm Hg diastolic) that antedates a pregnancy or at less than 20 weeks' gestation. Alternatively, this is the diagnosis if hypertension presents at 20 weeks' gestation or longer and persists beyond 42 to 74 days postpartum [4,48]. Clearly, the latter is a retrospective diagnosis and patients are said to have gestational hypertension until their hypertension is confirmed to persist well into the postpartum period. Independent of how the patient comes to have the diagnosis, the controversies that surround the management of chronic hypertension are similar to those for gestational hypertension: What antihypertensive agent or regimen is best? When should these patients deliver?

In an effort to avoid any argument over the ''best'' antihypertensive regimen to use, it is fair to note that not all patients respond to antihypertensive therapy uniformly. Instead of viewing one regimen as the ''best'', it is preferred to have a

Table 5
General classes of antihypertensive agents and their FDA Pregnancy Classification

Class	FDA class	Summary remarks
Angiotensin-converting enzyme inhibitiors (eg, captopril)	C (1^{st} trimester) D (2^{nd} and 3^{rd} trimester)	Reserved for use in specific instances (eg, cardiomyopathy, refractory to other medications) only after extensive counseling regarding risks and benefits
β-blockers (eg, labetolol)	C	Used frequently
Calcium channel blockers (eg, nifedipine)	C	Used frequently. Has advantage of possible tocolytic effect. Long-acting formulations are available.
Central acting α-agonists (eg, clonidine)	C	Rarely used. Crosses the placenta readily. Safety profile seems reasonable, except for rare cases of transient neonatal hypertension after third trimester exposure.
Peripheral acting α-antagonists (eg, hydrazaline)	C	Frequently used first-line drug for acute intervention. Drawback is need for repeated dosing.
Uncertain mechanism (methyldopa)	C	Frequently first-line agent. Long history with minimal adverse effects. Probably acts through central nervous system mechanism.

starting antihypertensive regimen in mind and remain open to veering from that regimen for clear indications (eg, side affects, potential for drug interactions, therapeutic failure). Angiotensin-converting enzyme (ACE) inhibitors have the distinction of having dual U.S. Food and Drug Administration (FDA) categories, depending on the trimester of pregnancy (Table 5). They are given a category D grade for second and third trimester use. Otherwise ACE inhibitors that are used during the first trimester, along with all other antihypertensive agents, are given the pregnancy risk factor designation C. Thus, pregnancy risk factor designation does not guide the selection of antihypertensive agent, except in the case of ACE inhibitors that are being considered after the first trimester. A long history of experience seems to dictate the often-used aldomet as a starting agent. When additional medications are needed, additive therapy seems to be the rule. Consideration can be given to starting a long-acting calcium channel blocker followed by a β-blocker or direct α-antagonist. Hospitalization may be warranted for patients who require three or more antihypertensive agents to allow for a period of prolonged maternal and fetal monitoring and assessment for superimposed pre-eclampsia. Clinical study supports the use of antihypertensive therapy to prevent superimposed pre-eclampsia [49].

Although the dictum exists that patients who have mild pre-eclampsia do not need to extend their pregnancy beyond 37 weeks' gestation because they increase their risk for more serious complications, no similar dictum exists for chronic hypertension. Should the dictum be the same? Delivery timing for patients who have chronic hypertension is not addressed in the literature. Therefore, this question can be addressed best by considering the risks and benefits of continuing the pregnancy beyond 37 weeks' gestation. Evidence supports the observation that patients who have chronic hypertension are at increased risk for superimposed pre-eclampsia. For example, in one of the earliest low-dose aspirin trials for the prevention of pre-eclampsia, 763 patients who had chronic hypertension were enrolled to receive placebo or 61 mg/d of aspirin. Superimposed pre-eclampsia occurred in about 25% of patients in each group [50]. Although variably quoted, the baseline risk for pre-eclampsia is much lower [1]. Not all patients who have hypertension behave the same; subgroups who have renal insufficiency, hypertension of at least 4 years' duration, and hypertension in a previous pregnancy are more likely to develop superimposed pre-eclampsia [4]. Why be concerned about the development of superimposed pre-eclampsia? The risk of placental abruption increases threefold in patients with chronic hypertension and superimposed pre-eclampsia compared with those who only have chronic hypertension [51]. In one study, placental abruption accounted for 15% of perinatal mortality [52]. The stillbirth rate is increased with superimposed pre-eclampsia [53] and there even is a twofold to threefold increased risk of fetal loss over baseline in cases without superimposed disease [54]. The loss rate rises for patients who have chronic hypertension and underlying renal disease (creatinine of 1.4 mg/dL or more) [4]. A policy of delivery at 37 weeks' gestation must be balanced with concerns of increasing cesarean section rates for failed induction of labor. The cesarean section success rate was 13.8% in controls compared with 26.7% for patients who had

chronic hypertension. These rates were 21.6% and 32.1% for patients who had gestational hypertension and pre-eclampsia, respectively [55]. A higher cesarean section rate seems intuitive; however, in this study cesarean section rates were unusually low by today's standards in the control group and the disease process itself (chronic hypertension) would seem to confer a less than optimal tolerance of labor—induced or naturally occurring. The potential for reduced placental function as pregnancy progresses could make fetal tolerance of labor less likely. One concern with a liberal policy of delivery at 37 weeks' gestation surrounds the greater risk for neonatal respiratory distress. At Ben Taub General Hospital in Houston, Texas rates of respiratory distress syndrome in the newborn at 37 weeks' gestation (almost all transient tachypnea of the newborn period) averaged 2.67% from 1995 through 2002; at 40 weeks' gestation, the rate was 1.2% (Joseph A. Garcia-Prats, MD, Joseph Schneider, MD, Leonard E. Weismen, MD, personal communication, 2004). Given the nature of the patient population (indigent Hispanic with suboptimal dating criteria), the rarity of hyaline membrane disease, and the rate of 1.2% at 40 weeks' gestation, a policy of delivery at 37 weeks' gestation seems warranted for patients who have chronic hypertension, especially those who have chronic hypertension and superimposed pre-eclampsia.

Gestational hypertension

When the hypertension criteria that are used to establish the diagnosis of pre-eclampsia develops first and proteinuria is not confirmed, patients are given a diagnosis of gestational hypertension [4]. Some of these patients may never develop pre-eclampsia and their blood pressure will return to normal by 12 weeks' postpartum. When this is observed, a retrospective diagnosis of gestational hypertension (transient hypertension during pregnancy) is given. Finally, hypertension can develop without proteinuria and persist beyond 12 weeks' postpartum. The diagnosis is considered to be chronic hypertension. The obvious problem is that unless proteinuria develops (ie, pre-eclampsia), a firm diagnosis cannot be made until after delivery. It is intuitive then, that patients be evaluated regularly for evidence of proteinuria and that some serial method of fetal assessment be initiated after the diagnosis is established. Perhaps the most pressing issues for patients who have gestational hypertension are the same as those of patients who have chronic hypertension during pregnancy: (1) What agents or regimens are most effective? The rationale behind choosing specific antihypertensive agents for the treatment of gestational hypertension usually is the same as for the treatment of chronic hypertension. (2) When should delivery be performed? Once again, the rationale that governs delivery timing in cases of chronic hypertension, mild pre-eclampsia, and chronic hypertension with superimposed mild pre-eclampsia seem to be similar. A policy of delivery at 37 weeks' gestation and watchful waiting until that time seems to be justified.

Chronic hypertension with superimposed pre-eclampsia

Chronic hypertension with superimposed pre-eclampsia is defined as chronic hypertension during pregnancy plus one of the following symptoms: no protein-

uria before 20 weeks' gestation and new onset proteinuria (0.3 g/24 h), sudden increase in proteinuria, sudden increase in blood pressure, thrombocytopenia (<100,000 cells/mm^3), or abnormal levels of alanine aminotransferase or aspartate aminotransferase [4]. Problems with establishing this diagnosis are inherent in the terms that are used to define the superimposed features such as "sudden onset" and "sudden increase." The difficulty in defining this entity objectively makes interpretation of the literature open to debate.

The population that presents before 34 weeks' gestation carries the greatest controversy with respect to management. Pregnancy prolongation for this group was similar to a group of patients who had severe pre-eclampsia. Patients received magnesium sulfate upon presentation, any of three antihypertensive agents, and dexamethasone to improve fetal lung maturation. Maternal and fetal monitoring was performed. Pregnancy prolongation was similar for the two groups: approximately 8 days when patients were at 24 to 28 weeks' gestation and approximately 10 days when patients presented at between 29 and 33 weeks' gestation. Fetal death rates were 5% for the group that had severe pre-eclampsia and 3% for the group that had chronic hypertension with superimposed pre-eclampsia [56]. The high fetal death rates seem to argue against significant attempts to prolong the pregnancy. Other investigators found that the risk of fetal loss was lower (1%) when compared with normotensive patients [53]; however, the rates of abruptio placenta were three times higher than in normotensive patients. These risks must be weighed against the morbidity and mortality that are associated with prematurity. Prematurity is five times more common in patients with chronic hypertension and superimposed pre-eclampsia than among normotensive patients [53].

There is limited literature to support a single management approach for patients who have chronic hypertension and superimposed pre-eclampsia. Individualization of care with delivery type and treatment guided by maternal disease severity, gestational age, and fetal response to maternal disease is warranted.

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Care of diabetes in pregnancy

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Diabetes mellitus (DM) is a condition of altered metabolism that is due to insulin resistance or insulin deficiency and leads to hyperglycemia [1]. Type 1 DM usually manifests at an early age with a sudden onset of insulin deficiency. This condition has been associated with an autoimmune attack of the pancreatic islet cells and detection of autoantibodies that are directed at these cells. Patients who have type 1 DM, because of their deficiency of insulin and dependence on other energy substrates, are prone to ketoacidosis if they do not take exogenous insulin. Older terms for this condition include ''insulin-dependent diabetes'' and ''juvenile onset diabetes.''

Type 2 DM is characterized by tissue resistance to the actions of insulin. For a given blood glucose level, insulin production by the pancreatic β-cell is inadequate. These diabetics, because they produce insulin, are not prone to ketoacidosis. They are, however, susceptible to nonketotic hyperosmolar states that can occur when severe hyperglycemia results in an osmotic diuresis and fluid intake is insufficient.

The physiologic changes that accompany pregnancy produce a state of insulin resistance. To spare glucose for the developing fetus, the placenta produces several hormones that antagonize insulin, including human placental lactogen, progesterone, growth hormone, and corticotropin-releasing hormone. These hormones also shift the principle energy sources to ketones and free fatty acids [2,3]. Most pregnant women maintain normal blood glucose levels, despite the increased insulin resistance, through enhanced insulin production and release by the pancreas in the basal state and in response to meals [4].

Gestational diabetes (GDM) is a state of carbohydrate intolerance that develops or is first recognized during pregnancy. In some women, β-cell production of insulin cannot keep pace with the resistance to insulin that is produced by the diabetogenic hormones from the placenta. The prevalence of GDM is proportional to the prevalence of type 2 DM in the population that is under

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examination because they share a similar pathophysiology—insulin resistance and inadequate insulin production. The prevalence of GDM in the United States is 2% to 5% [4,5]. It is the most common medical complication of pregnancy.

Diabetes in pregnancy is linked clearly to several maternal and fetal complications and results in substantial morbidity. These include fetal macrosomia, operative delivery, and birth trauma [6]; pre-eclampsia and hypertensive disorders [7]; metabolic complications in the neonate (hypoglycemia, hypocalcemia, and hyperbilirubinemia) [8]; prematurity, and perinatal mortality [9–12].

Rigorous identification and intensive treatment of pregnant women who have diabetes is critical to minimize or avoid the complications that can arise from unrecognized or inadequately treated hyperglycemia. This article reviews the rationale for various aspects of care of the pregnant woman who has diabetes.

Screening for diabetes in pregnancy

The American College of Obstetrics and Gynecology (ACOG) recommends that all pregnant patients should be screened for gestational diabetes. They do not, however, state which method is optimal to accomplish this screening; ''screening'' does not involve necessarily laboratory testing for hyperglycemia. Two methods predominate in screening for GDM: universal laboratory screening or selective laboratory screening that is limited to women who have risk factors for GDM. In risk factor–based screening, women who meet all of the criteria that are listed in Box 1 are deemed to be at ''low risk'' for GDM and may forego any form of laboratory glucose testing. The American Diabetes Association advocates the use of laboratory screening tests only for women who have risk factors because of cost-benefit considerations [13]. In patient populations that have a high prevalence

Box 1. Criteria for avoiding laboratory screening for gestational diabetes [13]

Age less than 25 years
Not a member of an ethnic group that has an increased prevalence of type 2 DM
Body mass index of up to 25
No history of glucose intolerance (GDM, DM, impaired glucose tolerance, or impaired fasting glucose)
No history of obstetric outcomes that are associated with GDM (macrosomia, stillbirth, malformations)
No known diabetes in a first degree relative

From American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 2004;27(Suppl 1):S88–90.

of type 2 DM and GDM, ''low-risk'' patients may be rare. Therefore, depending on the clinical setting, universal laboratory screening may be more effective.

One study in support of selective, risk factor–based screening used a scoring system to categorize women into low-, medium-, and high-risk categories [14]. Approximately 3000 women were stratified by using a point system. Low-risk women were not screened; intermediate-risk women were screened with a 1-hour glucose challenge test (GCT) cutoff value of 140 mg/dL, and high-risk women were screened with a 1-hour GCT cutoff value of 130 mg/dL. Using this strategy, laboratory testing was avoided in 35% of women, the detection rate improved to roughly 83% (up from 79%), and the false positive rate was reduced by 2.5%. The investigators concluded that if a woman's clinical picture was taken into account, a selective screening program for GDM could be effective. In a retrospective comparison between universal laboratory screening and risk factor–based screening criteria (using the American Diabetes Association [ADA] criteria in Box 1), more than 18,000 women were screened for GDM with 1-hour GCTs [15]. If only those who had risk factors had undergone laboratory testing, 3% of gestational diabetics would have gone undiagnosed. In this population, only 10% of women were ''low risk'' by all criteria, and, thus, were able to forego the 1-hour GCT. Therefore, in clinical settings with a high burden of GDM and type 2 diabetes, a risk factor–based screening algorithm is unlikely to be cost- and time-efficient. Furthermore, failure to apply the algorithm correctly in a high-risk population is more likely to result in missed diagnoses of GDM than in a low-risk setting.

The laboratory screening tool that is used most commonly is the 1-hour glucose challenge test that was advocated by O'Sullivan and Mahan [16]. This involves drinking a 50 g glucose load, without regard to timing of last meal; a plasma glucose level is obtained 1 hour later. Because this is a screening test, the cutoff value to define a ''positive'' result should take into account the prevalence of GDM in a given population. The threshold for ''positive'' must provide an appropriate balance between identifying as many people who have the disease as possible, without exposing too many normal patients to tests that are more dangerous, costly, or time consuming. The most commonly used cutoff value for the GCT is 140 mg/dL which results in approximately 15% positive tests. The validity of this threshold was corroborated recently [17]. By reducing the cutoff to 130 mg/dL, the sensitivity of the test (ie, the proportion of women who have GDM who have a ''positive'' screen) can improve to nearly 100%, at the expense of specificity [18]. In a low-risk population, the actual number of extra cases that is identified with this increase in sensitivity may be outweighed by the number of false positive screens in the range between 130 and 140 mg/dL. We use 130 mg/dL as our threshold because of the high prevalence of GDM in our San Antonio population (approximately 5%–7%).

For women who are at a low risk for GDM, screening should occur between 24 to 28 weeks' gestation; insulin resistance during pregnancy increases as a function of increasing gestational age to meet the growth requirements of the fetus, until approximately 32 weeks' gestation. Women who are at high risk should be tested at their first visit.

If a positive screening test result is obtained, a diagnostic 3-hour glucose tolerance test (GTT) should be performed. This test involves a 100 g glucose load after blood is drawn for a fasting plasma glucose level. Plasma glucose levels are obtained at 1, 2, and 3 hours postglucose load. Two different sets of values are used commonly to define a positive result. The set that was recommended by the ADA's Fourth International Workshop-Conference on Gestational Diabetes is Carpenter and Coustan's [19] modification of O'Sullivan and Mahan's [16] original values. The diagnosis of gestational diabetes is made if two or more glucose values meet or exceed the following thresholds:

Fasting: 95 mg/dL
1 hour: 180 mg/dL
2 hour: 155 mg/dL
3 hour: 140 mg/dL

These values are more stringent than the values which are cited by the National Diabetes Data Group (NDDG) [20], which essentially are the O'Sullivan and Mahan criteria [16]. Again, at least two values must meet or exceed these thresholds:

Fasting: 105 mg/dL
1 hour: 190 mg/dL
2 hour: 165 mg/dL
3 hour: 145 mg/dL

The precise thresholds above which all diabetes-related morbidity occurs, and below which none does, are not likely to be determined. Evidence does exist to show that lack of treatment of milder forms of gestational glucose intolerance results in increased rates of GDM-related morbidity, particularly excessive fetal growth. In the Toronto Tri-Hospital Study, women who had "borderline" GDM (met Carpenter and Coustan's criteria but not NDDG criteria) were not treated as diabetic and had more than twice the rate of macrosomia as women who had normal glucose testing (28% versus 13%) [21]. Similarly, women who had one abnormal value (using the higher NDDG criteria) also had increased rates of overgrown infants [22].

In the past, it was suggested that a carbohydrate loading period of 3 days should precede the 3-hour GTT to "prime" the pancreas for the GTT and, thereby, reduce false positive results. Several recent studies showed no difference in GTT results with or without this preparation [23–25]. Furthermore, this practice may delay the diagnosis.

Pre-existing diabetes

For the woman who has known type 1 or type 2 diabetes, optimal pregnancy outcome is most likely when there has been adequate preparation before

conception and early entry to prenatal care. Pre-existing diabetes has been associated with a five-fold increase in the incidence of major fetal anomalies compared with the general obstetric population; rates of 7.5% to 10% are reported commonly [26,27]. The precise mechanism for teratogenesis in diabetic women is not well-understood, but is believed to involve deficiencies in select membrane lipids, changes in the prostaglandin pathways, and generation of free oxygen radicals [28]. It is unlikely that hyperglycemia alone brings about the alterations that result in malformations.

Clinically speaking, the risk for major fetal anomalies and spontaneous abortion increases as the hemoglobin A_{1c} (HbA_{1c}) value increases. Major congenital defects that involve the heart and central nervous system are most common, with relative risks of 18.0 and 15.5 compared with nondiabetic women [29]. Greene and colleagues [30] found that women who had HbA_{1c} values that were less than 9.3% had a spontaneous loss rate of 12.4% and a major malformation rate of 3%. With HbA_{1c} values of 14.4% or more, the rate of spontaneous loss was 37.5% and the major malformation rate was 40%. These findings are similar to those of other investigators and lead to the conclusion that peri-conceptional metabolic control that results in HbA_{1c} values that are less than approximately 7.0% to 7.5% can reduce the frequency of congenital malformations to the background rate for the population [31]. This translates into a mean glucose of approximately 150 to 160 mg/dL, a target that should be readily achievable in most cases.

A significant proportion of women who have pre-existing diabetes lack sufficient understanding about the need to control their disease before attempting pregnancy. In one survey, 60% of women who had pre-existing diabetes had ''unplanned'' pregnancies. For purposes of this study, ''planned'' pregnancy was defined as: (1) desired, (2) one in which contraception was stopped for the purposes of becoming pregnant, and (3) the woman stated that she attempted to achieve good glucose control before getting pregnant [32]. Unplanned pregnancies occurred more often in unmarried, socioeconomically disadvantaged women. Although 40% of women who had planned pregnancies had consulted with a perinatologist or obstetrician before becoming pregnant, only 2% of the women who had unplanned pregnancies had done this. The groups also differed significantly in the quality and tone of the advice that they received regarding the expected prognosis for pregnancy outcome. Despite the two groups' similarity in terms of duration of diabetes and presence of diabetes-related complications, women who had planned pregnancies received more supportive and optimistic feedback. Women who had unplanned pregnancies often described being discouraged from becoming pregnant; despite this they became pregnant and, as a group, had significantly worse glycemic control on entry to prenatal care than women who had planned pregnancies.

Additional screening tests are recommended at entry into prenatal care for women who have pregestational diabetes. Because of micro- and macrovascular disease that is associated with diabetes, the following tests are recommended to identify the associated complications: 24-hour urine collection for protein and

creatinine clearance; serum creatinine; 12-lead EKG; and ophthalmologic examination (if not done within the last 12 months). Because of the autoimmune nature of type 1 diabetes, it also is valuable to obtain thyroid function tests.

Because there is a spectrum of severity in DM, it is useful to stratify women into categories to assess risk and prognosis. The modified White's classification of diabetes in pregnancy allows the clinician to take several factors into consideration, including duration of diabetes, age at onset, and presence of macro- and microvascular complications [33]. The validity and usefulness of White's [33] classification was reaffirmed by Diamond and colleagues [34] in 1987, who showed that the perinatal mortality rate increased as classification increased.

Prenatal care of pregnancies that are complicated by diabetes

Prenatal care in a pregnancy that is complicated by diabetes centers around optimizing glycemic control to prevent or minimize the complications that associated with the disease, while avoiding ketosis and poor nutrition. A multidisciplinary approach (that can involve obstetricians, perinatologists, dieticians, diabetes educators, internists and endocrinologists) is essential to management. Diet, exercise, patient education, and, if need be, medical therapies should be used.

The cornerstone of care of a pregnancy that is complicated by diabetes is proper diet. Medical nutrition therapy for diabetics is aimed at optimizing metabolic outcomes, preventing and treating chronic complications of the disease, and improving health by encouraging healthy food choices while addressing personal and cultural preferences and providing adequate energy and nutrients for optimal pregnancy outcomes [35]. Elements of dietary therapy include total calorie allocation, calorie distribution, and nutritional component management.

Total daily calorie intake is based on ideal body weight. The following guidelines are from the ADA [13]:

Underweight (body mass index [BMI] <19.8): 35 Kcal/kg/d
Normal body weight (BMI 19.8–29.9): 30 Kcal/kg/d
Overweight (BMI $\geq$30): 25 Kcal/kg/d

At our institution we have set minimum and maximum calorie allotments. The minimum Kcal intake per day is 1800 and the maximum is 2600.

Postprandial glucose measurements are influenced directly by the amount of carbohydrate in the consumed food. This is particularly important in the breakfast meal [36]. Insulin resistance is highest in the morning as a result of high cortisol levels. Pregnancy tends to accentuate this normal physiology. Therefore, the carbohydrate intake should be shifted to later in the day and the breakfast meal should be small. Lunch and dinner should each account for 30% of the daily caloric intake and the rest should be distributed as snacks. Our program encourages a diet of three meals and four snacks. We believe that smaller, more

frequent meals lead to better satiety, improved compliance with the diet, and reduced magnitude of postprandial peaks.

Typically, a traditional diet for diabetics contains 55% to 60% carbohydrate. Major and colleagues [37] described their success with a diet that contained 40% to 42% carbohydrate. Compared with a 45% to 50% carbohydrate diet, mild carbohydrate restriction resulted in improved glycemic control, less need for insulin, and fewer large-for-gestational age infants. We have used a diet that consists of 40% carbohydrate/35% protein/25% fat for approximately the past 5 years and have seen similar salutary effects on glucose control.

Exercise is another key component in diabetic care. Cardiovascular exercise reduces insulin resistance [38]. Fasting and postprandial glucose levels are lower in gestational diabetics who exercise and it may prevent the need for insulin treatment in some women [39,40]. The physiologic constraints of pregnancy should be taken into consideration when counseling women about exercise. The supine position should be avoided secondary to vena cava compression by the gravid uterus as should activities that require a great deal of balance (to prevent injuries from falls). The uterus should be palpated for contractions during exercise; exercise should stop if contractions are detected.

Patient education is a critical component in pregnancy that is complicated by diabetes; a patient's understanding of her disease enhances her ability to manage her disease effectively. In our program, upon entry the patient receives a half-day course that addresses the following topics: impact of diabetes on pregnancy, including potential adverse outcomes; the importance of glycemic control in minimizing or preventing these outcomes; emphasis on self-care, monitoring, and personal responsibility to optimize care; and the long-term implications of the diagnosis on the patient and her family. Insulin administration is addressed at initial teaching to avoid potential additional anxiety if, over the course of care, a patient requires insulin for improved glycemic control. Patients are counseled on the signs of hypoglycemia and the necessary immediate interventions. Each patient is issued a glucose monitor and is instructed on its use. To reinforce the concepts that were taught at the initial instruction, patients are seen in our diabetic clinic within 6 days of the education class.

The value of ongoing education during subsequent visits cannot be overstated. Improved patient knowledge and understanding leads to greater compliance with the program. Each clinic visit should be viewed as an educational opportunity. Previously-covered concepts can be reinforced and any barriers to effective treatment may be identified early if the clinician is vigilant in keeping these principles.

There is no established standard as to how frequently glucose levels should be checked in patients who have GDM. A commonly-used method involves daily monitoring with meters that have built-in memory so that results can be verified, analyzed, and reviewed with the patient during clinic visits. Langer and colleagues [41] demonstrated the benefits of an ''intensified'' approach to care of diabetes during pregnancy. One essential component of this regimen is frequent daily readings that provide information on the effectiveness of the current

treatment regimen. Using this approach, women are instructed to check their glucose levels 7 times per day: before and after each meal and at bedtime. Rates of macrosomia, shoulder dystocia, cesarean delivery, and neonatal hypoglycemia were reduced compared with women who were monitored less frequently with weekly fasting and 2-hour postprandial readings.

One randomized trial suggested that monitoring postprandial glucose determinations was more effective than preprandial values in managing women who had GDM and were taking insulin [42]. The group that was randomized to postprandial readings (goal: 1-hour postmeal values <140 mg/dL) had significantly less fetal overgrowth, fewer cesarean deliveries for cephalopelvic disproportion, and less neonatal hypoglycemia compared with women who checked their glucose levels before meals (goal: 60–105 mg/dL). Although postprandial readings are superior to preprandial readings, they have not been shown to be superior to a combination of pre- and postmeal readings. It is our belief that more readings provide a more complete picture of the ambulatory blood glucose profile and allow a better assessment of the success, or failure, of the current therapeutic regimen. Results from continuous blood glucose monitors in ''well-controlled'' nonpregnant type 2 diabetics support this belief. Such monitoring revealed unrecognized hypoglycemic episodes in 80% of patients and postprandial hyperglycemia after 57% of all meals [43].

The goal of monitoring is to keep blood glucose below glycemic targets. The current target values that are endorsed by the ADA and the ACOG are fasting values that are less than 95 mg/dL and 2-hour postprandial values that are less than 120 mg/dL [1,13]. They recommend instituting medical therapy when values exceed these goals.

Other aspects of monitoring include screening for ketones and adequate weight gain. These are important markers of adequate nutrition during dietary therapy. If a patient is compliant with the diet as directed and experiences ketonuria or inadequate weight gain, the total calorie allotment must be increased while remaining mindful of glycemic targets.

Ultimately, 15% of patients who have GDM will not be able to meet glycemic targets with diet therapy alone and will require medical intervention with insulin or a hypoglycemic agent. Insulin is dosed according to body weight, starting in the range of 0.7 to 1.0 units per kilogram body weight. The pregnant diabetic demonstrates insulin resistance and relative insulin lack; thus, it is typical to require large doses of insulin to achieve adequate glycemic control [44]. One common regimen involves giving two thirds of the total calculated insulin dosage in the morning, made up of two parts intermediate-acting to one part regular insulin. The remaining one third of the total daily dosage should be divided equally between intermediate-acting and regular insulin. The regular component is given before dinner and the intermediate-acting is given at bedtime. With advancing gestational age, the patient becomes more insulin resistant and insulin requirements increase [44]. The insulin dosage can be adjusted as frequently as every 3 to 4 days and can be increased from 10 to 20%, depending on the corresponding values that are obtained from patient monitoring.

Women who have GDM and type 2 diabetics tolerate larger adjustments than type 1 diabetics, in terms of the risk of hypoglycemia.

Another treatment option for women who are not controlled adequately with diet alone is the sulfonylurea drug, glyburide. In the past, there was concern over transplacental passage of sulfonylurea drugs leading to fetal and neonatal hypoglycemia. Studies that used human placental models demonstrated that the transplacental passage of glyburide is negligible [45]. We performed a study that compared insulin with glyburide in a randomized trial that involved 404 women who had GDM. No difference was found between groups in terms of mean blood glucose, large-for-gestational-age infants, macrosomia (greater than 4000 g), lung complications, hypoglycemia, or cord blood insulin levels. In addition, no glyburide could be detected in the cord blood of infants who were born to women who were taking it [46]. The criteria that we use for consideration of glyburide therapy are the following: gestational age of 11 to 33 weeks; fasting glucose on 3-hour GTT less than 110 mg/dL [47]; and no known sulfa allergy. For women who do not meet these criteria, we recommend insulin.

Antenatal testing

Documenting fetal well-being during the antepartum period is important for any woman whose pregnancy is complicated by pregestational diabetes (White's class B or higher). There is no unified opinion regarding the need for antepartum fetal assessment in women who have well-controlled, uncomplicated preexisting and gestational diabetes [48]. ACOG recommends that antenatal testing be performed on all pregestational diabetics, gestational diabetics who have poor glycemic control, or gestational diabetics who have another pregnancy complication [1]. The method of testing (eg, nonstress testing, biophysical profile) is left to the discretion of the provider guided by local practice.

Ultrasound is another method of fetal assessment. In women who have preexisting diabetes, a level II ultrasound should be performed at around 20 weeks' gestational age. This is done to screen for fetal anomalies; the rate of occurrence is proportional to the peri-conceptional hemoglobin A_{1c} level [29–31]. Another use for ultrasound is fetal weight estimation in women who are planning a vaginal delivery, given the increased risk of fetal overgrowth and shoulder dystocia in pregnancies that are complicated by diabetes. Because of the error that is inherent in estimating fetal weight, there is no widespread agreement on the usefulness of obtaining a fetal weight estimate by ultrasound to assist with decisions on how and when to deliver women who have diabetes. This is discussed in more detail below.

Delivery: when to deliver, how to deliver

Timing of delivery is a delicate balance in a pregnancy that is complicated by diabetes. After term has been reached, ongoing pregnancy exposes the fetus to the

risk of stillbirth and continued in utero growth that may make delivery more risky. Conversely, needless intervention places women at unnecessary risk for the complications that are associated with long labors and operative deliveries. Thus, it is important to discern accurately those pregnancies that would benefit from intervention by delivery from those that can be allowed to enter labor spontaneously, without detriment to the fetus or mother. Few prospective trials have been undertaken with regard to optimizing delivery outcomes in diabetics. It has been shown consistently that the cesarean delivery rate is higher in diabetics [49], even when skilled antenatal care has achieved near-normal rates of fetal overgrowth [21].

An additional consideration in the optimal timing of delivery is the fact that infants of diabetic mothers may have delayed pulmonary maturity and are at increased risk of respiratory distress syndrome (RDS). These risks seem to be related directly to the degree of glycemic control. It was established that poorly-controlled diabetes is associated with fetal pulmonary immaturity; the risk in well-controlled pregnancies parallels that of a nondiabetic population [50]. Other investigators found that the risk of RDS becomes equal to that of nondiabetic pregnancies at 38.5 weeks' gestation [51]. In the study by Piper and colleagues [50], no cases of RDS occurred after 37 weeks' gestation, despite "immature" results on the amniotic fluid tests for fetal lung maturity. Lung maturity testing in the setting of diabetes might be necessary only if early delivery is considered (35–37 weeks' gestation), if glucose control has been poor, or if gestational age is uncertain. Furthermore, tests for lung maturity only should be obtained in cases where delivery can be delayed safely if the test is negative.

Indications for delivery at term include: inability to achieve adequate glucose control; poor compliance with visits or prescribed treatment; previous stillbirth; and presence of chronic hypertension or vascular complications of diabetes. Our practice is to deliver all type 1 diabetics and type 2 diabetics who have White's classification D through R at 37 weeks' gestation. These women are at greatest risk of vascular compromise and have the highest potential for fetal demise [52]. Women with well-controlled class A diabetes, good compliance with care, and an appropriately-grown fetus are allowed to enter spontaneous labor, until 41 weeks' gestation is reached. Kjos and colleagues [53] studied a similar approach in women who had class A2 and B diabetes and compared it to labor induction at 38 weeks' gestation in a randomized trial. Expectant management prolonged gestation by 1 week and resulted in a doubling of the rate of macrosomic infants. The women who were managed expectantly had a similar cesarean delivery rate to those who were induced at 38 weeks' gestation. Half of the group who was managed expectantly underwent labor induction. The most frequent indication was abnormal antepartum testing, an indication that is not as frequent in our experience with milder degrees of diabetes at term. Depending on the setting, expectant management may result in fewer cesarean sections. Nonetheless, this remains one of the few prospective trials regarding the timing of delivery in diabetic women.

Macrosomia and shoulder dystocia occur more frequently in pregnancies that are complicated by diabetes [54]. These risks should be considered when planning

the mode of delivery. Also to be taken into consideration are past pregnancy outcomes (eg, previous shoulder dystocia or birth trauma, where recurrence rate for shoulder dystocia is approximately 15%) [55,56]. Based on the observation that most cases of shoulder dystocia in diabetic women occur when birth weight is greater than 4000 g [54], we recommend cesarean delivery without a trial of labor to women who have an estimated fetal weight that is greater than 4250 g. By implementing this practice, the rate of shoulder dystocia in diabetic women at our institution has been reduced by 80%; shoulder dystocia rates among macrosomic infants (birth weight >4000 g) decreased from 19% to 7% after implementing this practice. There was a small, but significant, increase in the cesarean delivery rate [57]. We use a threshold of 4250 g to account for ultrasound error, so that operative intervention is not overused.

Postpartum

For women who have pre-existing diabetes, the additional insulin resistance that is associated with pregnancy decreases rapidly in the postpartum period, as does the amount of medication that is required to maintain optimal control. In the short term, glycemic control does not have to be regulated as tightly as it was during the pregnancy. This allows the clinician some leeway in the continued treatment of the patient's diabetes. A good place to start is to resume the patient's pre-pregnancy treatment and adjust as needed to maintain optimal control. Another option is to continue insulin at a reduced dosage.

Gestational diabetes may be the first warning of inherent insulin resistance. A woman who is diagnosed with gestational diabetes has a significant lifetime risk of developing overt diabetes. Approximately one third of women who have GDM have GDM in a subsequent pregnancy [58–60]. Factors that increase recurrence risk are increased age, weight gain between pregnancies, and increased parity.

Women who have gestational diabetes need to have glucose tolerance reassessed in the postpartum period. The most commonly-used assessment method is the 2-hour GTT which identifies impaired glucose tolerance and overt diabetes. Twenty to 30% of women have abnormal values when tested early in the postpartum period [61–64]. Kjos and colleagues [62] found that 10% have impaired glucose tolerance and 9% have frank diabetes when testing took place between 5 and 8 weeks after delivery. The factors that increased the risk for abnormal GTT postpartum included: diagnosis of GDM at an earlier gestational age, higher glucose values on GTTs during pregnancy, increased age, increased parity, increased BMI, and increased birth weight. All of these risk factors suggest a higher degree of insulin resistance. The importance of postpartum testing cannot be understated. Early identification of impaired glucose tolerance affords the opportunity to institute therapeutic measures, such as exercise, diet, and weight control, that may prevent the progression to diabetes. Identification and treatment of overt diabetics early in the course of the disease offers the best

opportunity to delay or avoid the micro- and macro vascular complications that are associated with the disease.

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Thyroid disease and other endocrine disorders in pregnancy

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Endocrine disorders are encountered frequently during pregnancy and the postpartum period. Most of these conditions are treatable and may affect mother and fetus adversely if they are not evaluated and managed appropriately. This article summarizes maternal endocrine adaptation to pregnancy and outlines common problems and their treatment.

Hypothalamus and pituitary

Hypothalamic releasing and inhibitory hormones regulate anterior pituitary function. These substances are produced in hypothalamic nuclei and reach the pituitary by way of a portal circulation. Thus, thyrotropin-releasing hormone (TRH) releases thyrotropin (TSH) and prolactin; growth hormone–releasing hormone releases growth hormone (GH), corticotropin-releasing hormone (CRH) releases corticotropin (ACTH), and gonadotropin-releasing hormone releases the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Normally, prolactin is under inhibitory control by way of the hypothalmic neurotransmitter, dopamine. The posterior pituitary is a storage site for oxytoxin and vasopressin, which are produced by the paraventricular nuclei. Osmoreceptors in the hypothalamus increase vasopressin release when plasma osmolality increases. Oxytocin is involved in parturition and suckling; maternal concentrations increase during gestation. Nipple stimulation promotes its release which leads to stimulation of myoepithelial cells in the breasts and milk letdown.

Physiologic changes during pregnancy [1–3] are summarized in Box 1. The fetal pituitary and hypothalamus are functional midgestation.

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Box 1. Physiologic changes in the hypothalamic pituitary axis during pregnancy

Lactotroph hypertrophy and hyperplasia
Progressive increase in serum prolactin
Doubling or more of anterior pituitary volume
Decline in gonadotropins, LH and FSH
Decline in pituitary growth hormone
Production of a placental variant of growth hormone
Increase in CRH, mainly of placental origin
Placental CRH activates maternal and fetal pituitaries
Increase in ACTH and cortisol
Increase in cortisol stimulates placental CRH and leads to hypercortisolism
Decline in TSH in first trimester because of the thyrotropic effect of human chorionic gonadotropin (hCG)
Decline in plasma osmolality by 5 to 10 mOsm/kg as a result of resetting of osmoreceptors for vasopressin release
Decline in osmotic threshold for thirst experience
Increase in metabolic clearance of vasopressin as a result of to placental vasopressinase

Disorders of the hypothalamus

These may be congenital or acquired inflammatory (encephalitis), space-occupying (cysts, tumors), vascular, or degenerative. Craniopharyngiomas are vestigial remnants of Rathke's pouch. Six craniopharyngiomas were reported in pregnancy [4]; two had tumor recurrence and two previously undiagnosed cases presented with diabetes insipidus (DI) in pregnancy. One of these required surgery for deteriorating vision three days after delivery at 34 weeks' gestation.

Disorders of the anterior pituitary

Tumors, vascular mishaps, and inflammatory changes can affect the anterior pituitary. In the evaluation of these disorders, anatomic and hormonal derangements need to be considered.

Pituitary tumors: prolactinoma

Prolactinomas are, by far, the most common functioning tumors that are seen in the pregnant patient [5]. Although patients who have these tumors are usually amenorrheic and infertile, treatment with dopamine agonists, such as bromocriptine and cabergoline, restored gonadal function and resulted in pregnancy in thousands of patients worldwide. Given the physiologic enlargement of the pituitary during pregnancy, there has been concern for pregnancy outcome.

Effect of prolactinoma and its treatment on pregnancy and the fetus. Bromocriptine mesylate, taken orally two or three times per day with food, has been used for about 30 years in the treatment of prolactinomas. A dopamine agonist, it lowers prolactin, restores gonadal function, and shrinks the tumor for as long as it is administered. Krupp and Monka [6] collected data from 2587 pregnancies in 2437 women who were treated with bromocriptine during some stage of gestation. Its use was not associated with an increased risk of spontaneous abortion, multiple pregnancy, or congenital malformation. In addition, 546 children were followed postnatally for up to 9 years; no adverse effect on postnatal development was noted. Bromocriptine crosses the placenta [7]; however, in most women who were treated, the drug was discontinued upon confirmation of pregnancy. A new synthetic dopamine agonist, cabergoline, is available for prolactinoma treatment. It is long-acting, is taken twice a week, and has fewer side effects [8,9]. Although the experience with cabergoline use in pregnancy is limited and bromocriptine should be tried first, cabergoline appears to be safe in this regard.

Effect of pregnancy on the prolactinoma. Prolactinomas may be micro- (<10 mm) or macroadenomas (≥10 mm). The major risk to the mother is estrogen-induced increase in adenoma size that leads to neurologic symptoms, such as headaches, visual disturbances, and DI. In a review of this subject that used data that were collected from many studies, Albrecht and Betz [10] noted that of 352 pregnant patients who had untreated microadenomas, 2.3% had visual disturbances, 4.8% had headaches, and 0.6% had DI. The corresponding figures for 144 pregnant women who had untreated macroadenomas were that 15.3% had visual disturbances, 15.3% had headaches, and 1.4% had DI. The outcomes of 318 pregnancies in patients who had micro- or macroadenomas that were treated with surgery, radiation, or both before pregnancy were that 3.1% had visual disturbances, 3.8% had headaches, and 0.3% had DI. Symptoms of tumor enlargement were noted as early as the first trimester.

Using these data, patients who have prolactinomas and wish to conceive can be counseled. For microadenomas, the patient is reassured of her low risk of tumor complications; bromocriptine or cabergoline should be discontinued upon diagnosis of pregnancy. The patient mainly is monitored symptomatically; if desired, visual fields can be obtained. In the symptomatic patient who has a microprolactinoma, visual field, serum prolactin, and MRI without contrast are obtained. Patients who have macroprolactinomas should be advised of the significantly higher risk of tumor expansion during pregnancy. If the adenoma is extremely large or elevates the optic chiasm, the adenoma should be treated by transphenoidal surgery (and possibly postoperative radiation) before pregnancy is attempted. Postoperative dopamine agonist therapy will help to reduce serum prolactin and adenoma size further and may help to diminish the risk of symptomatic enlargement in pregnancy. If the macroadenoma does not elevate the optic chiasm and bromocriptine or cabergoline treatment substantially reduced its size, the chance of clinically important enlargement during pregnancy is

diminished and pregnancy can be attempted. The drug is discontinued and the patient is monitored for symptoms and evaluated; if the patient is symptomatic, treatment should progress as outlined above.

Management of prolactinoma complications during pregnancy. Bromocriptine has been used successfully in the treatment of tumor expansion during pregnancy [11]. It is given orally, 2.5 to 5 mg, two to three times daily with food, according to symptoms and is continued for the remainder of pregnancy. Glucocorticoids also may be given to expedite the recovery of visual fields. If the tumor expansion is unresponsive to bromocriptine, transsphenoidal surgery should be considered in the second trimester and delivery should be considered in the third trimester. Continuous use of bromocriptine in patients who have macroprolactinoma has been advocated [12] but is not recommended until its safety is more fully established.

Breast-feeding and postpartum care. Most patients who have prolactinomas can breast-feed safely. In a study of 14 women who had microadenomas and breast-fed for 6 to 14 months, serum prolactin was not significantly higher than it had been before pregnancy [13]. Serum prolactin can be measured 2 months after delivery or cessation of nursing; if it is elevated, dopamine agonist therapy can be resumed. Patients who have macroprolactinomas also can nurse if they are asymptomatic at delivery. If the patient is symptomatic at delivery or during nursing, treatment with dopamine agonists can be reinitiated. If the patient is not breast-feeding, therapy can be resumed a few weeks postpartum.

Acromegaly

Excessive growth hormone secretion, usually by pituitary adenomas, leads to the clinical features of acromegaly that include coarsening of facial features, prognathism, spade-like hands, and enlarging feet. Although menstrual irregularities are common in acromegalics, pregnancy can occur. Usually, diagnosis is based upon the lack of suppression of GH to less than 2 ng/mL (radioimmunoassays) or less than 0.3 ng/mL (immunochemiluminescent assays) and an elevated insulin-like growth factor I (IGF-I). IGF-I concentrations can be elevated in normal pregnancy; because of placental GH, special assays that use antibodies to recognize specific epitopes on the two hormones are necessary to distinguish pituitary from placental GH [14] . In addition, a TRH test can be helpful in diagnosis because 70% of acromegalics experience a GH response to TRH, whereas there is no response of placental GH [15]. Using MRI, a GH-producing adenoma is shown in more than 95% of documented acromegalics. Definitive treatment before conception is preferred. When pregnancy occurred, tumor expansion was found in approximately 10% of 70 patients in a series that was reported by Hermann-Bonert et al [16]. Despite soft tissue changes, these did not complicate delivery. Carbohydrate intolerance ($\geq$50% of cases), overt diabetes ($\geq$20%), hypertension (25%–35%) and cardiac disease have been reported. An algorithm for the management of acromegaly in pregnancy depends on the ac-

tivity of the disease, tumor size, and stage of pregnancy [16]. Response to bromocriptine was reported; if tumor expansion occurs despite such therapy, transsphenoidal surgery should be performed. Somatostatin analogs, octreotide, and lanreotide have been used as an alternative to surgery, despite documented transplacental passage [17]. There are no reports on the use of the newly-available receptor blocker, pegvisomant, in pregnancy; tumor expansion is be a potential concern. The maternal–fetal transfer of GH is minimal.

Cushing's syndrome

Cushing's syndrome is a state of hypercortisolism that results from excess pituitary ACTH, extrapituitary or ectopic production of ACTH, or an adrenal lesion (adenoma or carcinoma). The ovulatory disturbances of untreated Cushing's syndrome, especially pituitary-dependent Cushing's syndrome, makes this an uncommon diagnosis in pregnancy. In a series of 67 pregnancies in 58 patients [18], 40% had adrenal adenomas, 10% had adrenal carcinomas, less than 2% had ectopic production of ACTH, and the remaining had pituitary-dependent Cushing's syndrome or the etiology was not determined. The production of CRH and ACTH by the placenta could explain the exacerbation of Cushing's syndrome in pregnancy and the amelioration or remission that follows pregnancy [19].

Because weight gain, striae, edema, and hypertension are common in pregnancy, more signs, such as thinning of the skin, spontaneous bruising, and muscle weakness should be sought as signs of Cushing's syndrome. Because urinary free cortisol increases during normal pregnancy, a prolonged (8-day) low-dose (2 mg/d) dexamethasone suppression test is preferable. A high-dose dexamethasone suppression test (8 mg/d for at least 2 days) can help to distinguish pituitary dependent from other causes of Cushing's syndrome. Significant (75%) suppression of serum cortisol is more consistent with a pituitary etiology, whereas a lack of suppression of serum cortisol, especially with a low ACTH, strongly suggests an adrenal source. MRI of the pituitary and adrenals can provide confirmation; if necessary, inferior petrosal sinus sampling and CRH stimulation can help to distinguish pituitary from ectopic ACTH. There is one report of such testing in pregnancy [20].

In a series of 57 cases that was reported by Aaron et al [18], premature births occurred in 61% of cases and there were seven miscarriages and six stillbirths. Intrauterine growth restriction occurred in about one half of reported cases and neonatal adrenal insufficiency (suppression of fetal axis from transplacental passage of excess maternal cortisol) was reported. Maternal complications included hypertension (87%), abnormal carbohydrate tolerance (61%), congestive heart failure, and decreased wound healing; there were three maternal deaths in this series.

Treatment decreases the incidence of intrauterine fetal demise [19]. In the first trimester, transsphenoidal surgery or adrenal surgery should be performed according to etiology and to rule out adrenal carcinoma. Successful pituitary surgery also was reported in the second trimester [21]. In the third trimester, early delivery should be considered. Metyrapone blocks cortisol secretion and has been used [22]. Other cortisol-inhibiting agents, such as aminoglutethimide and

ketoconazole [23], are more problematic because of teratogenicity (ketoconazole), virilization of female fetuses (aminoglutetimide), or inadequate masculinization of male fetuses (ketoconazole). Mitotane should not be used in pregnancy.

Treatment of pituitary-dependent Cushing's syndrome by bilateral adrenalectomy may result in Nelson's syndrome (hyperpigmentation with an expanding intrasellar mass). In a series of 10 patients who had Nelson's syndrome during pregnancy, 5 required postpartum treatment of their pituitary tumor and only 1 required pituitary surgery during pregnancy [24].

Functionless pituitary tumors

Hormonally functionless pituitary tumors are less common. They usually are larger at diagnosis and are asymptomatic in their early stages. Because tumor expansion with visual field defects has been reported, the patient should undergo appropriate surgical treatment before pregnancy.

Hypopituitarism

Diminished anterior pituitary function may be seen during pregnancy and postpartum. In particular, two disease processes can affect the pregnant patient—Sheehan's syndrome and lymphocytic hypophysitis.

Sheehan's syndrome. The hyperplastic pituitary gland of pregnancy is more vulnerable to an inadequate blood supply. Approximately 4% of pregnant patients who were admitted for hemorrhagic collapse and were traced and evaluated had hypopituitarism. In most, lactation was poor or absent and 50% had permanent amenorrhea. In more than half of the cases, there was a long interval—often more 10 years—between the obstetric event and diagnosis. In a review of 15 pregnancies in patients who had Sheehan's syndrome and received hormonal therapy, there were two (13%) miscarriages and no stillbirths or maternal deaths [25]. In contrast, in 24 pregnancies among 11 women who had Sheehan's syndrome but no hormonal treatment, there were 10 (42%) miscarriages, 1 stillbirth, and 3 maternal deaths. Thus, an ongoing pregnancy does not rule out Sheehan's syndrome and this diagnosis should be considered in symptomatic patients. Low free thyroxine, low TSH, and low serum cortisol, especially during stress, are consistent with the diagnosis. Treatment with L-thyroxine (0.1–0.2 mg/d) and hydrocortisone, which is cortisol, (20 mg in the morning, 10 mg in the evening) or with prednisone (5 mg in the morning, 2.5 mg in the evening) is initiated. It is important to administer thyroxine after treatment with glucocorticoids has been initiated. There is no need for mineralocorticoids. Glucocorticoid requirements increase during stress and during labor. At this time, parenteral therapy is appropriate (25–75 mg hydrocortisone every 6 hours and with intravenous [IV] hydration). Dosages can be tapered to baseline in the early postpartum days. Treatment of hypopituitarism is outlined in Box 2.

Lymphocytic hypophysitis. This is an autoimmune disease with a predilection for women, especially in the setting of pregnancy. Although the official diagnosis

Box 2. Treatment of hypopituitarism in pregnancy

Glucocorticoids

Maintenance: hydrocortisone, 20 mg in the morning, 10 mg in the evening, by mouth or Prednisone, 5 mg in the morning and 2.5 mg in the evening
Stress dosages: double the above doses for duration of stress and taper down to maintenance dosage
During labor: hydrocortisone, 25 to 75 mg, IV, every 6 hours. Taper to maintenance early postpartum
Cesarean section: hydrocortisone, 100 mg, IV, before surgery, then 25 to 75 mg, IV, every 6 hours. Taper to maintenance early postpartum

Mineralocorticoids: not necessary
Thyroxine: L-thyroxine 0.1to 0.2 mg/d, by mouth. Avoid iron therapy at the time of thyroxine dosage. Monitor every 1 to 3 months with free T_4. Adjust dosage as needed
Vasopressin: L-deamino 8 D-argine vasopressin (DDAVP), by mouth, 0.05 to 0.2 mg twice or three times daily or DDAVP nasal spray, 10 to 20 μg, once or twice daily

is rendered pathologically (autopsy or biopsy), this potentially life-threatening condition should be suspected in women of reproductive age who present with hypopituitarism or evidence of a pituitary mass—headaches and visual symptoms that often lead to the discovery of a sellar mass—during pregnancy or postpartum [26]. A personal or family history of autoimmune disease may be elicited and hyperprolactinemia and persistent galactorrhea may be the presenting features in the postpartum patient; these are presumed to relate to stalk disturbances and the lack of dopamine that follows the inflammatory process. Exacerbation of the disease after delivery, even when it presented initially in pregnancy, also was documented. Replacement of deficient anterior pituitary hormones should be initiated promptly. In addition, steroids can be used to ameliorate visual symptoms; the sellar mass may regress spontaneously [27]. Even the hypopituitarism may resolve. Lymphocytic hypophysitis also may present as DI [28].

Disorders of the posterior pituitary

Vasopressin deficiency may be idiopathic (about 30%) or acquired secondary to cranial injuries, infections, tumors, and vascular lesions. Polyuria and polydipsia are the main symptoms. The diagnosis can be made by a water deprivation test that is performed under controlled circumstances. Increasing serum osmolality, in the face of low urine osmolality, and a return to normal

following vasopressin administration confirm a diagnosis of central DI. DI does not alter a women's fertility, course of pregnancy, labor (despite the possibility of concomitant lack of oxytocin), or lactation.

The effect of pregnancy on DI is noteworthy. Several distinct clinical entities that are encountered are summarized below.

Diabetes insipidus that antedates pregnancy

In a review of this subject, Hime and Richardson [29] noted that 58% of patients who had DI deteriorated, 20% improved, and 15% remained the same during pregnancy. Increasing concentrations of placental vasopressinase between Week 10 and midgestation led to increased metabolic clearance of vasopressin, and, hence, deterioration in most patients [3].

Transient arginine vasopressin–resistant but L-deamino, 8D-arginine vasopressin–responsive diabetes insipidus

This is attributed to excessively high quantities of vasopressinase and often is associated with liver abnormalities, such as fatty liver or HELLP syndrome (hemolysis-elevated liver enzymes, low platelets) [30]. Because vasopressinase is cleared by the liver, under such circumstances, excessive amounts are made available.

Transient diabetes insipidus in patients who have acquired or hereditary latent diabetes insipidus

Patients who have limited vasopressin secretory capacity may be unable to increase vasopressin output during pregnancy in the face of increasing destruction by way of vasopressinase. A history of hypothalamic pituitary insult may be obtained. In addition, unmasking of a mild defect in vasopressin action (nephrogenic D1) also may occur, with increased disposal of vasopressin that leads to decompensation. Female carriers of the X-linked recessive mutation of the renal vasopressin receptor gene occasionally have defects in renal concentrating ability (possibly due to nonrandom X-inactivation in the kidneys) which may be unmasked [31].

The treatment of choice for central DI is DDAVP or desmopressin acetate, a synthetic analog of vasopressin that is not affected by vasopressinase (see Box 2). It is available parenterally, orally, and in nasal spray and has little uterotonic action. Clinical experience that involved many infants who were exposed to DDAVP in pregnancy confirmed its safety; only low levels are expressed in breast milk which makes breast-feeding feasible [32].

Thyroid

Thyroid disorders are extremely common in young women of reproductive age. Although in large areas of the world iodine deficiency is the predominant etiology, in the western hemisphere, these disorders are related more commonly

to altered immunity. The hormonal and immunologic perturbations of childbearing and the dependence of the fetus on maternal iodine and thyroid hormone have profound influence on maternal thyroid function and fetal well-being. For appropriate antenatal and postnatal care, a basic knowledge of thyroid function, changes that occur in pregnancy, and common disorders is necessary.

Normal thyroid physiology

The thyroid gland is located anteriorly below the hyoid bone and above the sternal notch. The follicles that make up the gland consist of follicular cells that surrounding a glycoprotein called colloid. Hypothalamic TRH, which stimulates TSH production, is necessary for normal function. In response to TSH, T_4 and T_3 are produced. TSH controls all phases of iodine metabolism from uptake to secretion of the two hormones. Dietary iodine is reduced to iodine which is trapped by the glands and organified by binding to tyrosyl residues that are part of a glycoprotein called thyroglobulin; this process requires the enzyme peroxidase. Thyroglobulin is stored as colloid. Hormone secretion, also under TSH control, involves digestion of thyroglobulin and release of T_3 and T_4. T_4 (daily secretion 90 μg) and T_3 (daily secretion 30 μg) circulate highly bound to thyroxine-binding globulin; 0.3% of T_3 and 0.03% T_4 circulate free. It is the free hormone that is active. Only 20% of circulating T_3 is of thyroid origin; the remaining 80% comes from T_4 to T_3 conversion in the liver and kidneys. Free hormones enter the cell and bind to nuclear receptors; the affinity of T_3 for nuclear receptors is tenfold that of T_4, hence, the greater biologic activity of T_3. Three enzymes deiodinate T_4; monodeiodinase type I and II catalyze formation of T_3. Monodeiodinase type III catalyzes the formation of reverse T_3, an inactive hormone.

Maternal thyroid physiology

Three series of events that occur at different time points of gestation result in significant changes in thyroid function parameters. These changes, outlined by Glinoer [33], are described briefly and are depicted in Fig. 1.

1. Increased thyroxine-binding globulin (TBG) throughout most of pregnancy leads to reduced free thyroid hormones.
2. Transient stimulation of the thyroid by increasing hCG in the first trimester causes TSH to decrease to less than the lower limit of normal in 20% of women.
3. Alteration in peripheral metabolism of thyroid hormone by deiodinases. Placental type II deiodinase, converts T_4 to T_3 and maintains local T_3 production; type III deiodinase increases T_4 to reverse T_3 and T_3 to T_2. metabolism.

These changes are attained without difficulty by a normal gland with iodine sufficiency. This does not apply when thyroid function is compromised or when iodine supply is deficient.

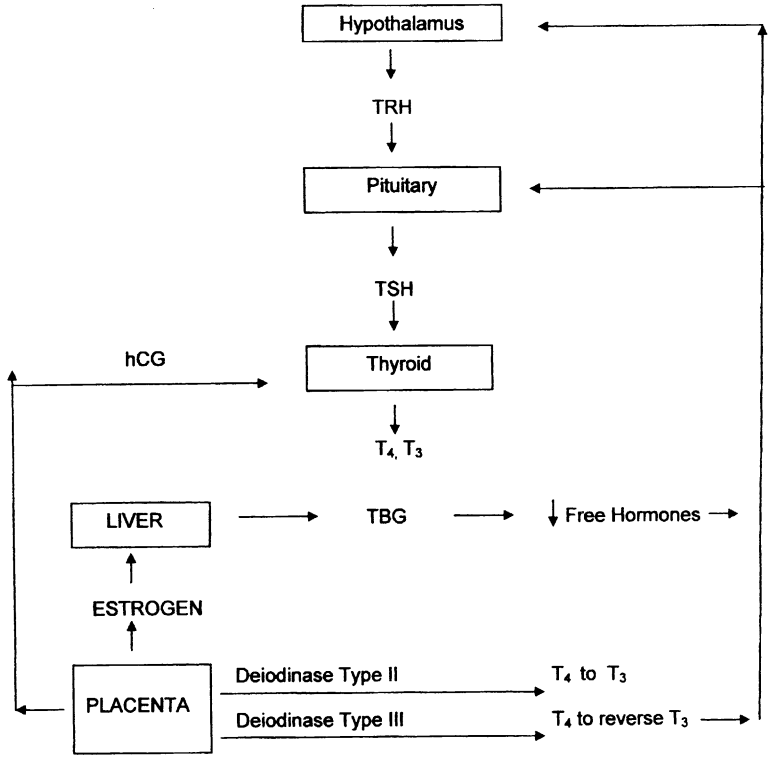

Fig. 1. Schematic representation of the physiologic adaptation to pregnancy, showing increased thyroxine-binding globulin (TBG) concentrations, increased human chorionic gonadotropin (hCG) with its thyrotropin-like activity, and alterations in peripheral metabolism of thyroid hormones in the placenta. Adapted from Glinoer D [33]. TRH = thyrotropin releasing hormone, TSH = thyrotropin, T_4 = thyroxine, T_3 = tri-iodothyronine.

Iodine deficiency and goiter

Although iodine deficiency usually is not a problem in the United States and parts of Europe, 1 to 1.5 billion people in the world are at risk and 500 million live in areas of overt deficiency. The World Health Organization recommends 200 μg of iodine daily for pregnant women (150 μg daily for nonpregnant adults). This increased requirement is needed because of increased renal iodine clearance and diversion of iodine to the feto–placental unit to allow fetal production of thyroid hormones. Borderline intake chronically enhances thyroid stimulation and leads to an increase in thyroid volume that can persist postpartum, especially in women who breast-feed. Neonates of iodine-deficient mothers also have greater thyroid volumes [34]. In the United States, studies of pregnant women have not revealed an increase in goiter. Iodine excretion of greater than 100 μg in 24 hours is reflective of sufficient intake.

Placental-fetal thyroid physiology

The fetal hypothalamic–pituitary portal circulation is functional by 10 to 12 weeks' gestation and active iodine trapping can be detected by 12 weeks' gestation. Remaining low till midgestation, fetal iodine uptake and T_4 concentrates begin to increase after this time [35]. Given the availability of placental type III deiodinase, most fetal T_4 is inactivated to reverse T_3. Fetal tissues that depend on T_3 for development (eg, brain structures) are supplied by local T_4 to T_3 conversion by way of type II deiodinase [36].

Although earlier studies suggested only limited placental T_4 and T_3 transfer, more recent studies showed a significant contribution of maternal T_4 to circulating fetal thyroid hormone concentrations. In addition, nuclear T_3 receptors have been identified in fetal brain as early as 10 weeks' gestation with a tenfold increase by 16 weeks' gestation. The first phase of maximum growth velocity of the developing brain that occurs in the second trimester corresponds to a phase during which the supply of thyroid hormones to the fetus is almost exclusively of maternal origin; low maternal T_4 concentration in the second trimester can result in irreversible neurologic deficit in the offspring. Concentrations of TSH, T_4, T_3, and reverse T_3 are measurable in the amniotic fluid and correlate with fetal, rather than maternal, serum.

Placental transfer of drugs affecting thyroid function

TSH does not cross the placenta but TRH that is administered antenatally can stimulate T_4 release and decrease the frequency of chronic lung disease in the neonate. Box 3 lists the agents that readily cross the placenta [37].

Laboratory evaluation of thyroid function during pregnancy

Total T_4 and total T_3 are elevated and T_3 resin uptake (an indirect laboratory measure of available binding sites) is reduced during pregnancy (increased TBG takes up more of the T_3 and leaves less for resin). The product of T_4 and T_3 resin uptake, which is the free thyroxine index, remains normal. Free T_4 and free T_3 can now be determined [38]. Free T_4 and a third generation TSH assay are the best ways of evaluating thyroid function. If TSH is suppressed, free T_3 also

Box 3. Placental transfer of drugs that affect thyroid function

Iodine
Thionamides
β-Adrenergic receptor blockers
TRH
Somatostatin
Thyroid-stimulating immunoglobulins and other antibodies

should be measured. TBG increases are seen in pregnancy, with estrogen therapy, and in hepatitis and can be inherited.

Drugs and thyroid function

Drug effect on thyroid function and metabolism is outlined on Box 4. Ferrous sulfate, aluminum hydroxide, and sucralfate may inhibit thyroid hormone absorption substantially; this is important in pregnant women who are taking iron and thyroid hormones. Amiodarone is an iodine-rich drug that is used for tachyarrhythmias. The iodine overload may cause fetal/neonatal goiter and hypothyroidism and can affect neonatal thyroid function in breast-feeding mothers who take it [39]. Although ^{131}I produces little reproductive toxicity in women, contraception generally has been recommended for 1 year following ^{131}I treatment for cancer. The incidence of stillbirth, preterm labor, low birth weight, and congenital malformations were not significantly different in women who were treated with ^{131}I; however, miscarriages were more frequent in women who were treated with ^{131}I in the year before conception [40,41]. Lactating women should not have diagnostic or therapeutic radioactive iodine administration.

Box 4. Effects of drugs on thyroid hormones and function tests

Inhibit thyroid function

Iodine, lithium

Inhibit T_4 to T_3 conversion

Glucocorticoids, ipodate, propranolol
Amiodarone, propylthiouracil (PTU)

Increase TSH

Iodine, lithium

Decrease TSH

Glucocorticoids, dopamine agonists

Inhibit T_4 and T_3 protein binding

Phenytoin, salicylates

Inhibit absorption of thyroid hormone

Ferrous sulfate, sucralfate, cholestyramine
Aluminum hydroxide

Disorders of the thyroid gland

Hyperthyroidism and pregnancy

The prevalence of hyperthyroidism in pregnant women ranges from 0.05% to 0.2% [42]. The symptoms of heat intolerance, sweating, fatigue, anxiety, and tachycardia also may be seen in pregnancy. Weight loss, tachycardia (>100 beats/min), diffuse goiter, and gastrointestinal symptoms, such as severe nausea and vomiting, may suggest hyperthyroidism. Biochemical confirmation is obtained by a suppressed TSH, elevated free T_4, or elevated free T_3. Thyroid-stimulating immunoglobulins, which are specific to Graves' disease, may be positive. The differential diagnosis of hyperthyroidism in pregnancy is outlined in Box 5.

Graves' disease. Graves' disease is the cause of 90% to 95% of hyperthyroidism that is seen in pregnancy and may be manifest by diffuse thyromegaly with or without bruit and ophthalmopathy. Mild cases with adequate weight gain, and good obstetric progress may be followed carefully but moderate and severe cases must be treated. Preterm delivery, perinatal mortality, and maternal heart failure are significantly more common in thyrotoxic women [43,44]. Of the thionamides that are available for treatment, PTU is recommended; the goal is to control maternal hyperthyroidism without causing fetal hypothyroidism [45]. The starting daily dosage may be 100 mgm (or in severe cases 150 mgm) every 8 hours. An occasional patient may require higher dosages. After the patient is euthyroid (it may take 6 to 8 weeks for major clinical effect), the dosage is tapered with further reductions as pregnancy progresses. Fetal goiter and bradycardia are consistent with overtreatment of the mother. In some patients, PTU can be discontinued at 32 to 36 weeks' gestation. Side effects include rash (5%), pruritis, fever, hepatitis, lupuslike syndrome, and agranulocytosis (0.1%). Methimazole is not used because of concern for cutis aplasia [46]. Also, there have been recent reports of methimazole embryopathy (choanal atresia, tracheo-esophageal fistula,

Box 5. Differential diagnosis of thyrotoxicosis in pregnancy

Graves' disease
Toxic adenoma
Toxic multinodular goiter
Hyperemesis gravidarum
Gestational trophoblastic disease
Subacute (painful) thyroiditis
Lymphocytic (painless) thyroiditis
Exogenous T_4 and T_3
Other: struma ovarii, follicular cancer, TSH tumor

and facial anomalies) [47]. PTU is not concentrated significantly in breast milk (10% of serum). If the mother wishes to breast-feed, the medication should be taken just after breast-feeding.

β-Blockers can control adrenergic symptoms. Propranolol (20–40 mg, two or three times daily) or atenolol (50–100 mg daily) may be used if necessary. Prolonged therapy has been associated with intrauterine growth restriction, fetal brachycardia, and hypoglycemia. Iodides, such as potassium iodide, 5 to 10 drops, twice daily, along with thionamides (started before iodides) and β-blockers are used to treat thyroid storm. Iodides readily cross the placenta and may cause fetal goiter; therefore, their use should be short-term (less than 2 weeks). In select cases, with noncompliance or other complications, partial thyroidectomy can be performed. It is best performed in the second trimester. Two weeks of iodine therapy (given along with PTU) will reduce gland vascularity before surgery.

Fetal and neonatal hyperthyroidism. Fetal and neonatal hyperthyroidism are produced by transplacental passage of Thyroid Stimulating Immunoglobins (TSI); these antibodies can be present even after surgery or ^{131}I treatment and can activate the fetal thyroid [48]. Maternal TSI in excess of 300% of control values are predicative of fetal hyperthyroidism [49]; features include a heart rate of greater than 160 beats/min, growth retardation, and craniosynostosis. Occasionally, fetal hydrops and death occur. Neonatal features include hyperkinesis, poor weight gain, vomiting, arrhythmias, exophthalmos, hepatosplenomegaly, craniosynostosis, and heart failure. By Day 2 of life, the maternal drug effects will have receded. Affected neonates are treated with β-blockers, PTU and iodine and digoxin as needed. Remission by 20 weeks is usual.

Hyperthyroidism that is related to human chorionic gonadotropin

In the first trimester, hyperthyroidism also may be mediated by hCG. Molecular variants of hCG (basic, truncated, and nicked molecules) may have greater thyrotropic effect and different glycoforms may have varying clearance rates. Several clinical scenarios may arise:

1. Gestational transient thyrotoxicosis (GTT): This occurs in the first trimester, between the 8th and 14th weeks of gestation [50] and has an overall prevalence of 2.4%, as shown in a prospective cohort study. The gland is not enlarged and the patient seldom requires treatment because of its transient nature. It may be symptomatic.
2. Hyperemesis gravidarum: This is a serious pregnancy complication that is associated with weight loss and severe dehydration [51]. Biochemical hyperthyroidism is found in most women. Treatment usually is supportive, although PTU therapy can be attempted if tolerated.
3. Gestational trophoblastic disease: Because hydatidiform mole and choriocarcinoma can be associated with extremely high hCG concentrations,

biochemical hyperthyroidism is seen in 50% of such women. Treatment of the condition restores thyroid function to normal. Thionamides and β-blockers are needed frequently before surgical treatment of the mole [52].

4. Recurrent gestational hyperthyroidism: Recurrent cases have been described [53]. In one case it was caused by a mutant TSH receptor that was hypersensitive to hCG [54].

Other causes of hyperthyroidism

Other causes of hyperthyroidism were outlined (see Box 5). If the etiology is total adenoma or toxic multinodular goiter, antithyroid medications should be administered during pregnancy with plans for definitive treatment postpartum (surgery or radioactive iodine).

Iodine deficiency, hypothyroidism, and pregnancy

Iodine deficiency

Worldwide, this is the most common cause of mental retardation [55]. Even in the United States, 7% of pregnant women had urinary iodine excretion that was less than 50 μg/L which is indicative of relative iodine deficiency. Iodine deficiency leads to four biochemical changes: (1) relative hypothyroxinemia, (2) preferential T_3 secretion, (3) increased TSH after the first trimester, and (4) supranormal thyroglobulin which correlates with goitrogenesis (also occurs in the fetus). It seems that maternal thyroxine that traverses the placenta is necessary for fetal brain development. T_3 receptors are found in the fetal brain; it is likely that local T_4 to T_3 conversion occurs. In iodine deficiency, the maternal T_4 supply is diminished and the fetus is less able to synthesize thyroid hormone. Endemic cretinism may result in areas of severe iodine deficiency and is characterized by severe mental retardation, deaf-mutism, squint, and other neurologic sequelae. This can be prevented only when the iodine deficiency is corrected before the second trimester, and, optimally, before conception [56]. A variant of this has emerged from Africa, where there is less mental retardation and the features are those of myxedema. In Africa, iodine deficiency is complicated by selenium deficiency [57]. Selenium is necessary for formation of monodeiodinase type I. The deficiency of this enzyme reduces maternal T_4 to T_3 conversion and makes more maternal T_4 available to the fetus. It is believed that borderline iodine deficiency can impact full intellectual capacity. The recommended iodine intake in pregnancy and lactation is 200 μg/day.

Hypothyroidism

Hypothyroidism is not uncommon in pregnancy. In a study in the United States of 2000 women who were between 15 and 18 weeks' gestation, 49 (2.5%) had TSH levels that were at least 6 mU/L [58]. Other studies have shown a lower prevalence of hypothyroidism. Hypothyroidism in pregnancy has been associated

with miscarriages, pre-eclampsia, placental abruption, low birth weight, prematurity, and stillbirth [59]. These outcomes can be improved with early therapy. Symptoms of hypothyroidism include more weight gain, lethargy, cold intolerance, constipation, hair loss, and dry skin; some may have a goiter. Biochemically, the TSH is elevated with or without a low free T_4. Hashimoto's thyroiditis is the most common cause; antithyroid antibodies (antithyroglobulin and antithyroid peroxidase) often are positive. Other causes of hypothyroidism include ^{131}I treatment for Graves' disease and thyroidectomy.

Drugs that are known to inhibit thyroid hormone synthesis include thionamides, iodides, and lithium. Aluminum hydroxide, cholestyramine, and, especially, ferrous sulfate and sucrafate, can interfere with the intestinal absorption of T_4. Hypothyroidism secondary to pituitary or hypothalamic disease also may occur. In secondary hypothyroidism, the TSH could be low or normal but the free T_4 is low.

Hypothyroidism must be treated promptly and a dosage of 0.1 to 0.15 mg of thyroxin should be initiated. The dose is adjusted every 4 weeks until the TSH is at the lower end of the normal range. Women who already are on T_4 and are euthyroid in early pregnancy should be rechecked approximately every 8 weeks because the requirements for thyroxin may increase during pregnancy. When data from several studies were pooled, TSH increased above normal in 45% of patients [60]. After thyroxin dosage adjustment, the TSH should be rechecked in 4 to 6 weeks. Increased requirements may be from real increased demand for T_4 in patients whose thyroid reserve is compromised [61] or from interference of T_4 absorption by iron therapy [62]. Iron should be taken at a completely different time from T_4, which should be taken on an empty stomach in the morning. After delivery, the dosage can be reduced to prepregnancy levels. The topic of thyroid hormone and intellectual development has received widespread publicity. In 1999, Haddow et al [63] reported on TSH that was measured from stored samples that were taken from more than 25,000 pregnant women. They located 62 women who had high TSH and matched them to 124 women who had normal values. Their 7- to 9-year-old children underwent 15 tests that were related to intelligence, attention, language, and other skills. The full scale IQ in children of hypothyroid mothers was four points lower; IQ was 7 points lower in children whose mothers were not treated. They concluded that undiagnosed hypothyroidism can affect fetuses adversely and recommended screening for hypothyroidism in pregnancy. The position statement of the American Association of Clinical Endocrinologists is as follows: TSH measurements before or in early pregnancy are reasonable. TSH should be determined in all pregnant women with goiter, positive thyroid antibodies, personal history of autoimmune disease, and family history of thyroid disease. Thyroxin should be administered promptly even if the TSH elevation is mild. Women on the therapy should be monitored during pregnancy [64].

Fetal hypothyroidism. Thyroid agenesis, inborn errors of metabolism, and maternal blocking antibodies may cause fetal hypothyroidism. Gruner et al

[65] reported on a case of fetal goitrous hypothyroidism in which fetal TSH was determined three times by cordocentesis to monitor weekly intra-amniotic T_4 administration that was given to reduce the goiter and aid neurologic development. Other reports of such therapy were reviewed and cordocentesis was believed to be appropriate to monitor such therapy.

Thyroid nodules, malignant tumors, non-toxic goiter in pregnancy

Most thyroid nodules are benign hyperplastic (or colloid) nodules; however, between 5% and 20% are true neoplasms, benign adenomas, or carcinomas. When a goiter or dominant nodule is found, biopsy is recommended. In a study at the Mayo Clinic, 40 pregnant women were evaluated for nodular thyroid disease and 39 had biopsies, 95% of which were diagnostic [66]. Most (64%) were benign, three (8%) were positive for papillary cancer, and nine (23%) were suspicious for papillary cancer or follicular/Hürthle cell neoplasm. Fine needle aspiration biopsy (FNAB) is safe in pregnancy and can be performed at any stage. It should be performed on solitary and dominant thyroid nodules. Fig. 2 outlines the decision-making process. The impact of pregnancy on papillary thyroid cancer was evaluated by Moosa and Mazzaferri [67]. Outcomes in pregnant and

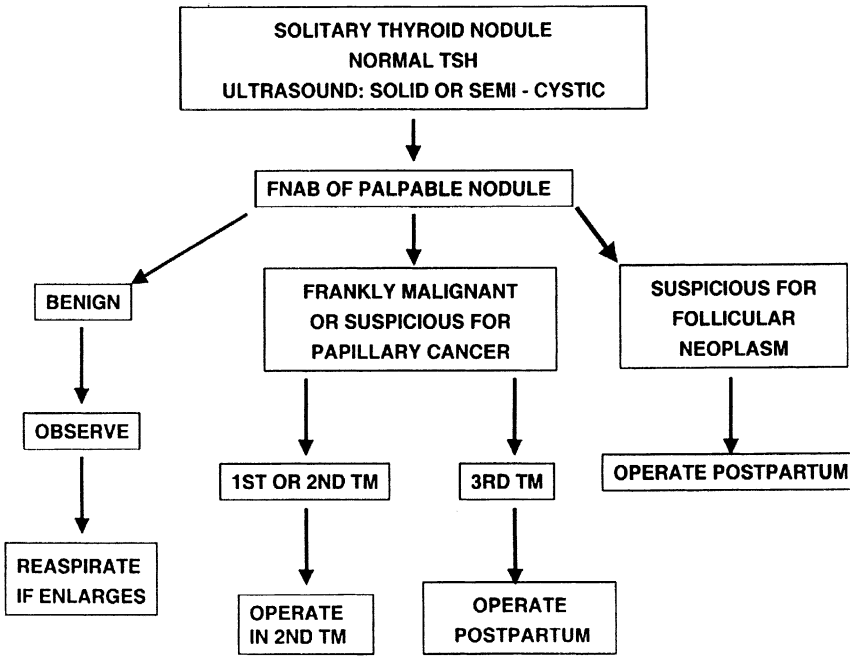

Fig. 2. Evaluation of a solitary thyroid nodule in pregnancy. Adapted from Tan GH et al [66]. TSH = thyrotropin, FNAB = fine needle aspiration biopsy, TM-trimester.

nonpregnant women were not significantly different and a similar conclusion was reached by a more recent study. If medullary thyroid cancer is suspected, early surgery is advised.

Postpartum thyroid disease

New-onset autoimmune thyroid disease occurs in up to 10% of all postpartum women [68,69]. Up to 60% of patients who have Graves' disease in the reproductive years give a history of postpartum onset. The major T- and B-cell immune changes in the postpartum period include overall T-cell deactivation, T helper 1 (Th1)-type T-cell function, loss of tolerance for fetal alloantigens, and enhanced IgG and autoantibody secretion. Fetal microchimerism (the presence of fetal cells in maternal tissues) is believed to play a significant role in postpartum autoimmune disease by triggering graft-versus-host reactions [70]. The onset of Graves' disease postpartum correlates with TSI production which peaks at 3 to 6 months postpartum. The prevalence of Graves' disease is estimated to be 11% in women who have postpartum thyroid dysfunction.

Postpartum thyroiditis (PPT), whose prevalence is 6% to 9%, typically presents with a transient hyperthyroid phase which begins 6 weeks to 6 months postpartum. A hypothyroid phase follows and can last for up to 1 year postpartum. Approximately 25% of patients present this way, 38% have hyperthyroidism alone, and 36% have hypothyroidism. Patients who have type I diabetes have a 25% incidence of PPT. The hyperthyroid phase has a limited duration of a few weeks to a few months. β-Blockers can be used to reduce symptoms; thionamides have no role because the hyperthyroidism relates to an outpouring of thyroid hormone from an inflamed gland. There is a 69% recurrence rate of postpartum thyroid disease in a subsequent pregnancy. The hypothyroid phase often requires treatment; however, the patient can be weaned off medication 6 months after therapy unless another pregnancy is planned. Other than derangements of thyroid function, the laboratory findings are positive antithyroglobulin or antithyroid peroxidase antibodies. PPT can be distinguished from Graves' disease by the finding of negative TSI antibodies and a low ^{123}I uptake (to be performed only in the nonlactating female). Depression and PPT are common postpartum events; several studies have been performed to evaluate their association. The data suggest some association between PPT, thyroid antibodies, and depression. Of four clinical trials, two demonstrated an association between PPT and depression [71,72] whereas two demonstrated an association between thyroid antibodies and depression [73,74]. The role of interventions, such as T_4 therapy, has not been evaluated systematically.

Some women remain permanently hypothyroid following PPT and others recover only to become hypothyroid later. It is recommended that women who have a history of PPT should be evaluated annually for the possible development of hypothyroidism. Postabortion thyroiditis also has been described [75].

Whether screening for PPT is worthwhile is a contentious issue; this was the topic of a recent controversy in therapeutics. It was agreed that women who present with symptoms should have a TSH test performed. In addition, high-

risk women (eg, those who have a history of PPT or type I diabetes) should be screened.

Parathyroid glands and calcium metabolism

Serum calcium is regulated tightly and maintained within normal limits by parathyroid hormone (PTH) and vitamin D. The physiologically-active vitamin D is 1, 25 dihydroxy D; its production is stimulated by PTH. Calcium circulates in three forms—ionized, protein-bound, and chelated fractions.

During pregnancy, calcium and phosphorus are transferred across a concentration gradient from mother to fetus; the net accumulation is 25 to 30 g by term. Maternal calcium absorption increases to meet these demands; this is stimulated by 1, 25 dihydroxy D of placental and renal origin. Although total serum calcium decreases (paralleling a decline in albumin) there is little change in ionized calcium [76]. PTH-related peptide (PTHRP) that is produced by the placenta and fetal parathyroid glands is the dominant regulator of active placental calcium transport; its actions mimic PTH. During lactation, the average daily loss of calcium in human milk is 220 to 340 mg; a small decrease in serum calcium is accompanied by an increase in PTH and 1, 25 dihydroxy concentrations.

Disorders of the parathyroid glands and calcium metabolism

Primary hyperparathyroidism and hypercalcemia

Hyperparathyroidism is rare in pregnancy. Of 750 parathyroid surgeries that were performed over a 21-year period, only 6 occurred in pregnant women; most harbored single adenomas [77]. The clinical features of associated hypercalcemia are summarized in Box 6. Ionized calcium should be measured in suspected cases; the diagnosis is confirmed by inappropriately elevated PTH concentrations [78]. The differential diagnosis of hypercalcemia includes malignant disease,

Box 6. Clinical features of hypercalcemia

- Nephrolithiasis
- Polyuria and thirst
- Weakness
- Constipation
- Anorexia
- Nausea/vomiting
- Arrhythmias
- Hypertension
- Depression
- Psychosis
- Obtundation

granulomatous disease, thyrotoxicosis, hypervitaminosis D and A, immobilization, and familial hypocalciuric hypercalcemia (FHH). The last is a benign, autosomal-dominant, inherited disorder with low urinary calcium excretion and mildly elevated PTH. Affected neonates of mothers who have FHH may manifest symptomatic hypercalcemia; if unaffected, they can become hypocalcemic because of suppression of fetal parathyroid function. Severe neonatal hypercalcemia may be the homozygous variant of FHH. Increased PTHRP production also may lead to hypercalcemia; increased production by hypertrophied breast tissue was reported in one case [79]. Hyperparathyroidism may present with acute, postpartum hypercalcemia that is due to loss of the protective effect of placental calcium transport.

Maternal complications of hyperparathyroidism include hyperemesis, renal calculi (36%), pancreatitis (13%), hypertension (10%), bone disease (19%), hypercalcemic crisis (8%), and psychiatric problems. Fetal morbidity and mortality also are significant with neonatal tetany (23.5%), stillbirth (9.8%), prematurity, and neonatal death [80]. Hypercalcemic crisis, with serum calcium that exceeds 14 mg/dL, may occur in late pregnancy from increased 1, 25 dihydroxy D production or postpartum, from loss of the protective effect of calcium transfer.

Surgical treatment of hyperparathyroidism is favored in the second trimester because there are less maternal and fetal complication in treated patients. Conservative treatment, with attention to hydration and the use of oral phosphate, has been used in the third trimester. Mild asymptomatic cases also may be managed conservatively. Life-threatening hypercalcemia requires hydration, furosemide, phosphates, and even hemodialysis. The effects of calcitonin are short-lived but it does not cross the placenta and was used in one case [81]. Bisphosphonates, such as pamidronate, given intravenously will decrease calcium. There are no data on their use in pregnancy. Four cases of parathyroid carcinoma during pregnancy were reviewed [82]; severe hypercalcemia and a neck mass were consistent features. Early surgical intervention is important.

Hypoparathyroidism

Primarily, hypoparathyroidism occurs in patients who have had neck surgeries; however, it can occur in other less common circumstances, such as with prior ^{131}I irradiation or Di George syndrome, or sporadically. PTH resistance (pseudohypoparathyroidism) also may occur [78]. Clinical features include tetany, paresthesia, stridor, cramps, and mental changes. An ECG may show prolongation of the Q-T interval. Neonatal hyperparathyroidism may develop secondary to maternal hypocalcemia and cause fetal bone demineralization and growth restriction; 6 of 16 such neonates died within the first 3 months of life [83]. Treatment of the mother with vitamin D, such as calcitriol (1, 25 dihydroxy D), 0.5 to1.0 μg/d is recommended; the dosage is adjusted to maintain normal calcium concentrations. In a previously-treated woman, the dosage may need to be increased in pregnancy (and reduced again postpartum) because of possible increased binding of vitamin D to vitamin D–binding protein. Production of

PTHRP by the breast in lactating women also can affect vitamin D requirements [84]. Acute symptomatic hypocalcemia is a medical emergency and should be treated with intravenous calcium (10 mL of 10% calcium gluconate over 10 minutes, followed by an infusion of 0.5–2.0 mg/kg/h of elemental calcium diluted with dextrose). Infants of mothers who are treated with vitamin D should have periodic calcium determinations.

Pregnancy-related osteoporosis

Osteoporosis is a disorder that is characterized by reduced bone strength (bone density plus bone quality) that results in an increased risk of fracture. In pregnancy, increased bone resorption by 14 weeks' gestation and a further increase by 28 weeks' gestation was reported, whereas markers of bone formation did not increase significantly until 28 weeks' gestation [85]. Thus, bone remodeling becomes uncoupled, with an increase in resorption in the first two trimesters; an increase in bone formation is only evident in the third trimester. Pain that occurred late in pregnancy was the most common presentation among 29 women who had idiopathic osteoporosis that was associated with pregnancy [86]. Fractures were more prevalent in the mothers of these women which suggested a genetic predisposition. Low vitamin D concentrations with failure of calcium accretion also may be operative in such patients. The natural history is improvement over time.

During lactation, calcium is mobilized from the maternal skeleton. A significant decrease in spine and distal radius bone density and increased bone hormone was shown in lactating women with an incomplete recovery 6 months after the cessation of breast-feeding [87]. In another study, early losses of bone density of the spine and hip were shown during 6 months' lactation [88]; however, the loss did not continue beyond 6 months and was restored mainly with the return of normal menses. Although some studies showed an adverse effect of extended and repeated lactation [89], parity and lactation have not been associated with low bone density or osteoporotic fractures in epidemiologic or case-control cohort studies [90].

Adrenals

Control of adrenocortical hormones

Aldosterone, produced in the zona glomerulosa, predominantly is under the control of the renin-angiotensin system, although ACTH and hyperkalemia also have a stimulatory role. Cortisol production by the zone fasciculata is under CRH-ACTH control, with diurnal variation. Adrenal androgens result from ACTH stimulation of the zone reticularis.

Physiologic changes during pregnancy

Increases in CRH of placental origin during the second and third trimester lead to increased ACTH and hypercortisolism [91]. The bound (increased corticosteroid-binding globulin) and unbound fractions of serum cortisol increase; the latter is reflected in increased 24-hour urinary free cortisol which may increase to concentrations that are as high as 250 mg (normal <100 mg). Renin activity increases and peaks at 12 weeks' gestation with a decline in the third trimester [92]. By the third trimester, aldosterone concentrations reach values that are five to eight times that of the nonpregnant state. The activation of this axis relates to decreased vascular responsiveness to angiotensin II. Testosterone concentrations increase (mainly bound) but free testosterone also increases in late pregnancy. dehydroepiandrosterone sulfate (DHEA-S) concentrations decrease as a result of an increase in metabolic clearance.

Disorders of the adrenal glands

Primary adrenocortical insufficiency (Addison's disease)

Autoimmune destruction of the adrenal glands accounts for 75% of cases of Addison's disease; other causes include hemorrhage, infection, and infiltrative disorders. Before appropriate treatment, the mortality of Addison's disease in pregnancy was high (more than 50%) [93]. Symptoms of lassitude, nausea, vomiting, pigmentation, weight loss, and anorexia should raise suspicion [94]. A rapid ACTH stimulation test is performed: 250 micrograms of synthetic ACTH is administered intravenously, and serum cortisol measured at baseline, 30 minutes, and 60 minutes. Although a cortisol level that is greater than 18 μg/dL and an increase that exceeds 7 μg/dL are considered normal, the mean levels in pregnancy were reported as 18 μg/dL, 23 μg/dL, and 26 μg/dL in the first, second, and third trimesters of pregnancy, respectively [95]. Treatment is as for the nonpregnant patient, with hydrocortisone (usually 20 mg in the morning and 10 mg in the evening) and fludrocortisone (usually 0.05–0.1 mg/d). Hydrocortisone (cortisol) dosage is doubled or tripled with intercurrent illness. Labor should be managed with stress dosages of hydrocortisone up to 300 mg over 24 hours with fluid replacement. The dosage is tapered postpartum. Breast-feeding has been discouraged because of the potential hazard of corticosteroids passing into maternal milk, but some investigators disagree [96]. Fetal growth may be suboptimal if the diagnosis is made late in pregnancy or postpartum.

Primary hyperaldosteronism

The clinical picture of primary hyperaldosteronism resembles that of the nonpregnant patient who has hypertension and hypokalemia. The cause may be an adrenal adenoma, carcinoma, or bilateral hyperplasia [97,98]. Low renin activity with high aldosterone concentrations are found biochemically. MRI may be used to localize an adenoma. Antihypertensives and potassium supplements

are used; laparoscopic surgery in the second trimester is acceptable. Spironolactone is contraindicated because of its feminizing effects.

Congenital adrenal hyperplasia

The congenital adrenal hyperplasias (CAHs) result from inherited enzymatic defects in adrenal steroidogenesis [99]. Biosynthetic defects early in the cascade usually are fatal or incompatible with reproduction. Deficiency of 21-hydroxylase is the most common defect (90%–95%) with an incidence of 1 in 14,000; 11-hydroxylase deficiency is the second most common defect; both are autosomal recessive. Each future offspring of parents of an affected child has a 25% chance of having the condition and a 50% chance of being a carrier.

A woman who has a diagnosis of 21-hydroxylase deficiency may become pregnant if her CAH is well-controlled and her cycles ovulatory. Her steroid replacement should continue during pregnancy with additional dosages for delivery. Cesarean section rates are higher because of abnormal external genitalia or a small bony pelvis from premature epiphyseal closure. Infants of women who are on suboptimal therapy may be virilized.

Prenatal diagnosis of 21-hydroxylase deficiency for offspring of known heterozygotes is possible. Chorionic villi sampling at 9 to 11 weeks' gestation is recommended; the tissue is subjected to DNA analysis of the 21-hydroxylase gene (CYP-21) using molecular genetic techniques.

Prenatal treatment of the mother with high-dosage glucocorticoids is effective in preventing virilization of an affected female fetus; however, it must be given before the end of the seventh week from conception (ninth week of gestation). After pregnancy is confirmed, all such mothers are treated with dexamethasone 20 micrograms per kilogram prepregnancy weight daily, by mouth. If the chorionic villus sampling determines that the fetus is male then the treatment is discontinued. If the fetus is female, the treatment is continued until the DNA analysis of the 21-hydroxylase gene becomes available. The glucocorticoids are discontinued only if the female fetus is considered to be unaffected. A review of 532 pregnancies that were diagnosed between 1978 and 2001 was reported by New et al [100]. Of 116 affected babies, 61 were female and dexamethasone administered at or before the ninth week of gestation was effective in reducing virilization. Maternal side effects included striae, weight gain, and edema. Algorithms that show the management of such pregnancies are available [99,100]. Similar treatment was effective in 11-hydroxylase deficiency CAH.

Long-term therapy with pharmacologic steroids. In a review of 260 pregnancies in women who received glucocorticoids in pregnancy, two infants had cleft palate, this concern for congenital anomolies being raised by animal experiments [101]. In addition, a prospective cohort study and meta-analysis of epidemiologic studies concluded that prednisone increases the risk of oral clefts by 3.4 fold [102]. During lactation, glucocorticoids have the potential to cause growth restriction in the neonate.

Pheochromocytoma

Pheochromocytomas are tumors of chromaffin cells; 90% of these tumors are located in the adrenal medulla and occur sporadically or as part of the familial multiple endocrine neoplasia, type 2 syndrome (MEN2). About 12% of pheochromocytomas are malignant; although rare, it is a potentially lethal cause of hypertension in pregnancy. Other symptoms include anxiety diaphoresis, headaches, and palpitations. Diagnosis involves measurement of vanillyl mandelic acid, catecholamines, and metanephrines in a 24-hour urine collection. Values are similar to those of nonpregnant patients; methyldopa, if used, must be discontinued before testing. The tumor may be localized by ultrasonography or MRI. In the second half of pregnancy, treatment with phenoxybenzamine (α blockade) is used beginning with 10 mg, twice daily; the dosage is increased until hypertension is controlled. When fetal maturity is achieved, cesarean section is performed with simultaneous or subsequent excision of the tumor during adrenergic blockade [103]. If the diagnosis is made before 24 weeks' gestation, surgery has been advocated with good fetal outcome [103]. Although medical therapy has been used successfully [104], potential teratogenicity of phenoxybenzamine and the unknown effects of long-term adrenergic blockade on the fetus have been put forward as arguments against such therapy. A few cases of malignant pheochromocytoma in pregnancy also have been reported [105] with the use of α-methylparatyrosine, a dopamine synthetic inhibitor, in one of them [106]. Several cases of pheochromocytoma as part of MEN2 also have been reported [107].

Hirsutism and virilization in pregnancy

This may occur secondary to ovarian disease or iatrogenic insult and may affect a female fetus [108]. Differentiation of the female external genitalia occurs between Weeks 7 and 12 of gestation and labial fusion may occur. Clitoromegaly may occur even after the twelfth week. Luteomas, which are solid bilateral benign ovarian tumors, occur more frequently in black multiparas; 80% of female infants who are born to virilized mothers who have luteomas are virilized. Hyperreactio luteinalis, cysts that affect white primigravidas who usually have high levels of hCG, also may cause maternal virilization but do not cause fetal masculinization. Aromatization of androgens by the placenta likely provides protection to the fetus. Often, rare causes of maternal virilization, such as with ovarian or adrenal tumors, also may occur. In addition, insulin-resistant patients who have polycystic ovary syndrome who achieve pregnancy may become extremely androgenized during pregnancy [109]; metformin was used in one such case [110].

Summary

Thyroid disorders are among the most common disorders of pregnancy. Although the presentation usually is not acute (eg, hypothyroidism), appropriate

management of these problems is extremely important for fetal and maternal well-being. Adequate replacement of thyroxine and judicious use of antithyroid medications may help to ward off maternal and fetal complications. Other endocrine disorders are less common but their presentation and consequences may be more dramatic. Knowledge of the endocrine adaptation to pregnancy of diseases that are related to pregnancy, and appropriate consultation with endocrine colleagues usually will ensure a safe pregnancy, delivery, and postpartum experience.

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Hemoglobinopathies in pregnancy

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Hemoglobinopathies are a diverse group of inherited disorders of hemoglobin production and function. They represent the most common single-gene disorders that are found in humans and are distributed in various frequencies throughout the world. In general, hemoglobinopathies can be classified broadly as disorders that result from structurally altered hemoglobin molecules (eg, sickle cell anemia) or disorders that arise from numerical imbalance of otherwise normal globin chain synthesis (eg, β-thalassemia). Recent advances in the treatment of these disorders have increased the life span and quality of life of affected individuals. It is increasingly common for women who are affected with hemoglobinopathies to reach childbearing age and to desire pregnancy. The unique physiologic changes of pregnancy may influence the mother's clinical condition significantly. In addition, the genetic nature of these conditions raises special consideration in obstetrics for affected women and their babies.

Overview of the hemoglobin synthesis and structure

Hemoglobin is a tetrameric protein that is composed of two polypeptide chains with a heme molecule attached to each chain. Hemoglobin tetramers are highly soluble and have reversible oxygen-carrying capabilities that are adapted precisely for the regulation of oxygen pick-up and delivery to tissue. Six distinct species of normal hemoglobin have been described in humans; three appear only during embryonic development and the other three are expressed variably during fetal and adult life. The globin genes that make up these hemoglobin species reside on chromosomes 11 and chromosome 16 (Fig. 1). Activation and deactivation of the different globin gene syntheses are regulated precisely during

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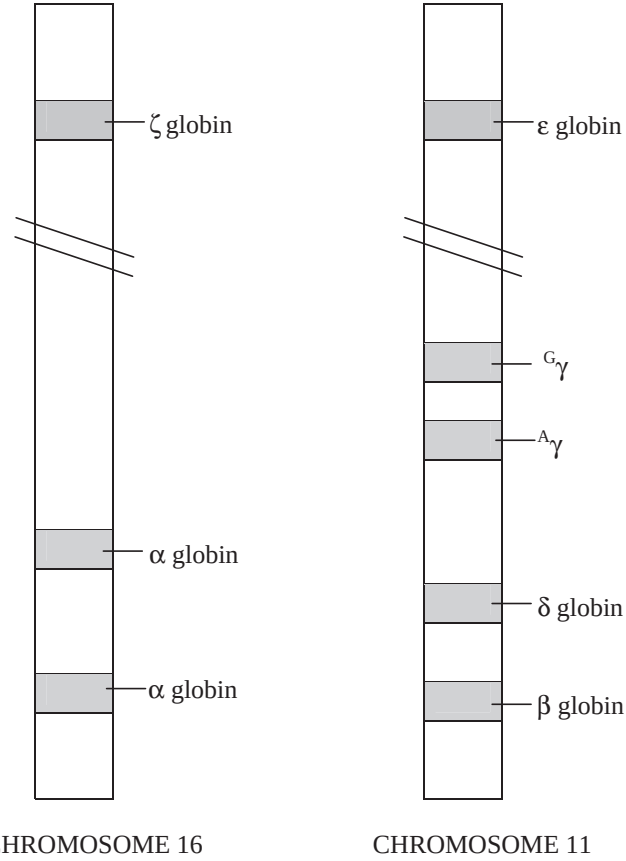

Fig. 1. Globin genes. Genes that code for the globin chains are found on chromosome 16 and chromosome 11. There are four α-globin genes, two on each chromosome 16, and two β-globin genes, one on each chromosome 11. Chromosome 11 also contains the δ-globin gene that codes for the β-like chain in HbA_2 (α_2/δ_2).

development. During the embryonic stages of fetal development, three hemoglobins (Hb)—Hb Gower-1, Hb Portland, and Hb Gower-2—predominate (Table 1). Hb Gower 1 (ζ_2/ε_2) and Hb Portland (ζ_2/γ_2) are unique in that these are the only human hemoglobin species that do not depend on α-globin synthesis [1]. After the switch from embryonic to the fetal phase, there is no gene substitute for α-globin. Following the embryonic phase, fetal hemoglobin (HbF)—composed of two alpha and two delta globin chains (α_2/γ_2)—predominates and remains the dominant hemoglobin species during in utero life. HbF has higher oxygen affinity that adult hemoglobin and allows transport of oxygen to peripheral tissues in the hypoxemic fetal environment. In the third trimester, the β− and δ-globin genes become active so that there is an increasing amount of adult hemoglobins HbA (α_2/β_2) and HbA_2 (α_2/δ_2). The proportion of adult

Table 1
Hemoglobin gene expression

Developmental period	Hemoglobin species	Globin chains
Embryonic	Gower 1	$\zeta_2 \varepsilon_2$
	Portland	$\zeta_2 \gamma^{G \text{ or } A}$
	Gower 2	$\alpha_2 \varepsilon_2$
Fetal	Hemoglobin F	$\alpha_2 \gamma_2^{G \text{ or } A}$
Adult	Hemoglobin A	$\alpha_2 \beta_2$
	Hemoglobin A_2	$\alpha_2 \delta_2$
	Hemoglobin F	$\alpha_2 \gamma_2^{G \text{ or } A}$

hemoglobin increases from 0% at 26 weeks' gestation to about 30% at term [2]. Because of the long life span of circulating red cells, HbF is slowly replaced by HbA. Infants generally do not become dependent on HbA synthesis until 4 to 6 month of age. One clinical consequence of this is that although disorders of α-globin synthesis may manifest in utero or at birth, disorders of β-globin synthesis tend to manifest clinically after 6 months of age.

In the adult, the predominant hemoglobin is HbA (α_2/β_2). HbA2 (α_2/δ_2) makes up from 2% to 3% of adult hemoglobin. In some cases, HbF (α_2/γ_2) persists, although normally at low levels (less than 2%). Increases in HbA_2 and the persistence of HbF may be important in decreasing disease severity in β-globin disorders [1].

Hemoglobin and erythrocyte function

The function of the erythrocyte (RBC) is linked tightly to the chemical characteristics of the hemoglobin molecule. The highly-soluble hemoglobin molecules are present as a viscous solution in RBCs in extremely high concentrations, 33 to 35 g/dL. The water and hemoglobin content of the red cell determine the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin content. The RBC normally has a discoid shape with a diameter of 7 to 8 μm. This unique shape allows the RBC to squeeze through capillaries that are as narrow as 3 μm in diameter. As they move through the circulation, RBCs must withstand severe mechanical and metabolic stresses and maintain an internal environment that protects hemoglobin from oxidative attack. Normally, about 1% of the RBCs are destroyed each day and are replaced by a virtually identical number of new cells [3].

In the hereditary hemoglobinopathies, abnormal globin chain structure can result in hemoglobins that tend to gel or crystallize, that bind oxygen abnormally, or that are unstable. Others disorders result in unequal rates of globin chain production with precipitation of abnormal tetramers. These various changes can render the RBC less able to withstand various stresses and results in accelerated destruction. This results in the clinical findings of hemolysis with variable

degrees of anemia. The hemolytic anemia that characterizes the hemoglobinopathies is further influenced by the overall physiologic state of the affected individual; these factors include oxidative stress, alterations in blood flow, increased metabolic demands, presence of infection, and available iron stores [3]. The physiologic changes of pregnancy can affect all of these factors.

Maternal adaptation to pregnancy

Pregnancy brings about myriad changes in maternal physiology and affects every system in the body, including the hematologic system. At times, normal findings in pregnancy can be similar in presentation to pathologic processes which makes it difficult to differentiate one from the other, especially in the presence of other confounding states. Adaptation of the mother to the physiologic demands of pregnancy may exacerbate the underlying pathophysiologic effects of the patient's hematologic condition. Of particular importance when dealing with hemoglobinopathies are the cardiovascular, hematologic, and respiratory alterations.

During pregnancy, maternal blood volume increases by approximately 1.5 L—1.2 is plasma and 300 mL is red blood cells. The increase begins during the first trimester, is most significant in the second trimester, and plateaus during the end of the third trimester [4]. Plasma renin and aldosterone activity are increased and lead to a volume overload as a result of sodium and water retention. Plasma osmolality is decreased as a result of changes in the lowered osmotic threshold for thirst and arginine vasopressin secretion threshold. The increased plasma volume leads to a mild dilutional anemia that is typically not less than a hemoglobin level of 11.0 g/dL; however, women who have hemoglobinopathies may experience a more profound drop in hemoglobin levels. If uncorrected, this may lead to suboptimal delivery of oxygen to maternal and fetal tissues.

Cardiac output increases as a result of increased heart rate and decreased systemic vascular resistance. Resting heart rate increases by an average of 10 beats per minute. Cardiac output is increased most notably in the lateral recumbent position. The increased plasma volume leads to an increase in preload. The increased demand on the maternal heart as a result of pregnancy can make evident the existence of cardiac compromise that is present, but asymptomatic, before pregnancy. In pregnancy, the cardiac axis is shifted laterally and a small pericardial effusion may be present; both can increase the silhouette on radiographic studies.

Pulmonary compensation in pregnancy includes an increased thoracic circumference and elevation of the diaphragm as a result of the rising uterus. Respiratory rate is unchanged. Tidal volume, minute ventilatory volume, and minute oxygen uptake are increased throughout pregnancy. No change is seen in lung compliance. Functional residual capacity and residual volume are decreased. Progesterone causes increased airway conductance and total pulmonary resistance. A mild respiratory alkalosis is seen that is essential for gas exchange across the placenta

[4]. The presence of abnormal hemoglobin can affect transmission of oxygen to the fetus.

Overview of hemoglobinopathies

As the most common of the single-gene disorders, hemoglobinopathies have a widespread distribution across the globe. It is estimated that approximately 370,000 affected births occur each year worldwide. According to the World Health Organization, an estimated 5% of the world's population are carriers of hemoglobin disorders [5]. The hemoglobin variants of the greatest clinical significance are hemoglobins S, C, and E. The HbS gene has the greatest frequency in West Africa; approximately 25% of individuals are heterozygous for HbS [6,7]; the Mediterranean, Caribbean, South and Central American, Arab, and East Indian populations also exhibit high frequencies of the HbS allele [8]. It is estimated that 4000 to 5000 pregnancies in the United States each year are at risk for sickle cell disease; approximately 0.2% of African Americans have sickle cell disease. [1]

Other common hemoglobin variants include HbE and HbC. HbE is the most common structural variant in the world. The distribution of HbE extends from eastern India through Southeast Asia and has its highest incidence in Thailand, Laos, and Cambodia. The highest frequency of the HbE allele was reported in eastern Thailand near the Vietnamese border—an area termed the "Hemoglobin E triangle"—where the carrier rate is as high as 25% to 30%. The HbE variant also is seen sporadically in parts of China and the Indonesian islands [6]. In areas of the United States that have large populations of immigrants from southeast Asia, this variant is found more commonly than HbS in newborn-screening programs [9]. HbC is restricted to parts of West Africa and is estimated to have a gene frequency in that population of approximately 25% [7].

The α- and β-thalassemias, the quantitative variety of hemoglobin disorders, also are seen across the globe. The greatest frequencies are recognized in areas of past endemic falciparum malaria, including the Mediterranean, southeast Asia, the Arabian Peninsula, Turkey, Iran, west and central Africa, India, and Pacific Islands [10]. β-Thalassemia is common throughout the Mediterranean region, Myanmar, India, southeast Asia, and the Middle East, with sporadic distribution in Melanesia [7]. α^{+}-Thalassemia is extremely common in parts of Africa, the Mediterranean, the Middle East, and throughout southeast Asia and the Pacific Island populations, whereas α^{0}-thalassemia is restricted to the Mediterranean region and southeast Asia [10].

Disorders that involve hemoglobin structural variants: sickle cell syndromes

HbS that results from the substitution of the amino acid, valine, for glutamine at the sixth position of the β-hemoglobin chain is, by far, the most common structural hemoglobin variant in the United States; it is found in about 8% of

African Americans [3]. The clinical manifestations of HbS are sickle cell anemia (HbSS) and sickle cell trait.

Sickle trait

Individuals who carry one HbS gene (ie, sickle trait) lead normal healthy lives. There are no hematologic manifestations—red cell morphology, red cell indices, and the reticulocyte counts are normal. On electrophoresis, individuals with sickle cell trait produce HbSA, composed of normal alpha chains and a combination of normal beta chains as well as beta chains carrying the sickle mutation HbSA (a2/βsβ). Because of the selective pairing of the α-globin with the normal β-globin chain, the concentration of HbSA is less than 50%, and may be as low as 30% on hemoglobin electrophoresis. A few complications can occur with sickle trait, most commonly hyposthenuria and renal hematuria. Splenic infarction was reported to occur under conditions of hypoxia and at high altitude [3].

During pregnancy, patients are more susceptible to bacteriuria and pyelonephritis. Pregnant women who have sickle trait should be followed closely for evidence of urinary tract infection and should be treated promptly [3] Hematuria may be seen in a carrier during pregnancy; however, no specific therapy is indicated. Genetic counseling and screening should be offered to the couple to determine the risk for fetal sickle cell disease.

Sickle cell disease

Sickle cell anemia is an autosomal recessive disease that is caused by inheriting two copies of HbS and results in the production of HbSS ($\alpha_2/\beta s_2$). Sickle cell disease affects 1 in 600 African Americans and people of Mediterranean or southeast Asian origin [11]. Sickle cell disease in pregnancy is less common than in the general population because affected women may not reach reproductive age as a result of the mortality that is associated with this syndrome. Although pregnancy complications are increased for the mother, fetus, and neonate, there have been significant improvements in outcome; patients are no longer counseled to avoid pregnancy except in extreme cases, such as those in whom the disease has resulted in pulmonary arterial hypertension which can increase maternal mortality up to 50% [12,13]. If possible, patients who have sickle cell disease should be cared for by a multidisciplinary team that has expertise in this field.

Pregnancy management in sickle cell disorders

Patients should be screened to ensure that they are receiving adequate nutrition. In addition to prenatal vitamins, it is recommended that patients who have sickling disorders receive a minimum of 1 milligram of folate per day. A complete blood count should be a part of the baseline laboratory tests that are ordered and a baseline ferritin level should be considered. Iron supplementation should be initiated if indicated [14].

Increased morbidity is associated with infections during the pregnancy; therefore, the patient must be monitored closely for any signs/symptoms of infection. Bacteriuria should be treated aggressively to prevent pyelonephritis. Patients should be given warnings to avoid sick contacts and be sure that their immunizations are up to date. Of particular concern is infection with parvovirus B19. This infection can cause an aplastic crisis in patients who have sickle cell anemia and cause life-threatening bone marrow suppression in the fetus [3]. If infection does occur, close follow-up of maternal and fetal hematologic status is important.

Women who have sickle cell anemia have an increased risk of preterm delivery. Between 30% and 50% of pregnancies deliver before 36 weeks' gestation; the average gestational age at delivery is 34 weeks [13]. Therefore, signs of preterm labor should be reviewed and treated promptly.

Therapy

In the nonpregnant state, hydroxyurea has been used in sickling disorders because of its ability to induce HbF, its ability to alter red cell–endothelial cell interactions, and its myelosuppressive effects on neutrophils. It has been associated with poor reproductive outcomes in rats, including postimplantation losses and reduced placental and fetal weight. Hydroxyurea should be discontinued 3 to 6 months before pregnancy because of possible teratogenesis [15].

Prophylactic blood transfusions have been used to treat pregnant women who have sickle disorders. Currently, their use is controversial. A comparative trial of prophylactic versus need-based transfusion showed no difference in prenatal outcome in the two groups. The group that was transfused had a lower incidence of painful crisis; however, other medical and obstetric complications occurred in equal frequency [16]. Multiple transfusions increase the risk of risk of blood-borne infections, isoimmunization, and increase the need for hospitalization during pregnancy. Generally, prophylactic transfusion is not recommended in pregnancy; however, it may be indicated in patients who have particularly severe disease manifestations. Transfusion usually should be reserved for symptomatic patients who are unresponsive to conservative management [16].

Fetal surveillance

Intrauterine growth restriction is common with this disease and may be due to vascular stasis in the uteroplacental unit [17]. Ultrasound examinations should be performed on a regular basis to evaluate fetal growth. Antepartum testing also can be useful to assess fetal well-being.

Sickle cell crisis

Sickle cell crisis is associated with ischemia and infarction of organs as a result of sickling of RBCs. Common precipitants are acidosis, dehydration, cold temperatures, altitude, stress, fatigue, menstruation, and infections [18,19]. The

usual presentation is pain that tends to be identified by the patient as typical of a crisis. The most common areas for pain are the lower back, chest, femoral shaft and hip joints, ribs, knees, abdomen, and head. At times, it can be difficult to differentiate an acute abdomen that requires surgery from a painful crisis that presents as abdominal pain [19]. This is made more difficult in the presence of a gravid uterus. It is imperative that all other possible causes of pain be ruled out before establishing the diagnosis of a sickle cell crisis.

Forty-eight percent of women who have SS disease experience a crisis during pregnancy [13]. Sickle crisis requires admission and treatment with intravenous hydration and pain control. It is advisable to have the patient evaluate her pain based on a visual scale; analgesia should be adjusted based on her feedback. Rapid relief should be the goal [20]. Nonsteroidal anti-inflammatory agents are not the therapy of choice as they might be in nonpregnant patients who have a mild crisis because of the concern for oligohydramnios and premature closure of the ductus arteriosus in advanced gestational age. Opiates are recommended; morphine is the preferred agent. Patients should be on a scheduled dosage with additional boluses if needed. Oxygen therapy should be given if the oxygen saturation is less than the patient's known steady-state. Adjuvant therapy, such as laxatives, antipruritics, and anxiolytics/sedatives should be considered [20]. Blood transfusion may be indicated if signs or symptoms of anemia are present (tachycardia, tachypnea, dyspnea, fatigue, decreasing hemoglobin, low reticulocyte count ($<100 \times 10^9$/L). Blood should be leukopoor and matched for antigens. In extreme cases, exchange transfusions may be required [20].

Acute chest syndrome

This syndrome presents as cough, chest pain, dyspnea, fever, leukocytosis, and infiltrate on chest radiograph with poor response to antibiotic therapy. This may result from infection, atelectasis, bone marrow embolization, rib infarction, microvascular occlusion, or lung infarction. The true cause is unknown [19]. High dosages of opioids often are needed for adequate pain control. Repeated episodes may lead to chronic lung disease.

Urologic manifestations

In addition to pyelonephritis, six other nephropathies have been associated with sickle cell disease. These include gross hematuria, papillary necrosis, nephrotic syndrome, renal infarction, hyposthenuria, and renal medullary carcinoma [21]. These conditions vary in presentation. A urinalysis with culture and sensitivity is necessary as is evaluation of renal function by chemistry and 24-hour urine collection. Hematuria should be treated with hydration and rest and usually resolves in 2 weeks. Papillary necrosis usually is more painful and may lead to ureteral obstruction that requires surgery. Nephrotic syndrome is worrisome because it forebodes renal failure [21]. Hyposthenuria is common and may lead to dehydration. Renal medullary carcinoma has been associated with sickle cell disease and

has a poor prognosis. The mean age of diagnosis is 21; the most common symptoms are flank pain, gross hematuria, and weight loss [22].

Special considerations should be given to the pregnant woman who has kidney disease. Women who have kidney disorders are at increased risk of developing pre-eclampsia and should be monitored closely for signs and symptoms of this condition.

Labor

Generally, delivery can be accomplished vaginally with cesarean section reserved for obstetric indications. Spontaneous labor is preferable because sickle cell crisis was reported to be associated with induction of labor. There is concern that the use of prostaglandins may lead to cell sickling, and, therefore, should be used with caution [23]. Cases of peripheral neuropathy that were induced by a vaso-occlusive crisis after spinal anesthesia have been reported [24].

Variant sickle cell syndromes

Several variant sickle cell syndromes are seen commonly. Sickle cell syndromes can result from inheritance of the sickle cell gene in compound heterozygosity with other mutant β-globin genes.

Hemoglobin SC disease

HbC results from a G-A point mutation in the first nucleotide of codon 6. This gene is present in about 2% of African Americans. HbAC ($\alpha_2/\beta_c,\beta$) and HbCC (α_2/β_{c2}) are benign conditions [25]; however, compound heterozygosity for HbSC results in sickle cell disease that generally is less severe than homozygous HbSS. Splenomegaly may be the only physical finding, The frequency of acute painful crises is about half that of homozygous sickle cell anemia and the life expectancy is 2 decade longer [3].

Although pregnancy can exacerbate symptoms in HbSC disease, the clinical course is generally milder than homozygous HbSS. In one study that compared outcome, 34% of SC patients and 50% of SS patient had at least one painful crisis in pregnancy [26]. Preterm delivery occurred in 20% of patients who had HbSC disease versus 45% of patients who had HbSS disease. The rate of pre-eclampsia was 8.7% and 20%, respectively. Some patients who have HbSC disease experience vaso-occlusive crisis for the first time during pregnancy. In symptomatic patients, pregnancy management should follow guidelines that are outlined for sickle cell anemia.

Sickle cell–β-thalassemia

When combined with sickle trait, a defect in the β-thalassemia gene produces a disease that is similar to sickle cell anemia. Approximately 10% of sickle

cell disease in the United States is caused by compound heterozygous HbS/β-thalassemia. Sickle cell–β-thalassemia is divided into sickle cell-β^+-thalassemia and sickle cell-β^0-thalassemia, which have, respectively, reduced or no amounts of HbA present. Patients who have sickle cell–β-thalassemia can experience vaso-occlusive crisis and other sickle cell complications. Most β-thalassemia mutations that are seen in the United States among African Americans are β^+-thalassemia with variable amounts of HbA present. The disease is most severe when only a small amount of HbA is present; it is milder if HbA constitutes 25% or more of the total hemoglobin and less HbS is produced [27]. Pregnancy management in symptomatic patients is the same as in homozygous sickle cell anemia.

Sickle cell–hemoglobin E disease

HbE is a structural variant that is found most commonly in individuals of southeast Asian origin. Although HbE (α_2/β_{e2}) and HbEA (a2/β_e,β) are benign, individuals who carry both the HbE and HbS genes may have significant clinical disease. Individuals who have HbSE ($\alpha_2/\beta_e\beta_5$) have mild hemolysis. Most commonly they do not have vaso-occlusive disease; however rare individuals may have a picture consistent with mild sickle cell disease [28].

Quantitative disorders of hemoglobin synthesis: thalassemia syndromes

The thalassemia syndromes is a group of genetic disorders that result in quantitative defects in the biosynthesis of the globin chain subunits. Occasionally, thalassemia-like syndromes can also result from diminished production of a structurally abnormal chain, such as in Hb Lepore disease or Hb E–β-thalassemia.

Pathophysiology

The clinical syndromes that are associated with thalassemia result from inadequate hemoglobin production and the accumulation of abnormal globin subunits. The decreased hemoglobin production leads to a microcytic, hypochromic anemia. Accumulation of unpaired globin subunits leads to ineffective erythropoiesis and hemolytic anemia [1]. The spectrum of thalassemia syndromes is broad and ranges from asymptomatic hypochromia and microcytosis without anemia to profound transfusion-dependent anemia. Although sickle cell anemia is the most common hemoglobinopathy in the United States, thalassemias, as a group, represent the most common single-gene disorder in the world. The classification of the individual thalassemia syndromes is based on the specific globin gene that is affected.

β-Thalassemia

The β-thalassemias are characterized by diminished production of β-globin chains which causes unmatched α-globin chains to accumulate and aggregate.

Clinically, this is manifest by microcytic hypochromic anemia, an abnormal peripheral blood smear with nucleated RBCs, and reduced amounts of HbA on hemoglobin analysis. More than 200 mutations in β-globin genes have been identified in patients who have β-thalassemia. Most of these are point mutations that result in the decreased synthesis of the β-globin chain [29]. The deficiency of β-globin synthesis may be compensated partially by an increase in δ- and γ-chain synthesis. This leads to variably increased elevated levels of HbA_2 ($a_2\delta_2$) and HbF ($a_2\gamma_2$) on hemoglobin electrophoresis. β- Thalassemia has three major clinically important syndromes: β-thalassemia minor, β-thalassemia major, and β-thalassemia intermedia.

β-Thalassemia minor (β-thalassemia trait)

Patients who have β-thalassemia minor are heterozygous for a β-globin mutation. Generally, affected individuals have mild or no anemia. The peripheral smear shows hypochromia and microcytosis with basophilic stippling. Splenomegaly is found occasionally. The HbA_2 level is greater than 5% in 90% of patients and the HbF level is greater than 2% in 50% of patients. Unlike iron deficiency, β-thalassemia minor is characterized by normal to increased proliferation of RBCs [3].

β-Thalassemia major (Cooley's anemia)

β-Thalassemia major, also known as Cooley's anemia, results from homozygous or double heterozygous mutations in the β-globin gene. In β^0-thalassemia, the most severe form, no β-globin chains are synthesized. In this case, only HbA_2 and HbF are found on electrophoresis. When small amounts of the β-globin chain are synthesized, the condition is termed β^+-thalassemia. Hemoglobin electrophoresis will show HbA, HbA_2, and HbF. β^+-Thalassemia is generally milder than β^0 thalassemia. δβ-Thalassemia, which is caused by deletion of δ- and β- globin genes, is the mildest variant. In this variant, only HbF is produced.

Patients who have thalassemia major have severe anemia and hepatosplenomegaly, and, without treatment, generally die in childhood. Modern treatment with regular transfusions and iron chelation therapy can result in normal growth and development and extends life expectancy into the third to fifth decades. This management prevents complications, such as congestive heart failure, fluid overload, and skeletal deformity. Splenectomy usually is necessary to enhance survival of the patient's own RBCs as well as transfused RBCs. Bone marrow transplantation is being used increasingly with good success. More than 1000 patients have undergone allogeneic bone marrow transplantation from sibling donors who were normal or had the β-thalassemia trait [30]. Successful pregnancy was reported after bone marrow transplant for β-thalassemia [31].

β-Thalassemia intermedia

Patients who have β-thalassemia intermedia carry two β-thalassemia mutations but present with symptoms later in life and have milder anemia than patients who have β-thalassemia major. They are not transfusion dependent but they may require transfusion periodically. Despite the low transfusion rate, iron overload occurs in these patients as a result of increased intestinal absorption of iron that is caused by ineffective erythropoiesis. The associated complications of iron overload present later, but may be as severe as those seen in patients who have β-thalassemia major [3].

β-Thalassemia–like variants

Hb Lepore

Hemoglobin Lepore is a hemoglobin variant that results in fused globin chains. Clinically, patients who are homozygous for Hb Lepore present with Cooley's anemia or β-thalassemia intermedia. Electrophoresis shows only hemoglobin Lepore and HbF. Hb Lepore accounts for 5% to 10% of the β-thalassemias that are seen in Greek and Italian populations [32].

Hemoglobin E– β-thalassemia

Compound heterozygotes for HbE and a β-thalassemia gene (HbE–β-thalassemia) have a clinical picture like β-thalassemia intermedia or β-thalassemia major [3]. Pregnancy management of these patients should follow the guidelines that are recommended for β-thalassemia major [28].

Pregnancy management in β-thalassemia syndromes

β-Thalassemia minor (heterozygous β-thalassemia)

Generally, β-thalassemia minor is well-tolerated in pregnancy. Pregnancy outcome and obstetric complications do not differ from the general population. Iron supplementation usually should be given only to women who have documented iron deficiency. Periconceptual folic acid supplement is recommended. Preliminary data suggest that the risk of fetal neural tube defects may be increased in pregnant women who are thalassemia carriers, possibly because of relative folic acid deficiency secondary to increased erythropoiesis.[33] The optimum dosaging of folate has not been determined; however, high-dose supplementation in the preconception phase and first trimester with at least 4 mg daily of folic acid should be considered based on benefits in other populations who are at higher risk for neural tube defects [34].

Although many patients may experience a decrease in hemoglobin, the need for transfusion is rare [35]. Erythropoietin was used successfully to increased

erythropoiesis and fetal hemoglobin levels in a patient who had β-thalassemia minor and experienced severe anemia during pregnancy [36].

Genetic counseling is an important aspect of prenatal care for these patients. Screening of the partner with MCV and hemoglobin electrophoresis should be offered to determine the fetal risk for β-thalassemia major.

β-Thalassemia major and intermedia

Because of the high rate of morbidity and infertility in patients who have β-thalassemia major, pregnancy experience was limited; most cases of pregnancy were restricted to patients who had β-thalassemia intermedia. Aggressive transfusion and iron chelation therapy has improved life expectancy and fertility significantly and decreased medical disability which has resulted in the possibility of pregnancy in patients who have β-thalassemia major [37]. More than 100 successful pregnancies in patients who have β-thalassemia major or β-thalassemia intermedia have been reported in the literature [37–46]

Preconception evaluation

A preconception evaluation is highly recommended for the thalassemic patient who is considering pregnancy. This evaluation should include assessment of the patient's transfusion needs, compliance with chelation therapy, iron load status, assessment for end-organ damage from iron overload, endocrine and hormonal function, and indirect Coombs status. Exposure or chronic infection with hepatitis B, hepatitis C, and HIV should be evaluated (Table 2). Genetic evaluation of the patient and her partner should be done to determine fetal risks for thalassemia. Patients who have significant iron overload with resultant myocardial dysfunction have significantly increased morbidity and mortality and are not good candidates for pregnancy. Other factors that adversely affect pregnancy outcome include the presence of antibodies to obstetrically significant RBC antigens, severe diabetes, liver dysfunction, active hepatitis, or HIV-related infection. Significant enlargement of the spleen, which is most common in β-thalassemia intermedia, was reported to be associated with dystocia and hypersplenism [37].

Infertility

Hormonal dysfunction that is due to iron overload in transfusion-dependent patients is a significant problem. This can lead to a variety of hormonal insufficiencies, including hypopituitarism. In one study of 62 women who had homozygous β-thalassemia, 52.8% had hypogonadotrophic hypogonadism [40]. Successful pregnancy can be achieved in these women using ovulation induction and assisted reproduction techniques [40,44].

Table 2
Suggested preconception/prenatal evaluation for patients who have homozygous β-thalassemia

System	Recommended testing
History and physical examination	Transfusion frequency
	Chelation therapy history
	Presence of major bone deformities
Genetic counseling	Partner screening for thalassemia or other hemoglobinopathies
Cardiac evaluation	Cardiac history
	Physical examination
	Electrocardiogram
	Resting echocardiogram
Endocrine	
Diabetes	Fasting blood sugar
	HbA1c
	Glucose tolerance testing in indicated
Thyroid	Thyroid stimulating hormone
	Free thyroxine
	Triiodothyronine
Renal	Electrolytes, blood urea nitrogen, creatinine
	Urinalysis
	Urine culture
Liver	Electrophoresis of plasma proteins
	Total protein
	Aspartate and alanine amniotransferases
	Alkaline phosphatase
	Prothrombin time
	Liver/gallbladder/spleen ultrasound
Infectious	Rubella titer
	Syphilis serology
	Hepatitis B serology
	Hepatitis C serology
	Human immunodeficiency virus testing
Hematologic	Hemoglobin level, complete blood counts
	Ferritin
	Indirect Coombs

Data from Aessopos A, Karabatsos F, Farmakis D, Katsantoni A, Hatziliami A, Youssef J, Karagiorga M. Pregnancy in patients with well-treated β-thalassemia: outcome for mothers and newborn infants. Am J Obstet Gynecol 1999;180(2 part 1):360–5.

Prenatal care

Folic acid supplement during the periconceptional period and beyond is recommended. A full evaluation of the patient's medical status should be performed (see Table 2). Ideally, pregnancy management should include an interdisciplinary team who is familiar with high-risk pregnancy and the care of patients who have thalassemia. It is important to confirm that the patient has completed her hepatitis B and pneumococcal vaccines if she is asplenic. Baseline evaluation for cardiac, endocrine, and hepatic function is recommended at initial care and should be repeated in the second and third trimesters. Ferritin levels

and blood counts should be followed regularly [37]. Fetal growth and well-being should be followed closely because of the increased risk of growth restriction in these pregnancies.

Anemia

Regular blood transfusions correct the anemia, suppress erythropoiesis, and inhibit increased gastrointestinal absorption of iron. Generally, the transfusion frequency increases during pregnancy. To avoid sensitization, RBC antigen typing should include Rh, Kell, Kidd, and Duffy. Usually, transfusions are given every 2 to 3 weeks. Most investigators recommend that transfusion therapy should be aimed at keeping the hemoglobin level at 10 mg/dL [37,43,45].

Chelation therapy

After the age of 10 or 11 years, patients who have transfusion-dependent β-thalassemia major are at risk of developing severe complications that are related to iron overload. Complications of iron overload include cardiac (dilated myocardiopathy and pericarditis), hepatic (fibrosis and cirrhosis), and endocrine (diabetes mellitus, insufficiency of the parathyroid, thyroid, pituitary and adrenal glands). Iron chelation therapy with deferoxamine (DFO) is a mainstay of the modern management of patients who have thalassemia; however, its use in pregnancy remains controversial. In most reports, chelation therapy was stopped during pregnancy because of fetal concerns. Maternal ferritin levels are reported to be stable or increase mildly during pregnancy without chelation, possibly because of the role of the placenta in binding iron [45]. In some cases, patients have been continued on DFO throughout pregnancy. Of 40 cases of reported exposures to DFO during pregnancy, no adverse fetal outcomes were reported [46]. More data are needed in this area; however, it is reasonable to stop chelation therapy during the first trimester in women whose iron store levels have been under good control prior to conception. In the case of significant myocardial dysfunction, consideration should be given to continuing treatment throughout the pregnancy. DFO does not alter iron excretion into breast milk or newborn iron metabolism, and, therefore, is compatible with breast-feeding [41,47,48].

Cardiac function

Heart failure that is due to chronic anemia and iron overload remains the leading cause of death in patients who have β-thalassemia major. Pregnancy-associated cardiovascular changes exacerbated underlying cardiac disease, even in women who had normal baseline cardiac function [39,40,42]. Women who enter pregnancy with impaired left ventricular function or poor chelation status have a high mortality rate [37]; however, in women who have normal baseline status, the pregnancy-associated changes in cardiac function seem to be transient and returned to baseline after pregnancy [39].

Delivery

The mode of delivery should be individualized. Patients who do not have myocardial disease can be delivered vaginally; cesarean section can be reserved for obstetric indications. Cesarean section or passive delivery should be considered if hemodynamic stability of the mother is a concern [37]. Intraoperative blood salvage was reported during cesarean delivery that was complicated by placenta accreta in a patient who had β-thalassemia intermedia [49]. Cord blood banking should be considered at delivery (see later discussion).

α-Thalassemias

α-Thalassemias include a group of syndromes that is characterized by deficient production of the α-globin chain. Unlike the β-globin chain, there are no developmental or adult substitutes for the α-globin chain. In addition, there are four α-globin genes, two copies on each chromosome 16 (see Fig. 1). The normal α-globin gene compliment is designated αα/αα. Most cases of α-thalassemia are due to deletions, rather than point mutations, of the α-globin genes. Individuals who carry deletions of two α-genes on the same chromosome have the α-thalassemia-1 haplotype (−−/), also known as *cis* deletion or α^0-thalassemia mutation. Individuals who carry two deletions on opposite chromosomes have the α-thalassemia-2 haplotype, designated (−α/) or α^+-thalassemia. In Asian and Mediterranean populations, both types of deletions are seen; however, the *cis* deletion (−−/αα) is predominant. In African populations, the *cis* deletion is extremely rare. In contrast, the frequency of trans α-thalassemia trait (−α/αα) in some black populations is reported to be as high as 30% [1]. Four classic α-thalassemia syndromes are recognized based on the number and configuration of α-globin deletions: silent carrier state, α-thalassemia trait, Hemoglobin H (HbH), and Hemoglobin Bart's (Hb Bart's).

Silent carrier state

When one α-globin gene is nonfunctional or deleted (heterozygous α-thalassemia-2 [−α/αα]) the individual has no clinical symptoms and no RBC alterations. This status is undetectable clinically and is known as the silent carrier state. DNA analysis is necessary to detect the silent carrier state [1].

α-Thalassemia trait

Deletions of two of the four α-globin genes result in α-thalassemia. This can be caused by heterozygous α-thalassemia-1 (−−/αα) or homozygous α-thalassemia-2 (−α/−α). Clinically, the condition is mild and generally results in no significant hemolysis or anemia. The red cell indices show microcytosis and hypochromia. Usually, the hemoglobin electrophoresis is normal; however, the

MCV is decreased. Diagnosis is made by genotyping at- risk individuals. The genotype does not influence clinical presentation; however, is important in assessing fetal risks since because only individuals with heterozygous α-thalassemia-1 (−−/αα) are at risk of having a fetus that has HbH or Hb Bart's.

Hemoglobin H disease

Deletions of three α-globin genes (−α/αα) result in HbH disease. Because of the marked impairment of α-globin chain synthesis, excess β-globin chains form a tetramer that is known as HbH. This tetramer precipitates and forms inclusion bodies—Heinz bodies—that are seen on the peripheral smear. HbH disease is seen primarily in southeast Asian and Mediterranean populations because of the prevalence of the α^0-thalassemia allele in these populations [1]. Generally, HbH disease is associated with a mild hemolytic anemia; however, there is a marked variability in clinical symptoms that range from asymptomatic to severe anemia with hemolysis and hepatosplenomegaly. Although the condition is usually detected after birth, in some rare cases HbH disease can lead to hydrops fetalis with intrauterine demise [50]. Patients who have HbH disease may experience hemolytic crisis in response to infections; fever; ingestion of oxidative compounds and drugs; hypersplenism; and pregnancy. In these settings, severe anemia may necessitate transfusion support. Overall, from 29% to 50% patients who have HbH disease need periodic transfusions [50]. Iron overload may occur in more than 70% of adult patients who have HbH disease [51]. Iron absorption is increased in HbH disease as a result of enhanced erythropoiesis. Therefore, even patients who are not transfused should be evaluated for iron overload and treated with iron chelation therapy when needed. Splenomegaly is common in HbH disease; 5% to 30% of patients eventually requiring splenectomy. In addition, cholelithiasis is common and affects about one third of patients [50].

Hemoglobin Bart's disease

Hemoglobin Bart's disease occurs when no functional α-globin chains are produced. The unmatched γ-globin chains form tetramers that are known as hemoglobin Bart's. Generally, fetal hydrops occurs that leads to stillbirth or neonatal death. Until recently, this condition was universally fatal. With support through intrauterine transfusion and neonatal intensive care, survival is possible in some cases [52–54]. Survivors have a severe transfusion-dependant hemolytic anemia that is similar to β-thalassemia major. Bone marrow transplant and cord blood transplant has been used successfully in some infants who have Hb Bart's disease [55].

As the number of survivors with Hb Bart's has increased, it has become apparent that limb reduction defects and hypospadias are common findings in this disorder. Hypospadias and other urogenital abnormalities are a frequent

feature of survivors and have been observed in 30% to 100% of male survivors [56,57]. Limb abnormalities have been reported in 8% of fetuses who have Hb Bart's disease [58,59]. Generally, these abnormalities are transverse limb reductions and have been diagnosed as early as 12 weeks gestational age by ultrasound [60].

Pregnancy management in α-thalassemia

α-Thalassemia trait

Pregnancy is well-tolerated in individuals who have α-thalassemia-1 or α-thalassemia-2. Generally, anemia is not present or is mild. Pregnancy outcome is equivalent to the general population.

Genetic screening is an important aspect of prenatal care in this condition. If both of the parents are carriers of the α^0-thalassemia haplotype ($--/\alpha\alpha$) there is a 25% risk for the fetus to be affected with Hb Bart's disease. Genetic testing for this condition can be performed as early as 10 weeks gestational age by chorionic villous sampling (CVS). Ultrasound screening was shown to be useful in detection of Hb Bart's disease (see later discussion).

If the couple opts to continue an affected pregnancy, close follow-up of the mother is necessary. In Hb Bart's syndrome, a higher incidence of obstetric complications has been described, including pre-eclampsia (61%), polyhydramnios (59%), and retention of the placenta (50%) [61].

Hemoglobin H

Generally, women who have HbH are able to have a successful pregnancy; however, pregnancy often causes an acute exacerbation of the chronic anemia. Maternal hemoglobin levels may decrease to 6.0 g/L or less and often require supportive blood transfusions. Increased risks of pre-eclampsia and prematurity have been described as well as the new onset of congestive heart failure [50].

Treatment during pregnancy for a patient who has Hb H is primarily preventive and supportive in nature. Baseline evaluation of the patient's overall status should be performed as early as possible, preferably preconception. This includes evaluation of baseline hematologic indices, iron load status, cardiac function, and liver function. The degree of splenomegaly and the presence of cholelithiasis should be documented. Periconceptual folic acid supplement is recommended; however, iron supplements should be given only in the presence of documented iron deficiency. Avoidance of oxidative compounds and medications, prompt treatment of infections, and alertness to the possibility of hypersplenism or aplastic anemia are indicated. If the patient has significant iron

overload, baseline evaluation of end-organ effects should be performed as outlined for β-thalassemia (see Table 2).

As with α-thalassemia, an important aspect of the maternal care should include screening of the patient for thalassemia carrier status. If the partner is a silent carrier of the α^+-thalassemia haplotype, there is a 25% risk that the baby will be affected with HbH. If the partner carries the α^0-thalassemia haplotype, there is a 25% chance of HbH and a 25% chance of Hb Bart's. Because the α^+-thalassemia haplotype is not detectable clinically, partners should have DNA-based genotype testing if standard evaluation with MCV and electrophoresis is normal [50]. As with α-thalassemia-1, if the couple is at risk for a fetus with Hb Bart's or HbH, prenatal diagnosis should be offered.

Genetic issues in hemoglobinopathies

The care of the pregnant patient who has a hemoglobinopathy must address the inherited nature of her condition in regards to herself and the fetus, and, increasingly, in regards to other family members. Although the patient who is affected with sickle cell trait or α^0-thalassemia may not experience any clinical symptoms or be aware of her carrier status, her fetus may be at risk of in utero demise or severe disease after birth. Genetic testing for the hemoglobinopathies, therefore, involves screening of asymptomatic individuals who are at high risk of being carriers. Prenatal diagnosis should be made available to couples who are known to be at risk for an affected baby. Recently, the value of cord blood as a source of stem cells for transplant has been recognized. The role of the fetus as a cord blood donor for other family members is also an important consideration in patients who have hemoglobinopathies.

Carrier screening

As the most common single-gene disorder in the worlds, the care of individuals who have clinically-significant hemoglobinopathy presents a significant public health problem. Modern treatment has improved life expectancy and quality of life greatly; however, the treatment is expensive and requires technology that is not accessible to many developing countries. This has resulted in great interest in population screening in endemic areas. Worldwide, over the past 30 years, carrier screening programs for the hemoglobinopathies have been implemented in many high-risk populations. As a general guideline, the foremost goal of a carrier screening program is to decrease the incidence of disease, and, thereby, decrease the burden of disease on society [62]. Carrier frequency, test sensitivity, pretest education, reproductive options that are available to couples who are at risk for having an affected child, and cost-effectiveness of the screening program are important factors that must be taken into consideration by any public health organization that attempts to organize population genetic

screening for any condition [63]. Historically, carrier screening programs for hemoglobinopathies have had variable success.

The first nationwide carrier screening program in the United States was for sickle cell anemia and is now acknowledged to have been disastrous [64]. From its inception, the sickle cell program lacked the resources and educational programs that are needed to enable people to understand the information that they are given. Laws that required widespread screening were passed nonetheless and many carriers mistakenly believed that they had the disease [64]. Stigmatization ensued and many carriers were denied health insurance. Eventually, this program was abandoned. The experience, however, provides insights into the potential pitfalls of implementing population-wide carrier screening programs.

In contrast, carrier screening for β-thalassemia in Cyprus, although socially controversial, resulted in the virtual elimination of affected homozygote newborns in that region [65]. The Cypriot population has one of the highest incidences of β-thalassemia major in the world; 1 in 1000 individuals are affected with the disease and 1 in 7 individuals are heterozygous [66]. The Cypriot government expends more than 40% of the drug budget of their Ministry of Health to provide medication free of charge to all patients who have β-thalassemia major. The island state opted to start a carrier screening program in an effort to limit new affected births and preserve federal funds to aid in the treatment of the existing patients. A comprehensive β-thalassemia program was implemented in three phases, with a separate objective for each phase. The first objective was prevention of carrier marriages through health education, population screening, and genetic counseling. Prenatal diagnosis became available during the second phase of the program which enabled the second objective of prevention of affected births. Health education, population screening, and genetic counseling also were critical parts of this phase. The objective of the final phase was to provide the public with full choice before marriage. The target population for screening included relatives of homozygotes and high school seniors. Although many of the target population were screened, few made use of the knowledge, which was attributed in part to fears of stigmatization and adverse effects on marriageability [67]. The state's church opted to play an active role in the program and with the Thalassemia Center, introduced a ''premarital certificate''—a certificate of having been tested for β-thalassemia—that must be presented to the church by any couple who requests a church ceremony for engagement or marriage. These strategies that were used by the Cyprus government resulted in a reduction in homozygote births from 53 in 1974 to 2 in 1990. Although parts of the Cyprus β-thalassemia screening program can be construed as directive, the impact on the prevalence of disease is unarguable. The program's implementers point out that the introduction of the premarital certificate was met with no resistance or protest and was applauded by the community [62].

It is clear that an organized public health effort and concomitant extensive public education are critical parts of successful implementation of carrier screening programs.

Prenatal screening recommendations

Currently, in the United States, identification of high-risk couples and voluntary screening is recommended. The American College of Obstetrics and Gynecology (ACOG) recommends that "the obstetrician-gynecologist should try to identify couples at increased risk for having offspring with a form of thalassemia or sickle cell disease" [68]. High-risk groups that were identified by ACOG include those of African American, southeast Asian, Chinese, or Mediterranean ancestry. Northern European, Inuit, Native American, and Mexican populations are considered to be at low-risk for hemoglobinopathies.

The appropriate screening test for individuals who are identified as high-risk for hemoglobin structural disorders is hemoglobin electrophoresis. Other tests that are used for general primary screening are hemoglobin S solubility testing, isoelectric focusing, and high performance liquid chromatography (HPLC). Solubility testing fails to identify other transmissible hemoglobin variants that play a role in fetal outcome. The hemoglobin S solubility testing is valuable as a rapid screening tool when the information is critical for immediate patient care.

MCV should be obtained for patients who are at increased risk for β- or α-thalassemia. Those who have an MCV level that is less than 80 μ^3 may be a carrier of one of the thalassemia traits and should undergo hemoglobin electrophoresis. Elevated HbF and HbA_2 that are greater than 3.5% are associated with β-thalassemia. α-Thalassemia can be detected only through molecular genetic testing. When an MCV is below normal, iron deficiency anemia has been excluded, and hemoglobin electrophoresis is not consistent with β-thalassemia trait, molecular genetic testing should be offered to detect α-globin gene deletions that are characteristic of α-thalassemia [68].

Approaches to prenatal diagnosis

If a couple has a significant risk to have a fetus who has a significant hemoglobinopathy, prenatal diagnosis should be offered. This is performed most accurately by direct DNA analysis, although ultrasound can be useful in screening for some α-globin disorders.

Ultrasound

Ultrasound is not a useful screen for structural hemoglobin disorders or in β-thalassemia; however, it may be useful in disorders of α-globin synthesis. Hb Bart's disease, and, at times, HgH disease results in fetal anemia as a result of the absence of α-globin chain synthesis and resultant lack of HbF. Hydrops fetalis is the classic sign of Hb Bart's disease but it may be a late finding and usually develops after 20 weeks' gestation. Only 7% of affected fetuses at 12 to 14 weeks' gestation and 33% of affected fetuses by 17 to 18 weeks' gestation show overt hydrops on ultrasound [69].

Increased placental thickness can be seen before the onset of hydrops. Ko et al [70] demonstrated that in a group of 51 affected fetuses, the placental thickness was above the mean in all cases and was two standard deviations above the mean in 90% of cases when measured between 14 and 23 weeks' gestation [70].Using a cutoff of two standard deviations above the mean for gestational age, ultrasound had a sensitivity of 72% and a specificity of 97% before 12 weeks' gestation. At more than 12 weeks' gestation, the sensitivity was 95% and reached 100% after 18 weeks' gestation [71]. Using a midtrimester placental thickness of more than 30 mm as a screening cutoff resulted in a sensitivity of 88.6%, a specificity of 90.2%, a positive predictive value of 78.5%, and a negative predictive value of 96.9% [72].

Cardiovascular changes are detectable by Doppler ultrasound in the early second trimester. Increased cardiac output, increased forward velocities in the ductus venosus, and increased middle cerebral artery flow were documented in affected fetuses between 12 and 13 weeks' gestation [73–75]. Cardiomegaly, as measured by the cardiac to thoracic circumference ratio, also is present as an early sign in affected fetuses. In a study of 345 pregnancies with 70 affected fetuses, the mean cardiothoracic ratio at 18 to 20 weeks' gestation was 0.55 in the affected group compared with 0.45 in the control group. Using a cutoff of 0.50, the sensitivity of this measurement was 98.6% and the specificity was 98.9% for prediction of Hb Bart's disease [76]. Ultrasound screening, if validated by further studies, may be useful in decreasing the need for invasive prenatal diagnostic testing by limiting invasive testing to cases where ultrasound indicators are present.

Prenatal diagnosis

Prenatal diagnosis of hemoglobinopathies was first performed by fetal blood sampling and estimating the relative rate of globin chain synthesis. Although this method was successful, the advent of gene mutation analysis has replaced fetal blood sampling in virtually all cases. Currently, prenatal diagnosis is accomplished most commonly by obtaining fetal DNA by CVS or amniocentesis. CVS is performed at 10 to 12 weeks' gestation and involves obtaining a sample of chorionic tissue by transcervical or transabdominal aspiration. The procedure has the advantage of being completed early in pregnancy and of yielding large amounts of DNA without the need to wait for the growth of cells in culture. The procedure-related complication rate is 1% to 2%. Amniocentesis is performed at 15 to 20 weeks' gestation and involves obtaining a sample of amniotic fluid by transabdominal aspiration. The procedure-related complication rate is 0.5% to 1.0% [32]. Fetal blood sampling by cordocentesis can be used to obtain DNA as well as to analyze globin chain synthesis. Fetal blood sampling at 12 to 14 weeks' gestation for diagnosis of Hb Bart's disease has been advocated for areas where resources for molecular studies are limited [77].

DNA diagnosis

Structural hemoglobin mutations

Prenatal diagnosis by direct mutation analysis is commercially available for the common structural globin chain mutations. HbS is caused by an A-T substitution in the second nucleotide of the sixth codon of the β-globin gene. This mutation destroys the recognition site for several restriction enzymes, including Mni I, Dde I, and Mst II [32]. Mutation analysis for diagnosis of sickle cell anemia is available using polymerase chain reaction (PCR) and restriction fragment analysis. HbC, the second most common hemoglobin variant in the United States, is caused by a G-A substitution in the first nucleotide of codon 6 on the β-globin gene and also is detected readily by mutation analysis. HbE results from a G-A mutation at codon 26 in the β-globin gene. This mutation abolishes an Mnl I restriction endonuclease site and also can be detected by PCR and RFLP analysis [32].

β-Thalassemia

The β-thalassemias are extremely heterogeneous at the gene level; more than 200 β-globin mutations have been described. The mutations are distributed geographically so that for a given high-risk population, there are only 4 to 10 dominant mutations. Therefore, the general approach to the molecular diagnosis for β-thalassemias is to identify and test for the region-specific mutations based on the patient's ethnic background. This approach identifies the mutation in more than 90% of the cases. If the mutation is not identified, screening for the broader range of mutations is performed. In the rare cases where a mutation is not found, DNA sequencing can be performed [32].

α-Thalassemia

Most α^--thalassemia alleles are caused by deletion of the affected α-globin genes. Generally, these deletions and common mutations are detectable by quantitative PCR or southern blot analysis [32]. Genetic screening and testing in α^--thalassemia is complicated by the fact that there are four α-globin chains; an individual who carries a single gene deletion is clinically undetectable. In addition, the reproductive implications of having two gene deletion varies depending on whether the deletions are on the same chromosome 16 (*cis*) or on opposing chromosomes (*trans*) (see later discussion).

Counseling issues

Although the inheritance of single-gene disorders is straightforward, appropriate genetic evaluation and counseling can be complex in the hemoglobinopathies. This is especially true when dealing with the common situation of

compound heterozygotes or hemoglobin-thalassemia variants. For example, couples who are heterozygous for a β-thalassemia mutation have a 25% chance of having a child who has β-thalassemia major and a 50% chance of having a child who has β-thalassemia minor. Heterozygous carriers of β-thalassemia who have a low MCV and elevated HbA_2 levels also may be heterozygous for α-thalassemia−1. Depending on the α-globin and β-globin genotypes of their partners, these individuals may be at risk of having offspring who have HbH disease, Hb Bart's disease, or β-thalassemia major.

Counseling and assessment of fetal risk also have to take into account the ethnic and likely geographic origin of the patient, especially in α-thalassemia. HbH disease and Hb Bart's disease only occur when one or both of the parents carry the *cis* mutation—heterozygous α-thalassemia-1 (−−/αα). The *trans* mutation also is found globally; however, the cis mutation is found almost exclusively in southeast Asia and in the Mediterranean region. Couples who have α-thalassemia from this region have a high probability of being heterozygous for α-thalassemia−1, and, therefore, have a 25% risk of Hb Bart's disease. In sub-Saharan Africa, where there is a high rate of α-thalassemia, the genotype is overwhelming due to homozygous α-thalassemia-2 (−α/−α). Couples who have homozygous α-thalassemia−2 do not have a risk for a fetus with Hb Bart's disease or HbH disease and fetal testing generally is not recommended [32].

If a fetus is found to be affected with a clinically-significant hemoglobinopathy, comprehensive counseling and support should be offered. The couple should receive information regarding the diagnosis, the expected natural history of the condition, and available treatment options, even if they are familiar with the condition because they already have an affected child. The clinical severity may differ considerably between affected individuals within the same family. Although the genotype is identical, there is considerable variability of phenotypic expression of the disorder as a result of the interaction of regulator genes and metabolic factors that play a role in the clinical course of the disease in affected individuals [32].

Because of these potential complexities, referral of at-risk couples to a center that has expertise in prenatal diagnosis, genetics, and genetic counseling is recommended.

Perinatal therapy

Preimplantation diagnosis

In couples who have a known risk for hemoglobinopathy, preimplantation genetic diagnosis (PGD) has been used successfully to achieve the birth of an unaffected fetus. This technique, although it has the disadvantage of requiring in vitro fertilization, avoids the need for termination of an affected pregnancy, and, therefore, may be more acceptable or the only acceptable option for some couples [78]. After oocyte harvest and fertilization, single-cell analysis usually is

done at the blastomere stage or by using polar body analysis. DNA analysis using PCR and restriction digestion, or, recently, direct sequencing of PCR products, is then performed [79–82].

In one series of 43 cycles, diagnosis was achieved for 236 embryos with implantation of 100 out of the 125 unaffected embryos. Of the remaining 10 pregnancies that continued beyond the first trimester, 9 were confirmed unaffected by second trimester diagnosis, whereas was one a PGD misdiagnosis [79]. Couples also have sought to use preimplantation diagnosis to produce a stem cell donor for an affected sibling, although ethical concerns have been raised regarding this procedure [83].

Intrauterine therapy

Intrauterine blood transfusion and exchange transfusion in utero has been used with good success to treat fetuses who were affected with Hb Bart's disease [52,53]. Before embarking on this course of treatment, however, the parents should be counseled carefully regarding the fetal and maternal risks of this treatment. A detailed ultrasound examination is important because of the association of limb defects. In addition to procedure-related complications, the patient should be aware of the increased risk of pre-eclampsia, preterm birth, polyhydramnios, and delivery complications that are reported in pregnancies with Hb Bart's disease [61]. The postnatal prognosis for the fetus should be considered. Survivors of in utero therapy have severe transfusion-dependant anemia and a recently recognized high incidence of urogenital abnormalities [54,57]. Bone marrow transplantation has been used successfully to treat Hb Bart's disease and would be an important therapeutic option. HLA typing of the fetus can be performed to determine the availability of an HLA-matched donor in the family. This information may be helpful to parents who are deciding whether to consider aggressive in utero therapy.

Intrauterine stem cell transplantation has been explored as an attractive alternative to postnatal transplant. The results have been disappointing to date, however, and show poor levels of donor chimerism and persistent transfusion dependency after birth [84,85].

Human leukocyte antigen typing and cord blood collection

Although transfusion/chelation therapy has improved outcomes significantly in individuals who have thalassemia, bone marrow or stem cell transplant is the only curative procedure for thalassemia and other hemoglobin disorders. Traditionally, most transplants have been performed using related donor bone marrow. Umbilical cord blood is a source of implantable stem cells and is being viewed increasingly as a valuable source of donor cells.

DNA analysis for hemoglobinopathies, especially in the thalassemias, is being combined increasingly with fetal HLA typing [86]. In an affected fetus, this information can be used to determine the availability of HLA-matched donors

within the family for an affected fetus at birth. The availability of a known HLA-matched donor significantly improves the outcome for an affected baby and may influence the parents' decisions regarding the pregnancy. Prenatal HLA typing also has been used to determine if the fetus would be a suitable umbilical cord blood donor for an affected sibling. Studies in cord blood transplant in related donors showed an acceptable engraftment rate and a lower risk of chronic graft-versus-host disease than is seen in traditional bone marrow transplant [87–89]. It also was suggested that cord blood could be used as a heterologous transplant for the affected mother [48], although clinical experience with this is limited. Cord blood may be a valuable resource so that families who have the potential for the birth of a child who has hemoglobinopathy should consider cord blood banking [89].

Pediatric considerations

Newborn screening

The United States' Newborn Screening Program functions to provide early identification of conditions for which appropriate, timely treatment can lead to a reduction in the mortality and morbidity that are associated with certain diseases [90]. Children who have sickle cell anemia are at an increased risk for bacterial infection as neonates. Prophylactic penicillin, in children who have the disease, decreases the risk for pneumococcal septicemia by 84%. This led to the implementation of newborn screening for sickle cell anemia [91]. Since then, the primary purpose of neonatal screening for hemoglobinopathies is the identification of infants who have sickle cell disease.

Neonatal screening also identifies affected or carrier infants who have other hemoglobin variants and some thalassemia syndromes [92]. Most infants who have β-thalassemia syndromes are not identified by neonatal screening [93]. In the United States, 41 states and the District of Columbia provide universal screening for sickle cell disease. Three states screen newborns in high-risk ethnic groups; the remaining 6 states provide no sickle cell disease screening [90]. The 9 states where screening is not routine have the lowest incidence of disease in newborns. The methods that are used by each state vary and include high performance liquid chromatography (HPLC), isoelectric focusing (IEF), and cellulose acetate electrophoresis. It is recommended that samples that screen positive initially should be retested using other DNA-based assays, HPLC, or immunologic tests.

The clinical interpretation of initial hemoglobinopathy newborn screening results can be complex. Confirmatory testing should be completed by 6 weeks of age. This stage of testing may be diagnostic or only may confirm the initial hemoglobin phenotype that was obtained through newborn screening [92]. Often, additional diagnostic testing is necessary. Most infants who have homozygous HbS show HbF and HbS by newborn screening. All infants who have a positive screen should begin to receive prophylactic penicillin by 2 to 3 months of age

and should continue to receive it until at least age 5 [92]. Infants who have HbS and S β^0-thalassemia also should receive prophylactic penicillin through 5 years of age. Diagnostic testing for other genotypes should be performed by 6 weeks of age and include hemoglobin separation; IEF; HPLC; cellulose acetate electrophoresis; citrate agar electrophoresis; and serial complete blood cell, MCV, and reticulocyte counts [92]. DNA analysis or family studies are diagnostic early in infancy; however, MCV, HbA_2 and HbF quantization and assessment of the cellular distribution of HbF are most informative between 6 months and 2 years of age [92]. Clinically significant nonsickle hemoglobinopathies, such as HbFC, HbFCA, HbFE, and HbF, require further analysis for accurate diagnosis. Newborn infants who express HbF in greater concentrations than HbA, may have severe thalassemia and should undergo repeat hemoglobin electrophoresis at 2 to 3 months of age. Family studies also should be considered. Some premature infants who have a normal hemoglobin profile also may exhibit HbF only.

Early diagnosis facilitates implementation of proper preventive health care measures to: (1) ensure the well-being of the affected infants, (2) ensure prompt treatment of potentially serious hemolytic crises and infections, and (3) alleviate unnecessary parental distress by early education and support by a multidisciplinary team.

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Thromboembolic disease in pregnancy

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Incidence and importance

Venous thromboembolic disease, although uncommon, is a major cause of maternal morbidity and mortality during pregnancy and the puerperium; it accounts for nearly half of all obstetric morbidity [1–8]. Thromboembolism is reported to occur in approximately 1 in 1500 deliveries [8,9]; a threefold to eightfold increased risk is reported in the puerperium [1–9]. Thromboembolic events include superficial thrombophlebitis, deep vein thrombosis, ovarian vein thrombosis, septic pelvic thrombophlebitis and thrombosis, and pulmonary embolism (PE).

Thromboembolic disease is the leading cause of maternal mortality in the Western world and is responsible for 17% of maternal deaths [1,4,6–11]. The incidence of PE depends on the adequacy of diagnosis and treatment of deep vein thrombosis (DVT) [6,12]. Untreated DVT may result in PE in up to 24% of pregnant patients, with an associated mortality rate of approximately 15% [4,5]. Appropriate treatment with anticoagulation decreases the rate of PE to 4.5% with a mortality rate of less than 1% [4,5].

The risk of venous thromboembolism (VTE) is five to six times higher in pregnant women as compared with nonpregnant women [1,3–11]. Although early studies suggested a postpartum predominance, these were affected by the practices of prolonged bedrest and hospitalization following vaginal and cesarean delivery and the use of high-dosage estrogen for lactation suppression. More recently, it was shown that events occur with equal frequency during the antepartum and postpartum periods [4,5].

Pregnant women who are younger than 35 years have decreased prevalence compared with older, pregnant women [3–6]. The prevalence also is higher in

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women who have congenital abnormalities; persistent presence of antiphospholipid antibodies; and well-defined inherited thrombosis risk factors, such as Factor V:R506Q mutation, factor II:G20210A variation, dysfibrinogenemia, antithrombin III deficiency, or protein C/S deficiency [1–14].

Women with a history of VTE have an approximately 3.5 fold increased risk of recurrent VTE during pregnancy [15].

Other risk factors for VTE include operative delivery, weight over 80 kg, increased parity, varicosities, trauma, infection, blood type other than type O, congestive heart failure, dehydration, shock, disseminated cancer, dysproteinemia, polycythemia vera, anemia (especially sickle cell), antiphospholipid syndrome, myeloproliferative disorders, mechanical heart valves, and family history [5,8,11,16].

Normal physiology

Hemostasis, the process of blood clotting and the subsequent dissolution of the clot following repair of the injured tissue, is necessary for survival. Hemostasis is composed of four major events that occur in a set order. The initial phase is vascular constriction. This is followed by phase 2, in which platelets become activated and aggregate at the site of injury, forming a temporary loose platelet plug. Fibrinogen is primarily responsible for stimulating platelet clumping. Upon activation, platelets release adenosine-5′-diphosphate, ADP, Thromboxane (TXA2), serotonin, phospholipids, lipoproteins and other proteins that are important for the coagulation cascade. Phase 3 involves formation of a fibrin mesh (clot), whereas phase 4 is dissolution of the clot through the action of plasmin (Fig. 1).

Two pathways—intrinsic and extrinsic—lead to the formation of a fibrin clot. Although they are initiated by distinct mechanisms, they converge on a common pathway (Fig. 2). The intrinsic pathway is stimulated in response to abnormal vessel wall in the absence of tissue injury, whereas the extrinsic pathway is

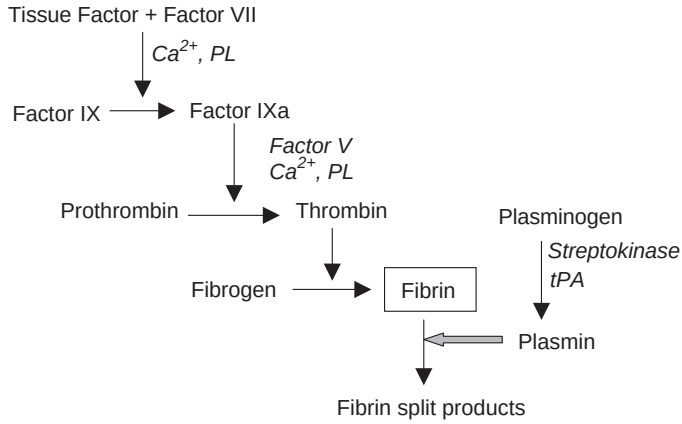

Fig. 1. Process of hemostasis. PL, phospholipid; tPA, tissue plasminogen activator.

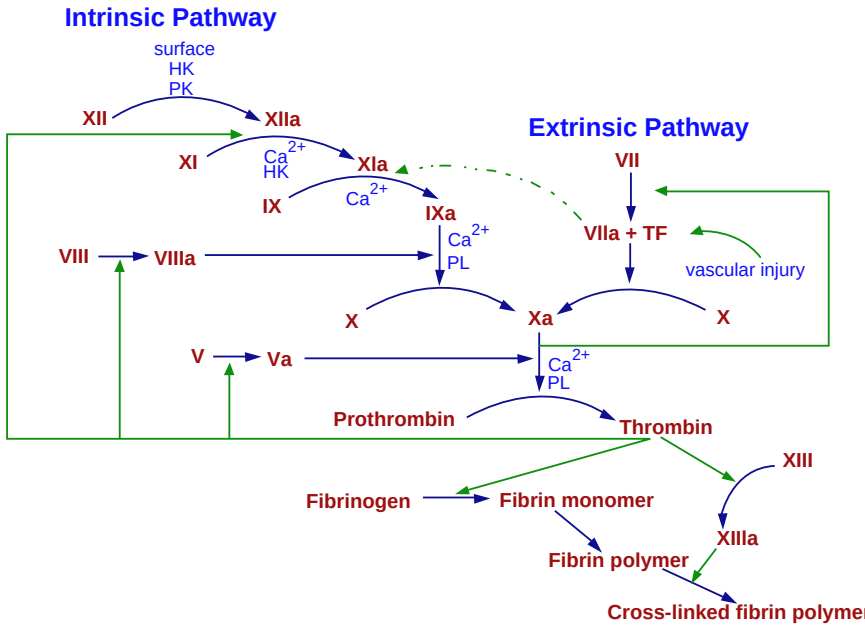

Fig. 2. Clotting cascade. TF, tissue factor.

stimulated in response to tissue injury. The cascade is complex, involves the interaction of many factors (Fig. 3), and has the potential to malfunction at any one of several points. Most often the malfunction results in a hypercoagulable state and increased risk of thromboembolic disease.

Pathophysiology

Virchow's triad of underlying factors in venous thrombosis—hypercoagulability, venous stasis, and vascular damage [17]—all occur in pregnancy [4–6,8,18]. The normal physiology of pregnancy may be prothrombotic, with evidence for increased markers of activated coagulation and coagulation factors. During pregnancy, increases in procoagulant factors, such as von Willebrand factor, factors V, VII, VIII, IX, X, XII and fibrinogen, occur with a decrease in factors XI and XIII, an acquired resistance to the endogenous anticoagulant, activated protein C, and a reduction in protein S, the cofactor for protein C (Fig. 4). These changes are accompanied by impaired fibrinolysis through increases in plasminogen activator inhibitors 1 and 2; the latter is produced by the placenta [5,19]. There also is a marked reduction in the release of tissue plasminogen activator (t-PA) in response to venous occlusion [20,21], coupled with a rapid inhibition of circulating t-PA in pregnancy [22,23]. Venous stasis occurs by the end of the first trimester and reaches a nadir at 36 weeks' gestation [3]. Endothelial damage to pelvic vessels can occur secondary to compression of the inferior vena cava and iliac veins by the pregnant uterus and resulting stasis [4] or during vaginal or

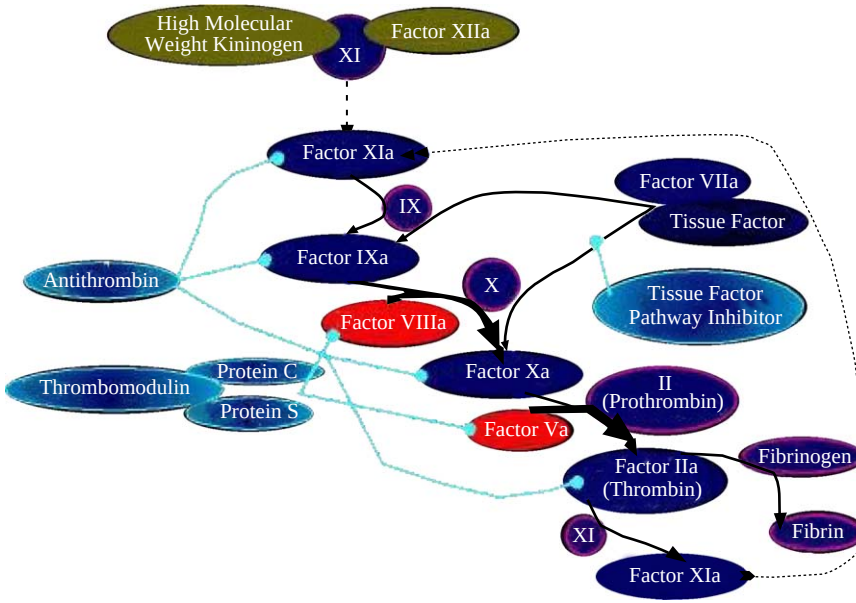

Fig. 3. Interaction of Clotting Factors.

abdominal delivery [3,8]. Thus, each element of Virchow's triad plays a role in the increased risk of thromboembolism during pregnancy and the puerperium.

Almost 90% of DVTs affect the left side in pregnant women compared with 55% among women who are not pregnant [3,24]. This may be due to compression of the left iliac vein by the right iliac and the ovarian arteries that cross the vein on the left side only. Furthermore, most cases of DVT in pregnancy are

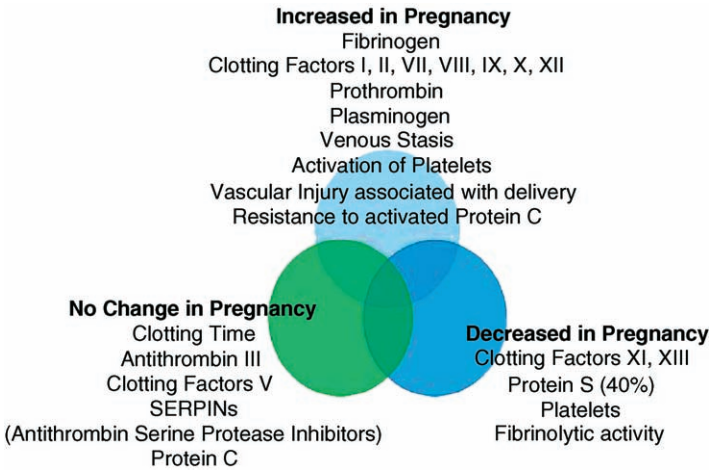

Fig. 4. Changes in pregnancy.

ileofemoral rather than calf vein thrombosis (72% versus 9%) and ileofemoral DVTs are more likely to lead to pulmonary thromboembolism [3,4].

Genetic/inherited coagulopathies/thrombophilia, intrauterine growth restriction, and pre-eclampsia

Thrombophilia is a term that refers to several specific abnormalities that result in an increased tendency toward hemocoagulation, which increases the risk of venous thromboembolic disease [10]. Acquired or hereditary thrombophilias occur in almost two thirds of women who present with recurrent miscarriages, pre-eclampsia, intrauterine (IUGR) restriction, abruptio placentae, or stillbirth that are associated with microvascular thrombosis in placental blood vessels [11,25–32]. Heritable coagulopathies are found collectively in 32% to 44% of women who have thromboembolic disease in pregnancy and the puerperium and in 10% to 15% of the Western population [2,3]. One study reported that the incidence of inherited or acquired thrombophilias in pregnancy that was complicated by severe pre-eclampsia was 68% [25].

It is apparent that thromboembolic disease during pregnancy is associated with a higher rate of inherited thrombophilia [2,3,10–12,14,18,25,33,34]. Recognized inherited thrombophilia abnormalities include factor V Leiden and prothrombin gene 20210A mutations, antithrombin III, protein C and protein S deficiencies, dysfibrinogenemia, and hyperhomocysteinemia. Acquired disorders include the anticardiolipin antibodies and lupus inhibitor [1,4,6]. Thrombophilia is a risk factor for thrombosis; however, the magnitude of risk varies with the specific type of thrombophilia.

Heritable coagulopathies may present as venous thrombosis at a young age. The recurrence rate is high; more than 50% of cases that present at a young age develop a repeat thrombotic event. Usually, a positive family history exists. Also, thrombotic events at unusual sites, such as the sagittal, mesenteric, or portal veins, may be associated with a heritable coagulopathy [12].

Inherited thrombophilia is found in approximately 50% of women who have a personal or family history of VTE [7,8]. Retrospective studies reported that the risk of thromboembolism during pregnancy among women who had thrombophilia in the absence of an anticoagulant was 32% to 44%; however, the rate depends on the type of abnormality and the presence of multiple abnormalities [3,14].

Congenital thrombophilia and fetal loss

Maternal thrombophilia carries an increased risk of fetal loss that is due to placental vascular disorders. A significantly higher prevalence of activated protein C resistance was reported in women who had recurrent miscarriages (including at least one second-trimester loss) [26,28]. A significantly higher prevalence of factor V Leiden mutations was reported in cases of recurrent miscarriage, particularly in the second trimester [27,29,34,35]. A higher fre-

quency of placental infarction in pregnancies that were associated with maternal and fetal carriage of factor V Leiden mutation also was reported [27,29,33]. Several investigators also reported an increase in fetal loss, stillbirth, IUGR, and early severe pre-eclampsia in women who had thrombophilia [31,32].

Antithrombin III deficiency

Antithrombin III is the most important factor in the inhibition of thrombin. It also inhibits factors IXa, Xa, XIa, and XIIa of the clotting cascade. Antithrombin's effects are potentiated by heparin and antithrombin levels are unchanged during pregnancy.

Antithrombin III (AT-III) deficiency is inherited as an autosomal dominant trait. It is a heterogeneous defect; 79 different mutations have been identified in the antithrombin gene. Of the known defects, 6 mutations that are associated with an increased risk of venous thrombosis have been identified [4].

Type I AT-III is associated with decreased antigenic levels and functional activity of AT-III. Type II displays normal antigenic levels, but decreased functional activity of ATIII. In a retrospective study of approximately 72,000 pregnancies, the risk of VTE was 1 in 2.8 in pregnant woman who had type I (quantitative) antithrombin deficiency and was 1 in 42 in pregnant women who had type II (qualitative) antithrombin deficiency [4].

One percent of patients who have thromboembolism have AT-III deficiency. Although uncommon, AT-III deficiency is associated with the highest risk of thromboembolic disease, with a prevalence in the general population of between 1 in 2000 and 1 in 4000 [35,36]. Individuals who have AT-III deficiency have a 70% lifetime risk of symptomatic thrombi or embolic disease; 2% to 3% of patients who are hospitalized for recurrent thrombi have an AT-III deficiency [36–38].

Almost two thirds of pregnant women who have a congenital AT-III deficiency experience a thrombotic event; most of these occur antepartum [14,39]. There is a 50 to 250 fold increased risk of thromboembolic disease in pregnancy. There also is a high (5.2 fold) increase of stillbirth in women who have AT-III deficiency.

The autosomal-dominant inheritance pattern dictates that the fetus carries a 50% risk of acquiring AT-III deficiency and should be tested after birth. AT-III levels that are less than 30% indicate a need for neonatal treatment with AT-III concentrate or fresh frozen plasma to prevent fatal neonatal thrombosis [40].

Protein C deficiency

Protein C, a vitamin K–dependent protein, exerts negative control of the clotting cascade after activation by thrombin (Fig. 5). Thrombin activates protein C by attaching to endothelial cells, promoting fibrinolysis, and inactivating factors Va and VIIIa [4]. Deficiency of protein C results in disruption of normal clot dissolution. In normal pregnancy, protein C activity is not altered. Resistance to activated protein C occurs in a significant number of pregnancies in

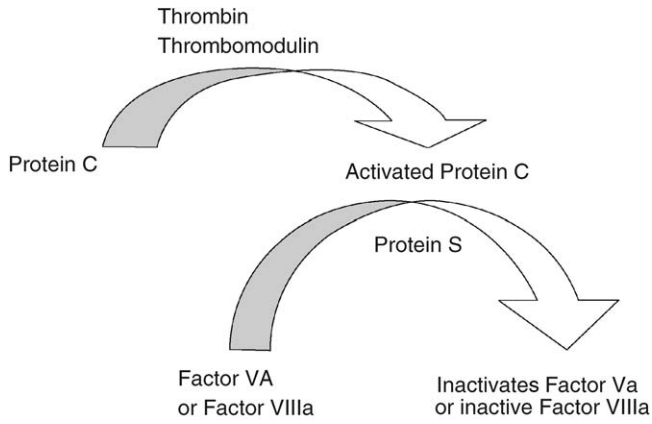

Fig. 5. Role of protein C and protein S.

the absence of the factor V Leiden mutation [1,41–44]. This is because the presence of factor V Leiden mutation impairs the ability of activated protein C and protein S to inactivate factor Va (see Fig. 5).

Protein C deficiency also is associated with an increased risk of pregnancy complications [17,45]. A twofold to threefold increase in the rate of stillbirth and a 16% rate of pre-eclampsia have been reported in women who have protein C deficiency [2,26,28,30].

Protein C deficiency is inherited in an autosomal dominant fashion. It is genetically heterogeneous, with more than 160 different mutations in the protein C gene [4]. Heterozygotes have protein C antibody levels that are 50% greater than those of normal individuals [41]. Autosomal recessive inheritance of protein C was observed in families with newborns who had severe thrombosis that resulted from homozygous or compound heterozygous protein C deficiency [42].

Heterozygocity for protein C deficiency is found in 0.3% of the general population and is a significant risk factor for venous thrombosis [30,46]. The lifetime risk of thromboembolic disease for women who have protein C deficiency is 50%. The risk of thrombosis in pregnancy was reported to range from 10% to 30% [14]; however, there is a 100-fold increased risk of thromboembolic disease in pregnancy for women who have Protein C deficiency. Postpartum, the thrombotic risk for women who have protein C deficiency is 7% to 19% [3].

Protein S deficiency

Protein S, a cofactor for protein C, is another vitamin K–dependent factor of hemostasis (see Fig. 5). Free protein S binds to protein C and dampens the clotting cascade. Total and free protein S decreases by 40% in pregnancy. Protein S deficiency is an autosomal-dominant disorder and has a prevalence of 0.08% [46]. Several mutations have been reported. Deficiencies in protein S vary

in the site of mutation and severity of disease. Heterozygous patients have levels of protein S that are 50% of those in normal individuals [4].

Women who have protein S deficiency have a 10% to 30% risk for thromboembolic events during pregnancy [14]. The lifetime risk of thromboembolic disease for women who have protein S deficiency is 50%. The neonate is at risk to inherit this disorder and should be evaluated at birth. Pregnancy complications that are associated with protein S deficiency include a twofold to threefold increase in the rate of stillbirth and a 16% rate of pre-eclampsia [25,31,32].

Activated protein C resistance/factor V Leiden mutation

Resistance to activated protein C (APC) was first described in 1993 [43]. In most cases, the defect results from the substitution of adenine for guanine at nucleotide 1691 of the factor V gene (G1691A); this causes the arginine at residue 506 of the factor V molecule to be replaced by glutamine (Arg506Gln). More than 80% of cases with APC resistance are carriers of the same mutation in a gene of factor V, a G to A transposition [8,44]. The resulting protein is the factor V Leiden mutation, the most common heritable thrombophilic defect in whites.

Factor V Leiden mutation manifests as resistance to APC. The presence of Factor V Leiden mutation impairs the ability of APC and protein S to inactivate factor Va (see Fig. 5). The prevalence of factor V Leiden mutation varies by ethnicity; it is 5% to 9% for Europeans, 2% for Hispanics, 1% for African Americans, and is low (< 1%) for Asians [14,46]. The lifetime risk of thromboembolic disease for carriers of the factor V Leiden mutation is 30% [2,14]. During pregnancy, a 25% to 30% risk of thromboembolic disease exists for those who possess the homozygous factor V Leiden mutation [14,47]. This is a 50-fold increased risk of thromboembolic disease during pregnancy compared with unaffected women who are pregnant [2,14].

Factor V Leiden mutation was found in 3% of healthy subjects and 19% of patients who were hospitalized with DVT [35,47]. Heterozygotes had a 7.9-fold increased risk and homozygotes had a 91-fold increased risk of first DVT in one study [45]. In a study of 43 women who had the factor V Leiden mutation from symptomatic families, the overall rate of pregnancy-associated thrombosis was 14% [48]. Postpartum, this risk may be higher [49]. Other studies indicated a lower risk of thromboembolism. In women who did not have a history of thrombosis, the presence of a heterozygous factor V Leiden mutation in the prothrombin gene was associated with a pregnancy-associated thrombotic risk of approximately 1 in 400 [2,37].

An increased risk of pregnancy complications also was reported for women who had the factor V Leiden mutation [29,47,50]. Pregnancy complications include an increased risk of late fetal loss, possible increased risk of pre-eclampsia, and placental infarcts. The factor V Leiden mutation was detected in 20% of women who had obstetric complications, compared with 6% of women who did not have obstetric complications [27].

Hyperhomocysteinemia

Homocysteine is generated from methionine metabolism. Hyperhomocysteinemia is an established risk factor for venous and arterial thrombosis. Many forms exist; however, the most severe form is inherited in an autosomal-recessive manner and involves homozygosity for the thermolabile variant of methylenetetrahydrofolate reductase (MTHFR) [16,51]. A common mutation in this enzyme is a C-T substitution at nucleotide 677 [4]. Pregnancy is associated with decreased concentrations of homocysteine. Reported incidence rates of hyperhomocysteinemia in pregnancy range from 1% to 11% [46]. Folic acid supplements lower homocysteine concentrations.

The mechanism by which homocysteine induces atherosclerosis and thrombosis is not understood completely. Hyperhomocysteinemia induces dysfunction of the vascular endothelium with loss of endothelium-dependent vasodilatation and endothelial antithrombotic properties and proliferation of vascular smooth muscle cells, all of which are key processes in current models of atherogenesis and thrombosis [4].

Hyperhomocystinemia carries a 10% lifetime risk of thromboembolic disease. No clear data regarding the risk of thromboembolic disease in pregnancy for women who have hyperhomocysteinemia exists, although one case-control study reported that 29% of women who have homozygous MTHFR deficiency experience a VTE [14].

Hyperhomocysteinemia has been associated with an increase in pregnancy complications, including abruption placentae and placental infarction [25]. Other pregnancy complications include a 10% risk of stillbirth, 20% risk of severe preeclampsia, 33% risk of severe IUGR, and increased incidence of neural tube defects. It may be useful to measure folic acid and vitamin B_6 and B_{12} in women who have adverse pregnancy outcome; a deficiency of these vitamins can lead to acquired hyperhomocysteinemia, which is treatable with folic acid and vitamin B_6 supplements [52].

Prothrombin 20210A

Prothrombin is the precursor molecule of thrombin. Sequence variation of a G to A transposition in position 20,210 of the prothrombin gene recently was identified as a genetic risk factor for thrombosis. This mutation results in increased plasma prothrombin and a twofold to fourfold increased risk for thromboembolic disease; it is believed to be present in 2% to 3% of the general population [14,46].

This mutation in the prothrombin gene was found in 6% of patients who had a first episode of VTE. The risk for venous thromboses is increased three-fold [8]. The relative risk for VTE in pregnancy and the puerperium among carriers of the G20210A prothrombin gene mutation ranges from 4 to 15 [53,54]. In women who do not have a history of thrombosis, the presence of a heterozygous G20210A mutation in the prothrombin gene is associated with a

pregnancy-associated thrombotic risk of approximately 1 in 400 [3]. The laboratory diagnosis for the presence of the prothrombin 20210A allele relies on DNA analysis [4].

In addition to increasing the risk of thromboembolic events, this gene has been associated with an increased risk of pregnancy complications. Ten percent of women who had pre-eclampsia, abruption placentae, fetal growth restriction, and stillbirth carried this gene, as compared with 3% of women who did not have these complications [25].

Dysfibrinogenemia

Dysfibrinogenemia is a familial disorder of qualitatively abnormal fibrinogens. Various types include Amsterdam, Bethesda I and II, Cleveland, Detroit, Baltimore, Leuven, Los Angeles, Metz, Nancy, Oklahoma, Oslo, Parma, Paris I and II, Saint Louis, Troyes, Vancouver, Wiesbaden, and Zurich I and II,. Each subtype has its unique major defect. All disorders result in prolonged thrombin time, with the exceptions of Oklahoma (normal thrombin time) and Oslo (shortened thrombin time but still has abnormal thrombosis). It is a group of rare disorders that has a 1% rate of occurrence among selected (a certain group) patients who have thrombosis [4]. Inheritance patterns include autosomal dominant and autosomal recessive [35]. Most patients who have dysfibrinogenemia are asymptomatic or develop a pure bleeding diathesis. Rarely, a patient may present with venous or arterial thromboembolism that can be accompanied by mild bleeding [55]. An abnormal reptilase time or thrombin time is used to identify patients who have this disorder [4,55].

Acquired thrombophilias

Lupus anticoagulant/antiphospholipid antibody syndrome

The antiphospholipid syndrome is diagnosed when the patient tests positive for the lupus anticoagulant, has IgG anticardiolipin antibody in medium to high levels (IgG isotype >15–20 GPL units), or has thrombosis or recurrent pregnancy loss. The lupus anticoagulant, first identified in plasma of patients who had systemic lupus erythematosus, is a monoclonal antibody that reacts to the phospholipids from blood platelet membrane platelet factor 3, and, therefore, prolongs the phospholipids dependent tests, such as activated partial thromboplastin time (aPTT) and Russel's Viper Venom Titer (RVVT). These antibodies are associated with thrombosis. Antiphospholipid antibodies may be transient; therefore, testing is recommended on two occasions that are at least 12 weeks apart. When thromboembolism occurs in an unusual site, such as the portal, mesenteric, splenic, subclavian, or cerebral veins, the diagnosis of antiphospholipid syndrome should be considered [4].

Recurrent fetal loss and death of the fetus at or beyond 10 weeks of gestation is associated with antiphospholipid antibody syndrome (APAS). APAS also is associated with congenital heart block, IUGR, and early severe pre-eclampsia.

Patients who have circulating antiphospholipid antibodies are at increased risk for venous and arterial thrombosis. The risk of thromboembolism during pregnancy has been reported to range from 5% to 22% [56]. Recurrent thrombosis in patients who have APAS is common; one study noted a 69% recurrence rate [56]. Diagnosis and management of APAS is discussed elsewhere in this issue.

Screening for thrombophilia

Screening for thrombophilia should be considered in women who have a personal or family history of VTE, history of stillbirth, severe IUGR, severe pre-eclampsia, or a first degree relative who has a specific mutation. If the screening is performed at the time of thrombosis during pregnancy, it should be recognized that pregnancy induces changes in hemostasis parameters. These changes may not resolve completely until 6 weeks postpartum. Therefore, diagnosis of a congenital deficiency should be confirmed after delivery and preferably associated with a family study [14].

Screening should include protein C antigen activity levels, protein S antigen activity levels (free and total), fasting homocysteine levels or the MTHFR mutation, AT-III antigen activity levels, prothrombin G20210A mutation, factor V Leiden mutation, anticardiolipin IgG and IgM antibodies, and lupus anticoagulant [46]. Currently, there is no recognized role for universal serum screening for thrombophilia in pregnancy [8,12,46]. AT-III and protein C and protein S assays are functional and immunoreactive assays. Free and bound protein S are measured. Assessment for factor V Leiden mutation in a nonpregnant woman should include functional assay for APC resistance. In pregnant women, there often is physiologic APC resistance due to low protein S; identification of the factor V Leiden mutation by way of polymerase chain reaction (PCR) is required to make the diagnosis.

Testing for hyperhomocysteinemia relies on fasting homocysteine levels or the identification of MTHFR mutation by PCR. Folate and vitamin B deficiency should not be present because this may confuse the results. Prothrombin 20210A is identified by PCR.

Treatment of inherited/acquired thrombophilias

Women who have a history of VTE during pregnancy, and, especially those who have thrombophilia, require individualized management that is based on the type of defect, the family history, and the presence of additional risk factors [8,10,11,14]. These risk factors are crucial in determining the dosage and duration of antithrombotic therapy during pregnancy and the puerperium and the thromboprophylactic strategy for future pregnancies [8]. Some investigators have recommended dividing women who have inherited coagulopathies into high-,

Table 1
Inherited thrombophilias

Thrombophilia	Inheritance mode	Risk for thromboembolism	Diagnostic test	Incidence	Recommended treatment	Other
Antithrombin III deficiency	Autosomal dominant	Very high	AT-III antigen activity levels	1 in 2,000 to 1 in 4,000 in general population	Therapeutic anticoagulation at diagnosis of pregnancy then at least 4–6 months postpartum	Type I: decreased antigenic levels and functional activity. Type II: normal antigenic levels, decreased functional activity of AT-III.
Factor V Leiden mutation		High (homozygotes) Moderate (heterozygotes)	DNA analysis for factor V Leiden mutation and APC resistance in pregnancy. Nonpregnant tests include functional assay for APC resistance, aPTT + APC then measure duration of prolongation.	Most common defect Prevalence 5–9%	Homozygous: therapeutic anticoagulation at diagnosis of pregnancy then at least 4–6 months postpartum Heterozygous: no antenatal anticoagulation, [a]antenatal ted stockings, postpartum prophylaxis 6 weeks	
Prothrombin 20210A		High (homozygotes) Moderate (heterozygotes)	DNA analysis for prothrombin G20210A mutation	2–3% of population	Homozygous: therapeutic anticoagulation at diagnosis of pregnancy then at least 4–6 months postpartum.	Associated with pre-eclampsia, abruption/fetal growth restriction, and stillbirth

					Heterozygous: no antenatal anticoagulation,[a] antenatal ted stockings, postpartum prophylaxis 6 weeks.	
Protein C	Autosomal dominant	High (heterozygous)	Protein C antigen activity levels		Heterozygous: therapeutic anticoagulation at diagnosis of pregnancy then at least 4–6 months postpartum	Neonates at risk. Two fold to three fold increased risk of stillbirth 16% rate of pre-eclampsia.
Protein S	Autosomal dominant	High	Protein S antigen activity levels. Test free and bound protein S.		Heterozygous: antenatal anticoagulation, antenatal ted stockings, postpartum prophylaxis 6 weeks.	Neonates at risk. Two fold to three fold increased risk of stillbirth 16% rate of pre-eclampsia.
Hyperhomocysteinemia		Low	Methionine load test/fasting homocysteine levels or the MTHFR mutation	10% Prevalence of homozygosity for MHTFR def in Europeans		Increase in placental abruption/infarction. 10% stillbirths. 20% severe pre-eclampsia. 1/3 severe IUGR.
Dysfibrinogenemia	Autosomal dominant and autosomal recessive	Low	Reptilase time or thrombin time	Rare–prevalence of 1%		

[a] In patients who have low or moderate risk and family history or combination defects consider antepartum anticoagulation.

medium-, and low-risk categories, based on the specific thrombophilic defect and any personal or family history of VTE [2,8,57]. Primary or secondary thromboprophylaxis should be considered in selected pregnant women who have inherited thrombophilias (Table 1).

In patients who are at highest risk for VTE disease (including those who have hereditary antithrombin deficiency, antiphospholipid antibodies, or a combined abnormality), therapeutic anticoagulation is advised starting in the first trimester.

Women who are at "high risk" (>10%) include those who have a history of idiopathic venous thrombosis or DVT while pregnant or on oral contraceptive pills; heterozygous protein C; combination defects; homozygous factor V Leiden; homozygous prothrombin 20210A; other hematologic, cardiac, or neurologic conditions, including artificial heart valves that requires anticoagulation; or who carry an additional hereditary risk factor; or have a positive family history of thrombosis [8]. Women who have the highest risk of VTE should receive therapeutic treatment dosages of heparin, preferably low molecular-weight heparin (LMWH), throughout pregnancy and should remain on anticoagulation for at least 6 weeks postpartum, or where appropriate, long term (see Table 1).

"Modest risk" includes women who have heterozygous protein S, heterozygous factor V Leiden plus a family history, or heterozygous prothrombin 20210A plus a family history [8]. Women who are at moderate risk should be treated with prophylactic fixed-dose LMWH throughout pregnancy and for at least 6 weeks postpartum (see Table 1).

Women who are at "low risk" are those who do not have a personal or family history of thrombosis and have heterozygous factor V Leiden or heterozygous G20210A mutation in the prothrombin gene (1 in 400) and women who had a single episode of thrombosis that was associated with a transient risk factor (eg, surgery or trauma) and no additional genetic risk factor [8,14]. Women at low risk should receive prophylactic fixed-dosage LMWH for 6 weeks postpartum.

Superficial thrombophlebitis: diagnosis and treatment

Thrombosis that is limited to the superficial veins of the saphenous system is treated with analgesia, elastic support, and rest. If improvement is not seen or if deep venous involvement is suspected, appropriate diagnostic measures are taken; anticoagulation is indicated if deep vein involvement is diagnosed. Risk factors for superficial thrombophlebitis include superficial varicosities or as a sequelae to intravenous (IV) catheterization [58].

Deep vein thrombosis: diagnosis

Most DVTs do not exhibit classic clinical signs and symptoms. Among patients who have signs or symptoms that are suspicious for a DVT, less than 50% have this diagnosis confirmed by objective testing [56,58]. The signs and

symptoms of DVT include pain, tenderness, swelling, a palpable cord, changes in limb color, and differences in the limb circumference of more than 2 cm [56,58]. Most DVTs occur on the left. Classic puerperal thrombophlebitis that involves the lower extremity, phlegmasia alba dolens or "milk leg," is abrupt in onset and is associated with severe edema and pain of the leg and thigh [58]. Calf pain, either spontaneous or in response to squeezing or stretching the Achilles' tendon (Homans sign), may be present.

DVT in pregnancy can present, or be associated, with lower abdominal pain that is due to periovarian collateral circulation or thrombosis. When coupled with the mild pyrexia and leukocytosis that may be found with VTE, this pain can be mistaken for other intra-abdominal disorders, such as urinary tract infection or appendicitis [3]. Positive D-dimer has a high sensitivity in nonpregnant patients, but is not a reliable marker in pregnancy because of the wide variability of normal lab values in pregnant patients [16,59].

Real-time ultrasonography, together with duplex and color Doppler ultrasound, is the procedure of choice to detect proximal DVT. This method of testing is noninvasive, safe, and simple to perform. Compression ultrasound uses firm compression with ultrasound transducer probe to detect an intraluminal filling defect. It largely has replaced impedance plethysmography (IPG) because of the limited experience with IPG in pregnancy and the high sensitivity (91%) and specificity (99%) of ultrasonography in the detection of DVT. Although venography or phlebography remain the gold standard diagnostic tests for DVT, they are invasive and are not used routinely in pregnancy.

MRI is reserved for specific cases in which ultrasound findings are negative or equivocal, but there is a strong clinical suspicion. MRI was reported to be 100% sensitive and 90% specific for the detection of venographically-proven DVT in nonpregnant patients [4,46].

CT scanning also may be used to assess lower extremity DVT. It has high sensitivity (95%) and specificity (96%) for detecting all DVT. Similar to MRI, there is little reported evidence for its use in pregnancy [46].

Pulmonary embolism: diagnosis

PE carries a significant risk of maternal morbidity and mortality. Signs and symptoms include dyspnea, tachypnea, cough, pleuritic chest pain, tachycardia, fever, anxiety, pleural friction rub, diaphoresis, cyanosis, hemoptysis, or a new murmur [4,56]. The most common symptoms are dyspnea and anxiety and the most common sign is tachycardia. Initial evaluation should include physical examination, pulse oximetry, and arterial blood gas followed by electrocardiogram and chest radiograph. Although several investigators have reported the use of D-dimer as the initial screening test for PE, this test is not reliable in pregnancy [59]. If there is pulmonary infarction (about 10% of PEs), hemoptysis, pleuritic chest pain, and a pleural friction rub or signs of effusion may be found. A PO_2 level that is greater than 85 mm Hg is reassuring but does not rule out PE. Electrocardio-

Table 2
Anticoagulation in pregnancy

Medication	Reversal agent	Prophylactic dosage indications	Therapeutic dosage indications	Prophylactic dosage	Therapeutic dosage	Complications	Laboratory monitoring
Heparin	Protamine sulfate	Certain hereditary deficiencies of a natural anticoagulant moderate risk.	Previous PE/DVT while pregnant or on OCPs APS + thrombosis heterozygous protein C combination defects homozygous factor V Leiden homozygous prothrombin 20210A ATIII acute PE DVT septic pelvic thrombophlebitis prosthetic heart valves rheumatic HD with current A Fib Other hematologic, cardiac, or neurologic conditions that require anticoagulation.	5000 U SQ q 12 h with consideration to increase to 7500–10,000 U SQ q 12 h in the third trimester, especially in obese patients.	Load = 5,000 U IV bolus Mix 25,000 U heparin sodium in 250 mL DSNS and start at 13 mL/hr (1320 U/hr) Check aPTT 6 hours after the bolus and adjust to target PTT as 1.5–2.0 × baseline. Continue IV heparin for 7–10 days. SQ heparin dosage is usually 2/3 the 24 hour IV dosage (eg, if the patient is on 1000 U/h or 24,000 U/d her SQ dose would be 16,000 U/d) Target aPTT of 1.5–2.0 × control. If subtherapeutic,	Bleeding (5–10% incidence). Thrombocytopenia (5–30% incidence). Osteoporosis (1–5% incidence). Hypersensitivity y <1% incidence. Increase in serum aminotransferase levels.	Calculate target PTT as 1.5–2.0 × baseline. Platelet count q 4 weeks.

					increase by 50 U/kg; if overanticoagulated, reduce by 50 U/kg and repeat aPTT		
LMWH		Certain hereditary deficiencies of a natural anticoagulant moderate risk.	Same as heparin	Enoxaparin (Lovenox 30–40 mg q 12 h; increase in 10±mg increments. Dalteparin (Fragmin) 2500 U q 12 h; increase in 1000 U increments or 5000 qd. Titrate these medications until trough levels are $\geq$ 0.2 units/mL of the antifactor Xa activity assay.	Enoxaparin (Lovenox) 1 mg/kg q 12 h. Dalteparin (Fragmin) 100 U/kg q 12 h. Titrate these medications until trough levels are $\geq$ 0.4mL units per mL of the antifactor Xa activity assay.	Bleeding thrombocytopenia increases in serum aminotransferase	Peak anti/Xa 0.35–0.70 3 hours postinjection
Coumadin	Vitamin K		Second or third trimester refractory to heparin or LMWH treatment postpartum				PT/INR INR 2.0–3.0

Abbreviations: DSNS, dilute solution normal saline; PT/INR, prothrombin time/International normalized ratio.

graph findings may include tachycardia, right shift axis with S1, Q3, and T3 changes and P pulmonale and nonspecific T-wave inversions. Chest radiography may reveal atelectasis or pleural-based opacity and a pleural effusion.

Traditionally, the diagnosis of PE has been evaluated by ventilation-perfusion scanning (V/Q). Approximately 40% to 60% of V/Q scans are nondiagnostic in the pregnant patient and further testing is needed [46]. Recently. spiral CT was shown to be useful in the diagnosis of PE. Spiral CT has high sensitivity and specificity (94%) in nonpregnant patients. Other abnormalities, such as pleural effusions, consolidation, emphysema, and pulmonary masses, may be seen with CT. Moreover, CT offers the most cost-effective strategy for diagnosis of PE in pregnancy [60]. Pulmonary angiography is the definitive test for PE. The morbidity rate is high, between 4% and 5%, with a 0.2% to 0.3% mortality rate, and, therefore, it is not used routinely as a first-line diagnostic test in pregnancy [4].

Ovarian vein thrombosis/septic pelvic thrombophlebitis diagnosis

Usually, septic pelvic thrombophlebitis is a diagnosis of exclusion. Clinically, it resembles endometritis with persistent fever, abdominal pain, and tenderness, despite adequate antibiotic treatment. Septic pulmonary emboli may be a complication and are associated with positive blood cultures. Septic pelvic thrombophlebitis usually occurs after cesarean delivery and the phlebitis may originate in the ovarian veins [61]. Diagnosis may be clarified by IPG or Doppler studies and has been made by laparoscopy [62]. Positive venography confirms iliac vein thrombosis. The condition can be life-threatening. Although one study found no difference between the eight patients who received antibiotics and the six patients who received antibiotics plus heparin, larger trials are needed before withholding heparin treatment in patients who have a diagnosis of septic pelvic thrombophlebitis [63]. Currently, reported evidence suggests that confirmation of the diagnosis requires heparin anticoagulation in addition to antibiotic coverage.

Treatment: heparin, low molecular-weight heparin, coumadin

Anticoagulants are the cornerstone of treatment of VTE and for the prevention of recurrent VTE in pregnancy. Current guidelines for clinical practice are based on expert opinion only, rather than high-quality evidence from randomized trials (Table 2). The literature is neither congruent nor conclusive. The most recent Cochrane review that evaluated eight trials and included 649 women concluded that there is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period [5]. The Cochrane review further concluded that large, randomized trials of currently-used interventions should be conducted.

Heparin does not cross the placenta, and, therefore, is the anticoagulant of choice. When PE is suspected clinically, therapy should be initiated immediately. A loading dose of 70 units/kg, IV, followed by a continuous infusion of

1000 units/h, should be given. The dosage is adjusted to keep the aPTT at approximately two times normal or the heparin level at 0.2 to 0.4 units/mL. This therapy should be continued for approximately 10 days and then switched to subcutaneous (SC) heparin in divided dosages. Anticoagulation should be continued throughout pregnancy and for 6 to 12 weeks postpartum [4].

Heparin is inexpensive; 5000 units given twice daily costs less than $1.00 a day. Heparin's primary mechanism of action is by binding to AT-III; the resulting complex has potent inhibitory activity against factors IIa (thrombin), IXa, and Xa. Contraindications to heparin include active bleeding, active ulcer disease, thrombocytopenia, allergy to heparin, central nervous system anatomic lesion, uncontrolled hypertension, bleeding diathesis, subacute bacterial endocarditis, and pericarditis [65].

In addition to a 5% to 10% incidence of bleeding, several other risks are associated with heparin administration. Thrombocytopenia occurs in 5% to 30% of patients who are treated with unfractionated heparin; this complication is seen primarily among patients who receive a full anticoagulant dosage. Thrombocytopenia that is due to heparin may be associated with arterial thrombosis. Osteoporosis occurs in 1% to 5% patients who receive long-term (>6 months) unfractionated heparin. A transient elevation in the serum aminotransferase level with unknown clinical significance is a common side effect that is noted in patients who receive unfractionated heparin.

LMWHs are fragments of unfractionated heparin that are produced by chemical or enzymatic depolymerization. Several low molecular-weight preparations are commercially available and have been used safely during pregnancy. One of the more common preparations is enoxaparin sodium or lovenox. The Society of Maternal Fetal Medicine, after review of the literature on the use of lovenox during pregnancy, found that lovenox is a safe and effective alternative for anticoagulation of the pregnant patient who has a nonprosthetic heart valve [64] Dalteparin (fragmin) is another LMWH that has been used in pregnancy and the postpartum period; it offers the advantage of once daily dosaging [66–68].

LMWHs are increasingly replacing unfractionated heparin in the prevention and treatment of VTE during pregnancy. Like unfractionated heparin, they combine with AT-III to exert an anticoagulant effect; however, the resulting complex of LMWH and AT-III selectively inhibits factor Xa and has less of an effect on factor IIa. Each LMWH is distinct; the compounds should not be used interchangeably. LMWHs have molecular weights that are between 4000 and 6500 d (compared with unfractionated heparin which has a weight between 5000 and 30,000 d). LMWHs have approximately 92% bioavailability compared with 30% bioavailability of unfractionated heparin. LMWHs also have a longer half-life (4 hours when given IV or SC) than unfractionated heparin (1 hour when given IV or 3 hours when given SC). LWMH offers important advantages over unfractionated heparin, including decreased rates of heparin-induced thrombocytopenia and osteopenia [57]. In addition, LMWH have a more predictable anticoagulant response, less effect on coagulation parameters, and a lower incidence of bleeding complications [69,70].

As with unfractionated heparin, there are risks associated with LMWH use. Transient increases in the serum aminotransferase levels were reported with the use of LMWH [71,72]. LMWHs may be associated with thrombocytopenia, although platelet counts of greater than 50,000 cells/mm^2 occur only rarely among patients who receive LMWH as compared with those who receive unfractionated heparin [72]. The major disadvantage of LMWH is the cost; it is more expensive than unfractionated heparin.

The full anticoagulation dosage of LMWH with enoxaparin is approximated using the formula of 1 mg/kg every 12 hours; with dalteparin the dosage is 100 units/kg every 12 hours (see Table 2) [73]. Anticoagulation prophylactic dosaging for enoxaparin is 30 to 40 mg every 12 hours; the dosage is adjusted in 10-mg increments as needed. The recommended dosage of dalteparin for anticoagulation prophylaxis is 2500 units every 12 hours or 5000 units per day which is increased in 1000-unit increments [67,69,73]. Routine laboratory measures, such as partial thromboplastin time (which is used to monitor unfractionated heparin), are not required when using LMWH. Some investigators suggest that for treatment dosages of LMWH, dosage adjustment based on anti-Xa levels usually is required as pregnancy progresses [57,72]; others recommend weight-based dosaging only.

Warfarin is the most widely used oral anticoagulant for the long-term management of DVT. Warfarin is a vitamin K antagonist that inhibits production of factors II, VII, IX, and X and protein C and protein S. The dosage varies with each patient. The effect of warfarin is measured with the prothrombin time and is expressed as the international normalized ratio. The target international normalized ratio during warfarin therapy is 2.5 to 3.0. Many drugs are known to interact with warfarin and can potentiate or inhibit its effects [74]. These drugs include erythromycin, fluconazole, metronidazole, and cimetidine.

Warfarin is rated as pregnancy category D and is not recommended for use in the first trimester. It has known teratogenic risks that include the fetal warfarin syndrome (FWS). The common characteristics of the FWS are nasal hypoplasia that results from failure of development of the nasal septum and stippled epiphyses. The bridge of the nose is depressed and results in a flattened, upturned appearance. Neonatal respiratory distress occurs frequently because of upper airway obstruction [75]. Other features may include birth weight that is less than the tenth percentile, eye defects, hypoplasia of the extremities, developmental retardation, seizures, scoliosis, deafness, congenital heart disease, and death. The critical period of exposure seems to be the sixth to ninth weeks of gestation. Exposure after the first trimester carries the risk of central nervous system defects and bleeding.

Warfarin has been used in refractory cases (patients who require anticoagulation during their pregnancy but are unable to achieve successful anticoagulation with heparin (refractory)) and women with mechanical heart valves. It also is used for 4 to 6 weeks postpartum for women who experience any VTE during pregnancy. Warfarin is highly bound to protein in the maternal circulation and little is secreted into human milk. Therefore, maternal warfarin seems to pose little risk to a nursing infant and has not produced reports of bleeding anomalies in breastfed infants

[76,77]. Although the risks in breastfeeding premature infants is low, oral supplementation with vitamin K_1 precludes any chance of hemorrhage because even modest dosages of Vitamin K_1 counteract high doses of warfarin [76,77].

Labor and delivery or elective cesarean section: intrapartum management of patients "therapeutically" heparinized during pregnancy

Ideally, patients who have been maintained on heparin during their pregnancy should be admitted for induction/delivery at term with a ripe cervix the day before the planned procedure. If the patient has been maintained on LMWH during pregnancy, some investigators suggest switching to unfractionated heparin at 38 weeks' gestation [73]. The patient should be started on IV heparin and subcutaneous (SQ) heparin or SQ LMWH should be stopped. If the last SC dose is more than 8 hours before labor, the patient should be rebolused with 5000 U, IV. If the last SQ dose was administered less than 8 hours previously, the patient may be started on an IV heparin drip. Infusion should be stopped after active labor has begun; no anticoagulation is recommended during delivery. For an elective cesarean delivery, the IV heparin should be stopped 4 hours before the procedure. LMWH and warfarin are restarted 8 to 12 hours after vaginal delivery and 18 to 24 hours postcesarean delivery and are continued 6 months postevent or up to 6 weeks postpartum. Women who have antiphospholipid antibodies and recurrent or severe DVT or women who have AT-III deficiency should be offered warfarin therapy indefinitely and may require lifelong anticoagulation.

If the patient requires an emergent cesarean delivery, the heparin should be stopped immediately. The patient should be typed and crossed for at least two units of packed red blood cells. Protamine should be considered and readily available (1 mg neutralizes 100 U heparin). For example, if a patient is on 1000 U/h IV heparin, give 10 mg protamine slow IV push. Caution should be used because protamine may cause hypotension or may act as an anticoagulant if too much is given. IV heparin should be restarted 18 to 24 hours postoperatively.

Particular caution should be used when considering the use of LMWH for patients who receive epidural or spinal anesthesia because epidural and spinal hematomas with associated long-term or permanent paralysis were reported in this group of patients [78]. Present recommendations suggest that epidural anesthesia should not be given to women who have used LMWH in the previous 24 hours [73]. Although epidural anesthesia provides significantly better pain relief in labor, if epidural anesthesia is not possible, parental pain medication should be used per patient request [79].

Labor and delivery or elective cesarean section: intrapartum management of patients who are "prophylactically" heparinized during pregnancy

Patients who have been maintained on prophylactic doses of anticoagulation during their pregnancy do not require IV heparin in labor. Treatment recom-

mendations for these patients include discontinuation of the SQ heparin at the onset of labor. Compression stockings may be used during the labor and delivery process. Postpartum SQ heparin or LMWH may be restarted 8 to 24 hours postdelivery and continued for 6 weeks postpartum.

Postpartum

Treatment for patients will continue 6 weeks to 6 months into the postpartum. Patients who have been treated prophylactically during their pregnancy usually are treated for 6 weeks postpartum. Patients who had a thromboembolic event during the pregnancy should be anticoagulated therapeutically for 6 months after the event. For patients who have mechanical heart valves, lifelong treatment is standard.

The choice of anticoagulation is practitioner- and patient-dependent. Warfarin offers an oral route of administration compared with the SC injections that LMWH and unfractionated heparin require. Warfarin and unfractionated heparin are less expensive than LMWH. LMWH, unfractionated heparin, and warfarin are safe for breast-feeding mothers [57,76,77].

Summary

Thromboembolic disease is a major cause of maternal morbidity and mortality during pregnancy and the puerperium. Anticoagulation during pregnancy remains an area of controversy and uncertainty. VTE is considered to be a multifactorial disorder in which acquired and genetic risk factors interact dynamically [8]. The risk of maternal VTE with underlying thrombophilia depends on the underlying thrombophilic defect, history of thrombotic events, and additional risk factors.

Inherited thrombophilias have been associated with pregnancy complications that include recurrent and repeated unexplained fetal loss, placental infarction, second trimester pregnancy loss, and increased rates of stillbirth. Patients who have known thrombophilia should be counseled that they are at increased risk of thrombosis associated in thrombogenic situations, including surgery, pregnancy, or immobilization.

Therapeutic anticoagulation treatment should be given, regardless of antecedent thromboembolic history, to women who have the most potent thrombophilias, including those who are homozygous for factor V Leiden mutation or the Prothrombin 20210A = Prothrombin mutation or those who have two coexisting thrombophilias, AT-III deficiency, or antiphospholipid antibody syndrome. Counseling should include discussions that women who have thrombophilia are more prone to coronary artery disease, stroke, and peripheral vascular disease. These women should have monitoring of blood pressure, lipid levels, and glucose and should be warned that the detrimental effects of smoking are increased.

Although the optimal treatment of thromboembolic disease is unknown, the practicing obstetrician must maintain a high level of clinical suspicion of

the serious, and, often fatal, condition. Moreover, the clinician must be aware of current treatment guidelines to prevent and treat thromboembolic complications. Prophylaxis is recommended for those who are at increased risk. Therapeutic anticoagulation is recommended for those who are at highest risk. LMWH is the treatment of choice for most situations because of its lower associated risk of serious complications.

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Autoimmune disease in pregnancy: systemic lupus erythematosus and antiphospholipid syndrome

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Autoimmune diseases most commonly occur in women of childbearing age [1]. Although some conditions such as ankylosing spondylitis are more common in men, over 70% of individuals with autoimmune diseases are women [1]. Many authorities have focused on the role of sex hormones as a cause of the predilection of autoimmune diseases in females. This is an attractive hypothesis that is supported by numerous animal studies. In the most widely studied animal model of systemic lupus erythematosus (SLE), the NZB/NZW F1 mouse, estrogens accelerate and androgens protect against the onset and severity of SLE [2–4]. Similarly, sex hormones exert influence on other autoimmune processes, including thyroiditis, streptococcal cell wall–induced arthritis, and Sjogren's syndrome [5–8]. Observations in humans also implicate sex hormones as a factor in autoimmune conditions, further supporting the hypothesis that sex hormones are associated with the expression and progression of autoimmune diseases such as SLE [9–12].

The dramatic physiologic changes in hormones during pregnancy—including the increase in estrogen—certainly affects the course of autoimmune diseases. The state of enhanced humoral immunity (antibody responses) and weakened cellular immunity suggested by some investigators leads to variable effects that are dependent on the specific disease process [13]. Cell-mediated autoimmune disorders such as rheumatoid arthritis tend to improve during pregnancy; diseases that are characterized by excessive autoantibody production, such as SLE, often worsen [14,15].

It is also important to consider the reciprocating interaction between the maternal immune system and gestational tissues. Wegmann and colleagues have suggested that the fetoplacental unit directs maternal immunity toward humoral responses by favoring certain cytokines and other inflammatory mediators

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[13,16]. Clinicians also must consider the ultimate effects of autoimmune conditions on the fetus. In addition to the association between some autoimmune diseases and increased rates of pregnancy loss, some conditions, such as neonatal lupus and myasthenia gravis, have direct immunologically mediated effects on the fetus. It also is necessary to consider the potential adverse effects of maternal treatment on the fetus and neonate.

This article focuses on SLE, which is often considered to be the "classic" autoimmune disease, and antiphospholipid syndrome (APS), which is associated with pregnancy loss and placental insufficiency.

Systemic lupus erythematosus

SLE is a multisystemic chronic inflammatory disease that affects patients in many different ways over a varying course of time and is characterized by periods of remission and relapse. The heterogeneous symptoms of SLE can make diagnosis difficult. SLE may affect numerous organ systems, most commonly the joints, skin, kidneys, lung, and nervous system. Patients also may suffer from systemic problems such as idiopathic fever, weight loss, myalgias, and fatigue (Box 1).

The lifetime risk of developing SLE for a white woman is 1 in 700 [17], with an overall incidence in the United States of 1 in 2000. The incidence varies among populations and is approximately two to four times higher in African Americans and Hispanics [17]. SLE, like most autoimmune diseases, has a clear predilection for women. The overall female-to-male ratio is 7:1 and is most pronounced between 15 and 50 years of age. It is most commonly detected in women who are in their 20s. [1] Therefore, SLE is the most frequently encountered autoimmune disease in pregnancy. Although no specific gene mutation for SLE has been identified, the disease likely has a genetic component: approximately 10% of affected patients have a relative who has SLE [18], and

Box 1. Frequency of clinical symtpoms in patients who have SLE

Fatigue: 80% – 100%
Fever: 80% – 100%
Arthritis: 95%
Myalgia: 70%
Weight loss: 60%
Photosensitivity: 60%
Malar rash: 50%
Nephritis: 50%
Pleurisy: 50%
Lymphadenopathy: 50%
Pericarditis: 30%
Neuropsychiatric disorders: 20%

Box 2. 1982 revised criteria for the classification of SLE

Malar rash
Discoid rash
Photosensitivity
Oral ulcers
Arthritis
Serositis (pleuritis or pericarditis)
Renal disorder (proteinuria >0.5 g/d or cellular casts)
Neurologic disorder (psychosis or seizures)
Hematologic disorder (hemolytic anemia, thrombocytopenia, leucopenia, or lymphopenia)
Immunologic disorder (anti-DNA, anti-Sm, positive LE cell, or false-positive serologic test for syphilis)
Antinuclear antibody

Four or more of the 11 criteria must be present, serially or simultaneously, for a patient to be considered to have SLE.

Data from the American Rheumatism Association.

monozygotic twin studies demonstrate that 50% of affected twins are concordant for the disease [19].

In 1982, the American Rheumatism Association revised previously set criteria for the diagnosis of SLE (Box 2) [20]. According to these criteria, a person must have had at least 4 of the 11 specific criteria to carry the diagnosis of SLE. Many patients have fewer than four clinical or laboratory features of SLE and do not meet strict diagnostic criteria. Although these patients should not be considered to have SLE, they are often referred to as having lupuslike disease. Such individuals may benefit from therapies for SLE and often require special care during pregnancy. A subset of these patients will ultimately develop the clinical syndrome.

Maternal outcome

Lupus flare

There have been several hypotheses regarding the association between estrogen and SLE. A relationship between estrogen and SLE is evidenced by the female predilection for the disorder [21]. Thus conditions that are associated with high estrogen levels, such as pregnancy, have the potential to exacerbate SLE. The incidence of flares during pregnancy ranges between 15% and 63% [22–26]. Branch and colleagues [27] recently investigated the relationship of steroid hormone levels in pregnancy to SLE activity. They reported that women

who had SLE had significantly lower serum levels of estradiol and progesterone than controls. Furthermore, the highest levels of estrogen and progesterone occurred in the third trimester, when patients with SLE had both the lowest disease activity and serum immunoglobulin levels. These data challenge previous studies that support a direct relationship between increased levels of steroid hormones and lupus activity and raise the question of whether or not estrogens and progesterones suppress disease activity.

As stated above, it is still controversial as to whether or not pregnancy causes SLE exacerbations. Studies published before 1985 suggested that pregnancy exacerbates SLE and emphasized a high risk for severe maternal morbidity or mortality. Maternal outcome has, however, been excellent in most recent series of SLE pregnancies. Many recent studies indicate little to no increase in lupus flares in pregnant women compared with nonpregnant controls. In one well-controlled prospective study of 80 women who had SLE during pregnancy, only 13% had flares that clearly were due to SLE [28]. Another group of investigators noted a high rate (70%) of flares in 61 SLE pregnancies [29]; however, a cohort of age- and disease- matched controls had a similar rate of flares (80%). In contrast, a few other studies have reported increased flares in lupus pregnancies [18,30–32].

Several reasons have been proposed to explain the differences among these studies. It is difficult to interpret available data, because control groups were often unmatched, and the SLE cohorts among the studies vary regarding patient characteristics, severity of SLE, and definition of lupus flare [33]. Also, many symptoms reflecting the normal physiologic changes of pregnancy (eg, palmar erythema, blushing, proteinuria, alopecia) may be mistakenly attributed to SLE. Finally, many series reporting high rates of SLE flare during pregnancy included patients who had mild symptoms and who did not require treatment [18,30–32].

Regardless of whether or not the rate of SLE flares increase during pregnancy, flares are common and may occur during any trimester or post partum. The precise risk of flare post partum is also controversial; older studies suggest a worsening of disease post partum [22,23,25], while recent works suggest the opposite [18,34,35].

Remission of SLE immediately before and at the time of conception (ideally for a period of 6–12 months) probably decreases the chances for SLE exacerbations during pregnancy and post partum [18,29]. It has been demonstrated that active disease at the time of conception, active nephritis, a systemic lupus erythematosus disease activity index score of 5 or more, and abruptly stopping hydroxychloroquine therapy are significant risk factors for lupus flares [1]. Some reports indicate a risk of flare of over 50% in patients who have active lupus nephritis at the time of conception [19,36,37]. Thus women who have SLE should be advised to delay pregnancy (whenever possible) until they are in a period of remission.

Renal disease

Approximately 50% of patients who have lupus will develop renal disease. Lupus nephritis is a result of immune complex deposition, complement ac-

tivation, and inflammation in the kidney. Several reports have emphasized the potential for a permanent decrease in renal function and maternal mortality after pregnancy in women who have active lupus nephritis [19,26,38–40]. On the other hand, more recent series indicate excellent outcome for most women who have mild renal disease [19,37,40–43]. A review of several retrospective reports, including 242 pregnancies in 156 women who had lupus nephritis, demonstrated that 59% of patients had no change in their renal function, 30% experienced transient renal impairment, and 7% had permanent renal insufficiency [39]. Two recent large series confirmed these findings [36,43].

It is clear that there is a strong correlation between the severity of the renal insufficiency before conception and the risk deterioration during pregnancy and post partum. The general consensus is that women who have a serum creatinine level above 1.5 mg/dL have a significantly increased risk of deterioration in renal function. [37–39,44] Conversely, patients who have serum creatinine levels below 1.5 mg/dL can be reassured that pregnancy will likely not increase the rate of deterioration of renal function. These effects appear to be independent of the specific type of nephritis as demonstrated by histologic studies.

Preeclampsia

Preeclampsia, a common complication in women who have SLE, occurs in approximately 30% of pregnancies. [45] Clinically apparent renal disease, underlying hypertension, and antiphospholipid antibodies all increase the risk for preeclampsia. In one prospective series, preeclampsia occurred in 7 of 19 (37%)

Table 1
Characteristics that may be useful in distinguishing SLE flare with lupus nephritis from preeclampsia

Test	Preeclampsia	SLE
Serologic		
Decreased complement	+	+++
Elevated Ba or Bb fragments with low CH50	±	++
Elevated anti-dsDNA	—	+++
Antithrombin III deficiency	++	±
Hematologic		
Microangiopathic hemolytic anemia	++	—
Coombs' positive hemolytic anemia	—	++
Thrombocytopenia	++	++
Leukopenia	—	++
Renal		
Hematuria	+	+++
Cellular casts	—	+++
Elevated serum creatinine	±	++
Elevated ratio of serum blood urea nitrogen/creatinine	++	±
Hypocalcuria	++	±
Liver		
Serum transaminases	++	±

—, not present; ±, rarely present; +, sometimes present; ++, often present; +++, almost always present.

women who had lupus nephritis, compared with 15 of 106 (14%) who did not [45]. The use of high-dose steroids also may predispose women to preeclampsia. The increased rate of preeclampsia in women who have SLE in the absence of known risk factors may be attributed to the unrecognized renal disease present in virtually all SLE patients [46].

In certain cases, it may be difficult to distinguish preeclampsia from a lupus flare or nephritis. Both disorders can be characterized by proteinuria, hypertension, fetal growth restriction, and multiorgan dysfunction. Often the two conditions coexist, and it may be difficult to make a definitive diagnosis. Ensuring the correct diagnosis is imperative, however, to determine clinical management. Table 1 outlines features that may prove helpful in the distinction between the two conditions. Renal biopsy may be used in those instances wherein certain diagnosis of lupus nephritis is required [47].

Fetal outcome

Pregnancy loss

Several factors have been associated with pregnancy loss in women who have SLE, including antiphospholipid syndrome (see later discussion), renal disease, active disease during pregnancy, and a history of fetal loss. Most [19,24,26,35,40,48–50] but not all [9,51,52] retrospective studies show an overall increased rate of pregnancy loss in women who have SLE compared with healthy women. The rate of pregnancy loss in these studies ranges from 8% to 41%, with a median of 22%. These numbers have been confirmed by a recent large case-control study. Fetal loss occurred in 21% of 481 pregnancies in 203 women, compared with 14% and 8% in two control groups [53]. Pregnancies conceived after the diagnosis of SLE had a higher rate of loss (27%) than those occurring before diagnosis (19%).

Prospective studies (Table 2) have detected a lower rate of fetal loss than retrospective studies, ranging from 11% to 29%. Results from these prospective studies may be biased favorably by intensified care and treatment in women who have recognized SLE.

Fetal growth retardation

Intrauterine fetal growth retardation (IUGR) also is common in women who have SLE and has been reported in 12% to 32% of pregnancies [30,32,40,58,59]. Many published series contain only limited data regarding IUGR and its relationship to SLE. One well-designed prospective study noted IUGR in 20 of 86 (23%) SLE pregnancies progressing beyond 20 weeks' gestation compared with 4% of controls [60]. Renal disease, preeclampsia, and antiphospholipid antibodies are considered the greatest risk factors for IUGR.

Table 2
Fetal outcome in prospective cohort studies of women after the diagnosis of SLE

Author	Pregnancies	Live births (%)	Therapeutic abortions (%)	Spontaneous abortions (%)	Fetal deaths (%)	Total losses (%)
Devoe and Taylor [22]	11	8 (73)	1 (9)	2 (18)	0	3 (27)
Deng et al [54]	102	80 (78)	0	17 (17)	5 (5)	22 (22)
Lockshin [28]	80	61 (76)	0	NA	NA	19 (24)
Nossent and Swaak [30]	39	33 (85)	0	4 (10)	2 (5)	6 (15)
Wong et al [32]	24	17 (71)	5 (21)	2 (8)	0	7 (29)
Derksen et al [55]	35	25 (71)	1 (3)	8 (23)	1 (3)	10 (29)
Huong et al [56]	99	76 (77)[a]	5 (5)	13 (13)	5 (5)	23 (23)
Lima et al [57]	108	89 (82)	2 (2)	7 (7)	10 (9)	19 (18)
Medians (%)	—	(76.5)	(2.5)	(13)	(5)	(23.5)

Completely elective pregnancy terminations were excluded.
[a] Includes four neonatal deaths owing to prematurity.

Preterm birth

Perhaps the most serious obstetric complication in pregnancies resulting in surviving infants is preterm birth. Preterm delivery has been reported in as few as 3% and as many as 73% of SLE pregnancies [36,49,61–65]. A recent, well-designed cohort study including careful obstetric detail noted a 50% rate of preterm birth in women who have SLE [66]. The most consistent risk factors for preterm birth are disease activity, chronic hypertension, and antiphospholipid antibodies (aPLs) [37,58,60,67,68]. In women who have SLE, preterm delivery typically occurs because of preeclampsia, fetal growth impairment, abnormal fetal testing, and preterm premature rupture of membranes.

Neonatal lupus erythematosus

Neonatal lupus erythematosus (NLE) is a rare syndrome, occurring in approximately one in 20,000 live births [69]. It is most commonly characterized by fetal and neonatal congenital heart block (CHB), skin lesions, and, less commonly, thrombocytopenia, anemia, and hepatitis [69]. Approximately half of infants who have NLE have CHB, half have skin disease, and 10% have both [69,70].

It now is clear that NLE is due to immunomediated damage from maternal autoantibodies crossing the placenta, most commonly SSA (Ro) [71,72]. SSB (La) antibodies are found in 50% to 75% of these women in conjunction with SSA (Ro) [69,72]. An important point to recognize is that maternal SLE is not a prerequisite for NLE, and many cases occur in otherwise asymptomatic mothers who have circulating autoantibodies. Some of these individuals will, indeed, ultimately develop connective tissue disorders [70,73]. However, autoantibodies alone are insufficient to cause NLE, as has been illustrated by reports of twins discordantly affected and a low (10%–25%) recurrence rate of NLE [70,74–76].

In these instances, other contributing factors such as certain HLA types, especially DR3, may increase the risk [72,77].

Clinical manifestations of NLE are variable. Cutaneous and hematologic disorders do not cause permanent morbidity and resolve by an age of 6 months, consistent with the disappearance of maternal antibodies [69]. In contrast, cardiac complications can be fatal [70,72,77]. Cutaneous lesions of NLE are red, scaling plaques present on the scalp and face with histologic characteristics consistent with cutaneous lesions in adults. Cardiac lesions associated with NLE are CHB and endocardial fibroelastosis. The anti-SSA (most commonly anti-SSA-52) binds to myocardial tissue and is associated with pancarditis, fibrosis, and calcifications replacing the atrial ventricular (AV) node [78] and, occasionally, the sinoatrial (SA) node [79]. The effect can be seen throughout the myocardium resulting in diffuse fibroelastosis [80]. CHB is usually detected in utero as fetal bradycardia with a rate between 60 and 80 beats per minute. It is typically recognized between 16 and 25 weeks' gestation. Fetal echocardiography demonstrates a structurally normal heart with AV dissociation. In some cases, CHB can cause fetal hydrops and fetal death in utero. These two events have prompted the use of antepartum steroid therapy or plasmapheresis [77,81,82] in an attempt to improve outcome. Some reports of improved cardiac function and resolution of CHB after steroid therapy are available [83], but the use of steroids for prophylaxis in women who have SLE and anti-SSA is of unproven efficacy and is not recommended. Despite persistent bradycardia, some infants who have CHB have good cardiac function and do not require intervention. The remaining 36% to 86% of infants need pacemakers [69,75,84,85]. Fifteen to 33% of neonates develop diffuse myocardial involvement and heart failure resulting in death during infancy [70,75,84,86]. Among survivors, a substantial proportion will become symptomatic, need pacemakers, or die [84,86]. Few data are available regarding long-term prognosis, and only a few cases of adult-onset connective tissue disease in patients who have NLE have been reported [86,87].

Clinical management of systemic lupus erythematosus pregnancy

Medical and obstetric management

Management of SLE should include preconception counseling regarding medical and obstetric risks as discussed above. Patients should undergo testing for renal function and hematologic abnormalities. The panel of tests should include serum creatinine, 24-hour urine for protein and creatinine clearance, hematocrit, and platelet count. In addition, patients should be tested for aPLs (see later discussion). Nonsteroidal anti-inflammatory drugs (NSAIDs) and cytotoxic agents should be discontinued before conception. Finally, conception should ideally be delayed until the patient has been in remission for at least 6 months.

During pregnancy, patients should be comanaged by an obstetrician and rheumatologist. Obstetric visits should be as frequent as every 2 weeks during

the first two trimesters and weekly during the third trimester. Blood pressure, urinalysis, and symptoms of lupus flare should be assessed at each visit. Ultrasounds should be obtained approximately every 6 weeks, beginning at 18 to 24 weeks' gestation, to assess for fetal growth restriction. Nonstress testing should be initiated at 32 weeks' gestation. Although advocated by some, serial testing for antinuclear antibody titers and complement levels have not been proved to improve outcome. In cases of NLE with heart block, vaginal delivery is safely possible with fetal pulse oximetry. Cesarean section delivery should be performed for the usual obstetric indications. Additional specialized care may be required for women who have aPL, renal disease, hypertension, or SLE flare. Box 3 summarizes management of SLE in pregnant patients.

Medications

The medical management of SLE includes four categories of drugs: NSAIDs, antimalarials, corticosteroids, and cytotoxic agents (Table 3). NSAIDs and aspirin are the most common anti-inflammatory agents used in the treatment of SLE. Unfortunately, their use during pregnancy is associated with significant fetal morbidity. For this reason, these agents should be avoided during pregnancy. Glucocorticoids are the most effective treatment for SLE considered safe for routine use during pregnancy given their lack of teratogenic effects. Hydrocortisone, prednisone, or prednisolone are preferred because these steroids largely are inactivated by 11-β-hydroxysteroid dehydrogenase in the placenta [88]. Less than 10% of active drug reaches the fetus, and the risk of fetal adrenal suppression is extremely low. Dexamethasone and β-methasone (fluorinated corticosteroids) should be avoided because they are inactivated to a much lesser degree by the placenta.

Potential maternal side effects of glucocorticoids include osteopenia, glucose intolerance, infection, sodium and water retention, hypertension, cataracts, and avascular necrosis. These agents may also contribute to an increased risk for gestational diabetes, preeclampsia, preterm premature rupture of membranes (PPROM), and fetal growth restriction during pregnancy [89–92]. Despite these side effects, the benefits of steroids outweigh the risk in women who have SLE. The smallest effective dose of glucocorticoids should be used to effectively control symptoms. "Stress" doses should be administered at the time of labor and delivery in patients who are receiving chronic steroids (more than 3 weeks' duration).

Because of concerns for untoward fetal effects, most other immunosuppressive drugs are reserved for refractory cases of SLE. Azathioprine has been associated with fetal growth impairment [91] and neonatal immune suppression [93]. The cytotoxic agents cyclophosphamide and methotrexate may be human teratogens and are best avoided. Antimalarial drugs can accumulate in melanin-containing tissues and have been associated with ear [62] and eye [94] damage in case reports. However, normal fetal outcome after exposure to antimalarials has been reported [95,96], and the benefits may outweigh the risks in severe cases. In fact, a recent prospective study demonstrated that stopping hydroxychloroquine

Box 3. Management protocol for patients who have SLE

Priorities

A. Avoid medications that are harmful to the fetus
B. Prompt detection of pre-eclampsia and uteroplacental insufficiency
C. Discern between lupus exacerbations and pre-eclampsia
D. Appropriate detection and treatment of lupus flares

Management

A. Preceonception counseling
   1. Discuss potential pregnancy complications including pre-eclampsia, preterm labor, miscarriage, fetal death, fetal growth restriction, and neonatal lupus
   2. Clinically evaluate lupus activity; delay pregnancy until remission
   3. Evaulate patient for nephritis, hematologic abnormalities, and antiphospholipid antibodies
   4. Discontinue NSAIDs and cytotoxic agents
B. Antenatal care
   1. Frequent visits to assess SLE status and to screen for hypertension
   2. Serial ultrasounds to evaluate interval fetal growth
   3. Antenatal surveillance at 32 weeks or earlier if indicated
C. Treatment of SLE exacerbations
   1. Mild to moderate exacerbations
      a. If the patients is taking glucocorticoids, increase the dose to at least 20–30 mg/d
      b. If the patient is not taking glucocorticoids, start 15–20 mg/d of prednisone
   2. Severe exacerbations without renal or central nervous system manifestations
      a. Rheumatology consult and consider hospitalization
      b. Glucorticoid treatment 1.0–1.5 mg/kg; expect clinical improvement in 5–10 days
      c. Taper the glucocorticoids once the patient demonstrates clinical improvement
      d. If patient cannot be tapered off high doses of glucorticoids, consider starting cyclosporine, plaquinil, or azathioprine

3. Severe exacerbations with renal or central nervous system involvement
   a. Hospitalization and rheumatology consult
   b. Initiate intravenous glucocorticoid treatment, 10–30 mg/kg/d of methylprednisolone for 3–6 days
   c. Maintain patient on 1.0–1.5 mg/kg of oral prednisone
   d. When the patient responds, taper the glucocorticoid
   e. For unresponsive patients, consider starting cyclophosphamide or plasmapheresis

treatment during pregnancy was associated with a significant increase in the risk of lupus flares [37]. Therefore, if a patient requires this medication to control her disease, stopping the drug is relatively contraindicated. In fact, hydroxychloroquine is rapidly gaining favor as a first line therapy for the treatment of SLE, even during pregnancy.

Table 3
Medications used for patients who have SLE

Medication	Pregnancy category	Recommendations
NSAIDs	B	Avoid, especially in the third trimester.
Hydroxychloroquine	C	Limited data are available on the use of hydroxychloroquine in pregnancy. Teratgenicity is based on studies of chloroquine. Stopping hydroxychloroquine is associated with an increased risk of SLE flares; therefore, recommend continuing medications if needed to control SLE.
Glucocorticoids	B	Avoid fluorinated glucocorticoids, because they cross the placenta. High doses are associated with significant maternal side effects and subsequent fetal side effects. Avoid empiric treatment and minimize dosage.
Cyclosporine A	C	Extensive experience with the use of cyclosporine in pregnant renal transplant patients. Not an animal teratogen. Appears to be safe in humans. Long-term follow up studies are limited.
Azathioprine	D	Teratogenic in animals. Appears to be safe in humans.
Cyclophosphamide	D	Associated with cleft palate and skeletal abnormalities. Avoid if possible, but may be needed in severe cases of proliferative nephritis.
Methotrexate	X	Embryolethal and thus should be avoided. Also associated with multiple congenital anomalies (aminopterin syndrome).

Management of lupus flares

Lupus flares in pregnancy are usually mild and are most commonly manifested by skin lesions or joint pain. However, patients may present with severe nephritis, stroke, seizures, or psychosis as a result of a lupus exacerbation. Treatment of lupus flares depends on the severity of the patient's symptoms, and with few exceptions can be controlled with NSAIDs, hydroxychloroquine, and glucocorticoids. In general, with the exception of methotrexate, cyclophosphamide, and NSAIDs, the benefits of medical therapy for the treatment of severe lupus flares far exceed the risks. Although these medications should be used prudently, there are circumstances wherein they are indicated in pregnancy.

Severe lupus nephritis may present with acute renal insufficiency. As discussed above, the differential diagnosis includes preeclampsia and, in transplant patients, acute rejection. The distinction among these possible etiologies may require biopsy for definitive diagnosis. Frequently, glucocorticoids may provide adequate treatment; however, proliferative nephritis may require cyclophosphamide. A recent study reported that low-dose cyclophosphamide is as effective as high-dose regimens, with fewer side effects [97]. Lack of response to medical management and serum creatinine levels above 3.5 mg/dL require dialysis.

Treatment of neuropsychiatric SLE is complex secondary to its many different clinical manifestations. These include peripheral neuropathy, headaches, seizures, chorea, stroke, mood disorders, and psychosis. Other etiologes of neurologic symptoms (eg, metabolic abnormalities, infection, and intracranial lesions) must be considered as well. Infection is especially common in SLE patients with chronic steroid use. Thus a complete evaluation for infection including lumbar puncture is necessary. In addition, radiologic imaging and electroencephalography are often helpful in excluding other neurologic abnormalities. Treatment of lupus cerebritis is empiric, without evidence to guide optimal treatment. Typically, glucocorticoids are used as first line therapy, with cyclophosphamide used in refractory cases. Hydroxychloroquine is also gaining popularity. Patients presenting with evidence of thrombotic stroke require anticoagulation.

Antiphospholipid syndrome

APS is an autoimmune disorder defined by certain clinical and laboratory features as well as the presence of circulating aPLs (Box 4). aPLs are a heterogeneous group of autoantibodies that bind phospholipids, proteins, or a phospholipid–protein complex. Approximately one third of patients who have SLE also have aPLs. Individuals who have SLE and APS are considered to have secondary APS, while those who have APS and no other connective tissue disorders have primary APS [51,98–100]. Several aPLs have been described, but the two best characterized are the lupus anticoagulant (LA) and anticardiolipin antibodies (aCL). LA detection in plasma uses phospholipid-dependent clotting tests such as the activated partial thromboplastin time and the Russel viper venom

Box 4. Suggested clinical and laboratory criteria for the diagnosis of APS

Clinical criteria

Pregnancy Loss
- Recurrent spontaneous abortion[a]
- Unexplained fetal death

Thrombosis
- Venous thrombosis
- Arterial thrombosis, stroke

Autoimmune thrombocytopenia

Other disorders
- Autoimmune hemolytic anemia
- Transient ischemic attacks
- Amaurosis fugax
- Chorea gravidarum
- Livedo reticularis

Laboratory criteria

Lupus anticoagulant

Anticardiolipin antibodies

$>15-20$ IgG binding units[b]

At least one clinical and one laboratory criterion are required to carry the diagnosis of APS.

[a] Three of more spontaneous abortions with no more than one live birth.

[b] See text for details.

time. If LA is present, clotting time is prolonged because of antibody interference. Other tests are then performed to exclude other reasons for prolongation of clotting times. aCLs are detected using immunoassays that are standardized using standard sera obtained from the Antiphospholipid Standardization Laboratory, Atlanta, Georgia. These aPLs have been associated with significant medical and obstetric complications (see later discussion) [99–102].

Obstetric complications

The association between APS and pregnancy loss has been confirmed in numerous retrospective studies, with rates of pregnancy loss quoted as high as 90% [49,67,101,103–106]. Prospective studies have since confirmed this association [67,89,107–112].

An unusually large proportion of pregnancy losses associated with aPL are second or third trimester fetal deaths. Midtrimester fetal deaths account for only a small percentage of all pregnancy losses in the general population [113]. However, one cohort study of pregnancy losses in 76 women (333 pregnancies) with APS reported that 50% of the losses were fetal deaths [114]. Eighty percent of these women suffered at least one fetal death.

Recurrent spontaneous abortion also is associated with aPL. Several case control studies have demonstrated a higher proportion of positive tests for LA and aCL in women who have recurrent pregnancy losses compared with controls [27,115–119].

As opposed to recurrent pregnancy loss and fetal death, aPL rarely are associated with sporadic early pregnancy loss, which are most commonly attributable to genetic abnormalities [120]. A large case-control study of 331 women suffering their first pregnancy loss failed to demonstrate a correlation between aPL and either spontaneous abortion or fetal death [121]. This is not surprising given the myriad causes of spontaneous abortion.

Pregnancies that result in live births often are complicated by fetal growth restriction, preeclampsia, uteroplacental insufficiency evidenced by abnormalities in antepartum surveillance, and preterm birth [67,107]. IUGR occurs in 15% to 30% of women who have APS [62,67,122,123]. Abnormal fetal heart rate tracings prompting delivery has been reported in up to 50% of women who have APS [62,67,101,123]. Half of all pregnancies in a large cohort study of women who had APS had abnormal fetal heart rate tracings, prompting iatrogenic preterm birth [67]. Placental insufficiency can be evident in fetal heart rate tracings as early as the second trimester [124]. Preeclampsia in women who have APS is often severe and presents relatively early in gestation (second trimester). Several investigators reported an 11% to 17% rate of aPL in women who have preeclampsia [125–128]. In one series from the University of Utah, 16% of individuals with severe preeclampsia presenting before 34 weeks' gestation had clinically relevant levels of aPL [125]. However, a recent study failed to demonstrate an association between aPL and preeclampsia [88]. Preterm birth is usually iatrogenic and due to preeclampsia, IUGR, or abnormal fetal testing, and occurs in one third of women who have APS [67,112,122,123]. Delivery before 34 weeks is most likely in women who meet clinical and laboratory criteria for APS (see later discussion) [67,123].

Medical complications

Perhaps the most serious medical complication associated with aPL is thrombosis [99,100,102]. Approximately 70% of thrombotic events are venous and occur in the lower extremities, but arterial thromboses and cerebrovascular accidents also are common [129]. Atypical thromboses in unusual sites should prompt suspicion of APS and further investigation. aPL are present in approximately 2% of individuals who have unexplained thrombosis [130] and in approximately 5% of patients who have thrombotic strokes who are less than

50 years old [64,131]. Transient central nervous system manifestations of ischemia also are common in APS patients [132]. Most thrombotic events in women who have APS occurred in association with estrogen-rich states such as pregnancy or oral contraceptive use [67,123,132]; oral contraceptives that contain estrogen should, therefore, be avoided. In addition, patients who have aPLs and a history of thrombosis are at increased risk for recurrence (reported to be 33%–69% without treatment). The risk may be decreased with the use of lifelong anticoagulant therapy [132–134]. Initial reports indicated that coumarin dose should be adjusted so that the international normalized ratio is maintained between 2.5 and 3.0 [133]. However, standard-dose coumarin intended to achieve an international normalized ratio of 2.0 to 2.5 may be of similar efficacy [135].

Autoimmune thrombocytopenia also has been linked to aPL [51,136], occurring in up to 40% of patients who have primary APS [9]. The thrombocytopenia associated with APS is difficult to distinguish from ITP. Fortunately, they are treated in a similar fashion. Other medical complications include autoimmune hemolytic anemia, livedo reticularis, chorea gravidarum, cutaneous ulcers, renal insult, pulmonary hypertension, and transverse myelitis [51,98,100,137–139]. Postpartum complications include a severe illness characterized by fever and cardiopulmonary disorders that may be life-threatening [138].

Antiphospholipid antibody testing

Few areas of medicine have generated as much controversy and confusion as laboratory testing for aPL. Clinicians should recognize the limitations of available assays and use a laboratory experienced in aPL testing.

Three antibodies—LA, aCL, and the false-positive serologic test for syphilis—are the aPLs that have been most widely studied. Of these, LA and aCL are correlated most strongly with clinical problems and are recommended for routine use.

Lupus anticoagulant

LA is a misnomer, as it is present in patients who do not have SLE and predisposes to clotting, not bleeding. It is detected in plasma by any one of several phospholipid-dependent clotting assays, such as the activated partial thromboplastin time, dilute Russell viper-venom time, plasma clotting time, or kaolin clotting time. The sensitivity of these assays may be laboratory-dependent and is affected by the reagents and phospholipids used.

These assays use phospholipids as a template for the interaction of the enzymes and cofactors in the clotting cascade. LA binds to phospholipids or epitopes created by protein-phospholipid interactions, interfering with clotting factors and leading to a prolongation of clotting times. This observation prompted the term *lupus anticoagulant.*

Factors other than LA may cause prolonged clotting times. For this reason, a confirmatory test must be used to confirm the presence of LA (Fig. 1). The affected patient's plasma is mixed with normal plasma. If a clotting factor

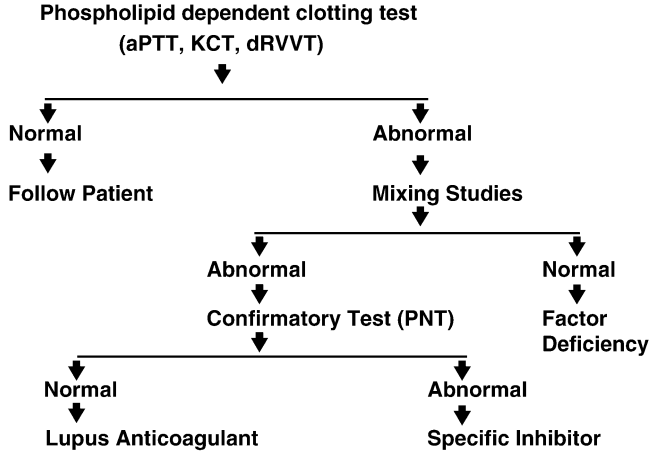

Fig. 1. Detection of lupus anticoagulant. Abbreviations: aPTT, activated partial thromboplastin time; dRVVT, dilute Russel viper venom time; KCT, kaolin clotting time; PNT, platelet neytralization test.

deficiency is responsible for the prolonged clotting time, the addition of normal plasma (and the deficient factor) will correct the clotting time. In contrast, if LA is present in the affected plasma, the clotting test will remain abnormal. A second confirmatory test involves the addition or removal of phospholipid, which would bind LA, and thus normalize the clotting time. For example, if LA is present, preincubation of plasma with phospholipid will bind LA and normalize the clotting time. LA is not quantified, but simply reported as present or absent.

Anticardiolipin antibody

aCL is detected by immunoassays using cardiolipin as the antigen. Results from assays use international standard sera to assign numeric values termed GPL (IgG aCL), MPL (IgM aCL), or aPL (IgA aCL) units. In turn, these units are semiquantitated and reported as negative and low-, medium-, or high-positive.

Low-positive aCL, isolated IgM aCL, and aPL are of questionable clinical significance [140]. Medium- high-positive levels of aCL (as well as LA) correlate best with aPL-related disorders and thus form the diagnostic criterion for APS [98,99]. Positive tests for aPL should be confirmed on two occasions, several weeks apart [99,141].

Many women who have LA have aCL, and those who have aCL have LA, but the correlation is imperfect [107,142]. Regardless, both independently correlate with the clinical features of APS, and testing for both LA and aCL in patients suspected of having APS is recommended.

Other antiphospholipid antibodies

Several other aPLs can be detected using a variety of immunoassays. Examples include antibodies specific for phosphatidylserine, phosphatidylcholine,

phosphatidyl-ethanolamine, phosphatidylinositoI, phosphatidylglyceroI, and phosphatidic acid. aPLs other than LA or aCL, such as antiphosphatidylserine antibodies, may be present in patients who have APS or clinical disorders associated with aPL [27,119]. Most of these individuals, however, also have LA or aCL [27], casting doubt about an independent association between the clinical features of APS and aPL other than LA and aCL.

Indications for aPL testing are shown in Box 5. Clinicians should recall that aPLs, especially low-titer and the IgM isotype, are occasionally present in healthy individuals and are of questionable clinical significance [143]. Thus testing normal individuals is ill-advised, because positive tests for aPL in the absence of APS-related disorders are likely meaningless.

Pathogenesis of antiphospholipid syndrome

The obstetric complications of APS are all results of abnormal placental function. These observations, in conjunction with the association of APS with thrombosis, led to the hypothesis that thrombosis in the uteroplacental circulation is responsible for pregnancy loss in women who have APS. Decidual vasculopathy also has been proposed to contribute to placengtal insufficiency and fetal loss [101,144–147]. Evidence of thrombosis or infarction was present in 82% of placentas from women who have aPL and fetal death in a large case-control study [148]. These findings are, however, nonspecific and not present in all women who have APS and fetal demise [149].

Box 5. Indications: for antiphospholipid antibody testing

Recurrent spontaneous abortion[a]
Unexplained second or third-trimester fetal death
Severe preeclampsia prior to 34 weeks' gestation?
Unexplained venous thrombosis
Unexplained arterial thrombosis
Unexplained stroke
Unexplained transient ischemic attack or amaurosis fugax
SLE or other connective tissue disease
Autoimmune thrombocytopenia
Autoimmune hemolytic anemia
Livedo reticularis
Chorea gravidarum
False-positive serologic test for syphilis
Unexplained prolongation in clotting assay
Unexplained severe intrauterine growth retardation?

[a] Three or more spontaneous abortions with no more than one live birth and other causes of pregnancy loss excluded.

Multiple mechanisms have been proposed to explain the placental thrombosis, decidual vasculopathy, and episodic vascular thrombosis associated with aPL. Most attention has focused on the potential for aPL (or anti-β_2GP-I) to initiate a cascade of thrombogenic mediators after binding to damaged endothelium, platelets, or gestational tissues [150,151]. Potential mechanisms of fetal loss associated with aPL are shown in Fig. 2.

Management of antiphospholipid syndrome in pregnancy

Pregnancy loss and obstetric complications in untreated patients who have APS has inspired the use of medical therapy to improve fetal outcome. Current treatments have three goals: suppress the immune system (prednisone and intravenous immunoglobulin [IVIG]), prevent thrombosis (heparin and aspirin),

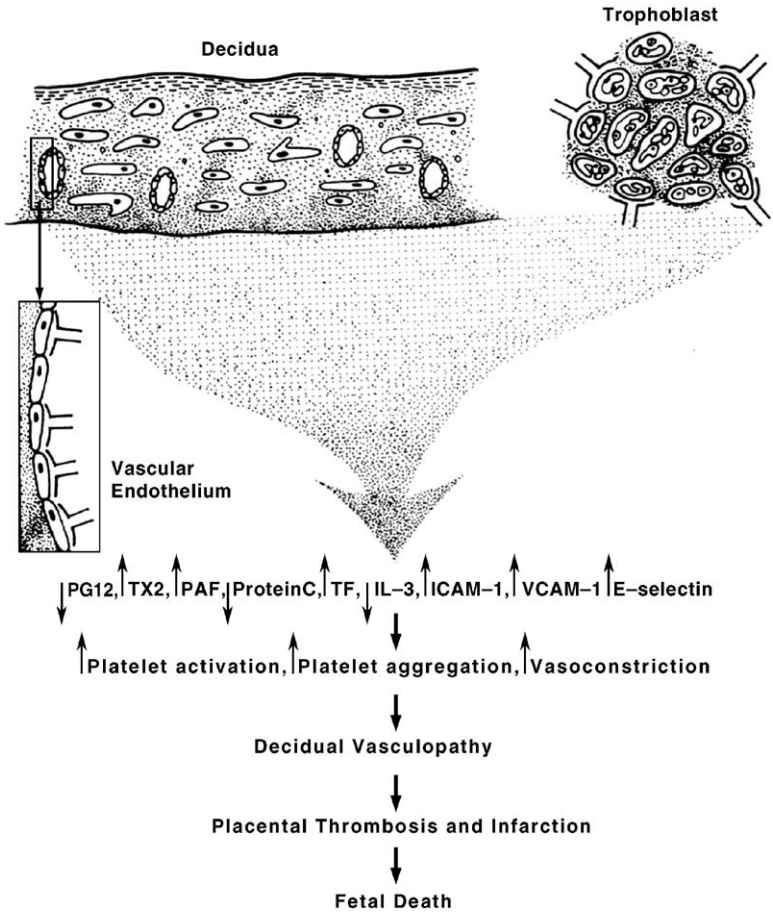

Fig. 2. Proposed mechanisms of fetal loss associated with antiphospholipid antibodies.

and improve placental blood flow by decreasing the thromboxane-to-prostacyclin ratio (aspirin). A summary of the management of APS in pregnancy is depicted in Box 5.

Prednisone

Initially, high-dose prednisone (at least 40 mg/d) in combination with low-dose aspirin (80 mg/d) was used to treat APS in pregnancy, resulting in successful pregnancies in 60% to 70% of cases [101,145,152]. A small, randomized trial comparing prednisone and heparin in the treatment of APS showed the two to be of similar efficacy, with higher complication rates in the prednisone group [67]. Since that time, heparin has been the first line treatment of choice [24].

Heparin

Heparin is considered first line therapy for APS during pregnancy and should be initiated after confirmation of a viable pregnancy. Several case series have reported an approximately 70% rate of live births after treatment with unfractionated heparin in combination with low-dose aspirin [67,89,153]. Patients who have no prior history of thrombosis should be treated with thromboprophylactic doses of heparin (10,000 to 20,000 units of unfractionated heparin daily). Patients who have a history of thrombosis should receive a dose of heparin that will provide full anticoagulation. The goal of therapy is to maintain the activated partial thromboplastin time 1.5 to 2.5 times the normal value. Because LA causes a prolongation of the activated partial thromboplastin time, this test cannot be used to monitor anticoagulation in patients who test positive for the lupus anticoagulant. Rather, anti–factor Xa levels are followed. Anti–factor Xa levels should fall between 0.4 and 0.7 U/mL for full anticoagulation with unfractionated heparin.

Side effects of heparin include bleeding, thrombocytopenia, and osteopenia. The risks of bleeding and osteopenic fracture increase with increasing doses of heparin, thus providing rationale for using prophylactic doses in patients who have no history of thrombosis. Osteopenic fracture occurs in 1% to 2% of women treated with anticoagulant doses of unfractionated heparin during pregnancy. Therefore, calcium and vitamin D supplementation and weight-bearing exercises are encouraged. Heparin-induced thrombocytopenia occurs in up to 5% of patients treated. Platelet counts should initially be followed for 3 weeks because this complication is detectable within 21 days of starting treatment.

Low molecular weight heparin has been used safely during pregnancy [154,155] and appears promising in the treatment of APS. The recommended dose of enoxaparin is 1 mg/kg administered subcutaneously in two equal doses 12 hours apart to accomplish full anticoagulation. However, due to increased plasma volume and renal blood flow in the pregnant patient, the pharmacokinetics of enoxaparin are altered by pregnancy. Thus, intermittent monitoring of anti–factor Xa levels should be performed to ensure adequate dosing. The target anti–factor Xa level for full anticoagulation using low molecular weight heparin is 0.5 to 1.1 U/mL. Low molecular weight heparin appears to carry less risk for

osteopenia and thrombocytopenia than unfractionated heparin. However, it is more expensive and has a longer half life, making it less convenient. If possible, heparin should not be used in combination with high-dose prednisone because of an increased risk of osteopenic fractures and lack of improvement in fetal outcome with combination therapy [67].

Box 6. Management of patients who have APS

Goals of therapy

A. Embryonic and fetal survival
B. Prompt detection of uteroplacental insufficiency and preeclampsia
C. Prevention of thrombosis

Management

A. Preconception counseling
   1. Review pregnancy risks, such as miscarriage, fetal death, preeclampsia, fetal growth restriction, unteroplacental insufficiency, and preterm birth
   2. Evaluate the accuracy of the diagnosis; confirm the presence of antiphospholipid antibodies, if necessary
B. Antenatal care
   1. When a live embryo is detected, start subcutaneous unfractionated heparin 10,000–20,000 units/d in divided doses or the equivalent doses of low molecular weight heparin; full anticoagulant doses should be used in patients who have had prior thrombosis
   2. Calcium supplementation and axial skeleton weight bearing exercise
   3. Frequent assessment for the development of preeclampsia
   4. Serial ultrasounds to evaluate interval fetal growth
   5. Fetal surveillance starting at 32 weeks or earlier if there is evidence of placental insufficiency
   6. If a patient has a history of a thromboembolic event, or suffers an acute episode during pregnancy, start therapeutic doses of heparin to maintain PTT 1.5–2.5 times normal or low molecular weight heparin 1 mg/kg twice a day
   7. If using low molecular weight heparin, anti–factor Xa levels should be checked every trimester to maintain through levels of 0.5–1.1 U/mL.

Intravenous immunoglobulin

Treatment with IVIG has resulted in successful pregnancies in a handful of women who have APS [156–158]. In most of these women, IVIG was used as an adjunctive therapy with heparin or prednisone and low-dose aspirin. IVIG has generated considerable enthusiasm because associated obstetric complications have been rare [158]. However, the high cost of IVIG prevents its use as primary therapy. Also, a pilot study did not indicate improved outcome when IVIG was added to a regimen of heparin and low-dose aspirin [159].

Other aspects of management during pregnancy

Ideally, patients who have APS should undergo preconception counseling regarding their medical and obstetric risks. If the diagnosis is uncertain, LA and aCL should be confirmed. There is no evidence of benefit to serial testing during pregnancy or in titrating medicines to suppress antibody levels. As is the case in other autoimmune disorders such as SLE, patients who have APS should undergo intensive surveillance (eg, weekly clinic visits and biweekly nonstress tests) for preeclampsia, IUGR, and uteroplacental insufficiency at the appropriate times in gestation. Antenatal testing may be useful in more severe cases as early as 24 to 25 weeks' gestation [124].

Postpartum considerations

Thromboprophylaxis (or full anticoagulation if appropriate) should be continued through 6 weeks post partum. Coumarin may be safely used while breastfeeding. After delivery, women who have APS should be counseled regarding their substantial risk for the development of nonobstetric disorders associated with aPL because they are at risk for major medical complications such as thrombosis or development of SLE [132]. Patients who have prior thromboses and APS should receive lifelong anticoagulation with coumarin [133,135]. Lifelong treatment with low-dose aspirin may decrease the risk for thrombosis in women who have not had prior thrombotic events [160]. Finally, oral contraceptives containing estrogen are absolutely contraindicated in patients who are not taking anticoagulant therapy.

Box 6 summarizes a management strategy for patients who have APS.

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Seizure disorders in pregnancy

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Seizure disorder affects 1.1 million women of reproductive age in the United States [1,2]. In 1995, the annual cost of treatment of patients who had epilepsy was estimated to be 12.5 billion dollars [3]. Epilepsy has an impact on many aspects of women's health, particularly with respect to reproduction [4–6].

Management of seizure disorder in pregnancy

Effects of pregnancy on epilepsy

There are conflicting reports on the effect of pregnancy on epilepsy. Knight and Rhind [7] found that 45% of women who had epilepsy had an increased frequency of seizures, 5% experienced a decrease, and 50% had no change. Other investigators found an increase in seizure frequency in 37% of women, but noted that this often was associated with medication noncompliance or sleep deprivation [8]. Pregnancy had either no effect or an ameliorating effect on seizure frequency in nearly two thirds of women who had epilepsy. A review of the published literature from 1938 to 1985 revealed increases in seizure frequency, from 23% to 75%, among pregnant women who had epilepsy [9]. This study concluded that 33% of women who have epilepsy experience an increase in seizure frequency during pregnancy. Other researchers found that women who have poorly-controlled epilepsy (ie, high prepregnancy seizure occurrence) are more likely to have an increase in seizures during pregnancy [10]. Among women who have an increase in seizure frequency during pregnancy, most returned to prepregnancy seizure rates after delivery.

One explanation for an increase in seizure rate during pregnancy may be changes in anticonvulsant pharmacokinetics. Increased clearance and volume of distribution can result in decreased serum drug concentration; however, this is

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offset by the relative decrease in protein binding sites because of decreased plasma albumin. As a result, free levels of antiepileptic drugs may increase. It is recommended that if checking medication levels, one should check the free fraction [2,11]. Measurement of the free fraction of phenytoin provides an accurate assessment of therapeutic range; however, was suggested that for all other antiepileptic medications, dosaging should be adjusted on a clinical basis [12]. Table 1 lists common anticonvulsant medications, dosages, serum levels, and indications for use.

In addition to changes in pharmacodynamics, there may be decreased patient compliance with medication regimens. The reasons for decreased compliance may be secondary to other symptoms of pregnancy, such as nausea and vomiting, or it may stem from fears of the medications' effects on the fetus. When addressing this issue with patients, it is important to discuss the potential complications that are associated with uncontrolled seizures. Trauma during seizures may result in placental abruption, premature rupture of membranes, or preterm delivery. Seizures also have been associated with significant fetal heart rate decelerations [9,17]. Finally, sleep deprivation, a common complaint during pregnancy and the puerperium may increase seizure frequency [15,18].

Effects of antiepilepsy drugs on fetus

Seizure disorders are associated with an increase in congenital anomalies over the general population, whether treated with anticonvulsant medication or not. Most currently-used antiepilepsy medications have been implicated as teratogens,

Table 1
Commonly encountered antiepilepsy drugs [13–16]

Drug	Common dosage	Doses	Therapeutic levels	Indications
Carbamazepine	600 mg	qd-qid	6–12 μ/ml	Partial or generalized tonic-clonic seizures
Gabapentin[a]	300 mg	qd	70–120 μmol/L	Partial seizures and secondarily generalized seizures
Lamotrigine[a]	25–50 mg	qd	10–60 μmol/L	Partial seizures and secondarily generalized seizures
Levetiracetam[a]	500–1500 mg	bid	35–120 μmol/L	Partial seizures
Oxcarbazepine[a]	300–600 mg	bid	50–140 μmol/L	Partial seizures
Phenobarbital	120 mg	qd-bid	10–40 μ/mL	Partial or generalized tonic-clonic seizures; myoclonic, clonic, or tonic seizures; or status epilepticus
Phenytoin	300 mg	qd-bid	10–20 μ/mL	Partial or generalized tonic-clonic seizures or status epilepticus
Primidone	500 mg	qd-bid	5–15 μ/mL	Partial or generalized tonic-clonic seizures
Valproic acid	1000 mg	qd-bid	50–100 μ/mL	All generalized seizures or partial seizures

[a] Tentative target ranges. A wide range of serum concentrations are associated with clinical efficacy.

with older medications having higher reported rates of malformation [19]. First trimester exposure, during the period of organogenesis, presents the highest risk of teratogenesis [20,21].

Major malformations are structural abnormalities with cosmetic, medical, or surgical importance. Frequent major malformations that are seen in infants of women who have epilepsy are cleft lip/palate, congenital heart disease, neural tube defects, and urogenital defects [18]. Compared with the general population, infants of women who receive antiepileptic medications during pregnancy have a relative risk of fetal cardiac defect of 2.5 (95% confidence interval [CI]: 1.4–3.5), a relative risk of oral cleft of 2.5 (95% CI: 1.4–4.2), and a relative risk of urogenital defect of 2.5 (95% CI: 1.2–5.0) [22]. An anomaly that does not represent a risk to the health of the infant is considered a minor malformation.

In 1974, Annegers et al [19] reported that women who had epilepsy and took antiepilepsy medications during pregnancy had a malformation incidence of 71 in 1000 liveborn infants; the malformation incidence in infants of women who did not take antiseizure medication was 18 in 1000. The most common malformations included cleft lip or palate and congenital heart defects. Among women who took antiseizure medications, 43 in 1000 infants had congenital heart disease and 21 in 1000 infants had facial clefting. There was no incidence of heart defect or facial clefting among women who had seizure disorders who were not on medications during pregnancy. Annegers et al [23] additionally reported that pregnancies that were complicated by fetal malformation also were associated with significantly greater seizure activity during pregnancy. This led to the speculation that the seizures may be the cause of the malformations, rather than the medication.

Kaaja and colleagues [24] recently published a study that calls into question the idea of whether seizures are potentially teratogenic. The investigators prospectively followed 970 pregnancies in women who had epilepsy. Seventy six percent (740/979) of the infants were exposed to antiepileptic medications during the pregnancies. The rate of major malformation was 3.8% among infants who were exposed to medication and 0.8% among those who were not exposed. Regression analysis revealed an independent association between malformations and the use of carbamazepine, valproate, or oxcarbazepine; low serum folate; and low level of maternal education. Seizure activity during the first trimester was not associated with major malformations. This was the first study to report an association between oxcarbazepine and major fetal anomaly.

Certain antiepileptic drugs have been associated with an increase in specific malformations. Antenatal exposure to carbamazepine is associated with an increased risk of craniofacial defects, fingernail hypoplasia, developmental delay, and neural tube defects. The incidence of neural tube defects that is associated with carbamazepine exposure is 0.5% to 1.0% [25]. Valproic acid, or valproate, also is associated with a tenfold increase in the incidence of neural tube defects, or a 1% to 2% risk [26]. A European meta-analysis confirmed a significant relationship between valproic acid and carbamazepine use during pregnancy and major congenital malformations [20]. Adverse outcomes among infants of

women who were treated with valproate increase with increasing dosage. In a recent report, severe adverse outcomes were associated with doses of valproate that were greater than 1000 mg/d [27]. Trimethadione was reported to be associated with up to a 50% chance of fetal malformation or mental retardation, and, therefore, is contraindicated in pregnancy [28,29].

Fetal anticonvulsant syndrome, formerly referred to as fetal hydantoin syndrome, is seen in approximately 11% of fetuses who are exposed to antiepilepsy drugs in utero; some features of the syndrome may be seen in up to 33% of fetuses. The syndrome, which is similar to fetal alcohol syndrome, is characterized by growth deficiency, microcephaly, dysmorphic facial features, and mental deficiency [21,30]. There is increasing evidence that genetic susceptibility may play a role in the manifestation of this syndrome. Malm et al [31] presented three families in which all offspring were affected by fetal anticonvulsant syndrome. All siblings were affected by developmental delay and the morphologic features of anticonvulsant syndrome. Because one would predict a smaller proportion of affected siblings, this suggests an underlying genetic vulnerability.

There continues to be limited evidence regarding the teratogenicity of newer antiseizure medications (eg, gabapentin, lamotrigine, felbamate). The North American Registry for Epilepsy and Pregnancy was established as a prospective monitoring system to aid in the evaluation of the impact of these new anticonvulsant medications [32]. There is some anecdotal evidence to suggest that lamotrigine is associated with low rates of malformation [13]. Results from the data that were collected through the gabapentin pregnancy registry were published recently. Mountouris [33] reported that the major malformation rate among women who took gabapentin during pregnancy was 4.5%; this is slightly higher than the background rate of malformation in the United States. The rate of minor malformation was 2.2%. Furthermore, malformations that were observed were different than the cardiac, orofacial, and urogenital malformations that typically are associated with antiepileptic drugs. The population that was studied was extremely small; ongoing tracking of women who have epilepsy and are taking the newer medications must continue. A case series of three patients who were managed on levetriacetam as monotherapy reported no adverse effects [34]. There has been only one report of oxcarbazepine associated with a major anomaly [24].

Studies have shown that polypharmacy (ie, treatment with more than one anticonvulsant) is associated with an increased risk of teratogenicity compared with single agent therapy [35,36]. Therefore, monotherapy is one of the major therapeutic goals for a pregnant woman who has epilepsy [2,36–38].

A study by Canger and colleagues [39] supports the contention that the use of antiepilepsy medication during pregnancy is the primary risk factor for the increased incidence of congenital malformation. The researchers prospectively followed 444 pregnancies in women who had epilepsy from the 20th week postconception until delivery. Of the women studied, 427 were exposed to antiseizure drugs during pregnancy. Monotherapy was predominant (69.2%), with double-therapy (23%) and triple-therapy (2.2%) in the remainder. No abnormalities were reported in the infants of women who did not receive medical therapy for their

epilepsy. Malformations were identified in 9.7% of infants of women who were on monotherapy or polytherapy; 5.3% were classified as severe structural anomalies. There was no significant difference in the rate of anomalies among infants who were born to women who were on monotherapy (10.5%) compared with polytherapy (9.6%). The researchers speculated that this finding, which is in contrast with other studies, may be due to the low rates of polypharmacy. Valproic acid was associated with significantly more anomalies than any other antiepilepsy drug (15.9%) (carbamazepine [7.1%], primidone [8.6%], phenobarbital [4.8%], phenytoin [3.2%], and clonazepam [0%]). There were no cases of severe structural malformations with phenytoin monotherapy. Furthermore, there was no correlation between the rates of malformation and the frequency of seizures.

Holmes and colleagues [40] examined the incidence of malformation and diminished performance on intelligence tests in children who were born to mothers who had seizure disorders that were not treated with anticonvulsant medications during pregnancy and who did not experience seizures during pregnancy. They found no significant differences in the incidence of malformation or intelligence among these children when compared with a matched control group.

There is evidence that exposure to antiepilepsy medications in utero has long-term effects on children. A study that evaluated the long-term neuropsychologic consequences of maternal epilepsy and its treatment found that antiepileptic drugs were associated with an increase in abnormal EEG patterns in school age and adolescent children [41]. Minor neurologic dysfunction was noted with increased frequency in offspring of women who were exposed to anticonvulsants in utero as compared with offspring of women who had seizures but took no medication. This effect was greater in women who received more than one anticonvulsant. They also found a significant decrease in intelligence quotient scores in children who were exposed to polypharmacy in utero. When examining specific drugs, it was found that the use of primidone in conjunction with other antiseizure medications explained the compromised IQ scores. Primidone was correlated negatively with IQ score.

Anticonvulsant therapy during pregnancy has been associated with early onset neonatal hemorrhagic disease [42]. The hemorrhagic disease usually occurs within the first 24 hours of life and is characterized by a deficiency in the neonatal coagulation factors II, VII, IX, and X, with normal levels of factors V, VIII, and fibrinogen. This pattern is similar to vitamin K deficiency. There is evidence to suggest that maternal vitamin K_1 supplements may prevent this [43,44]. It is recommended that pregnant women who have epilepsy receive vitamin K_1, 10 to 20 mg orally per day, beginning at 36 weeks' gestation. This recommendation does not replace the recommendation of the American Academy of Pediatrics that all newborns receive 0.5 to 1 mg of vitamin K_1 intramuscularly, immediately after delivery [45]. Despite therapy, some infants die from their coagulopathy [46]. Aminoff [47] recommended that prothrombin and partial thromboplastin times be sent from the cord blood of infants of epileptic mothers at delivery. Infants who have abnormal laboratory values can be treated with fresh frozen plasma or factor concentrates as appropriate.

Preconceptional counseling and prenatal care

Before conception is the ideal time to counsel a woman who has epilepsy about the effects of the seizure disorder and anticonvulsants on pregnancy, as well as the possible effects of pregnancy on seizure disorders. Ideally, all women would see a physician before conception. Because up to 50% of pregnancies in the United States are unplanned, this is the exception, rather than the rule [48]. One study that assessed prenatal care of women who had epilepsy found that only 3% of women were evaluated by an obstetrician in the 3 months before conception [49]. A survey among women who had epilepsy found that 34% stated that they had received no advice regarding pregnancy and seizure disorders [50].

Fifty-four percent of women who had epilepsy who were surveyed in a British study reported that they had not been informed that antiepileptic medications might affect the fetus. Seventy-five percent were not referred to specialists for consultation during pregnancy. With respect to folic acid supplementation, the researchers uncovered a discrepancy based upon age. Sixty-three percent of younger women (19–34 years) reported receiving information about folic acid and epilepsy, whereas only 34% of older women (35–45 years) reportedly received this information [51].

Women who have epilepsy and seek medical advice before conception should be counseled that all anticonvulsants have been associated with increased rates of fetal malformation [38,52,53]. Minor congenital anomalies increase to a rate of 6% to 20% (Box 1). Nulman and colleagues [54] found that minor anomalies were significantly more common among offspring of women who had epilepsy and were treated with either phenytoin or carbamazepine during pregnancy than among nonepileptic controls.

Major malformations occur at approximately double the background incidence for the general population (4%–6%) [55]. Major defects include congenital heart disease, neural tube defects, orofacial defects, and urogenital defects. Women who have epilepsy should be referred for genetic counseling during pregnancy and should be offered maternal serum screening.

Box 1. Minor congenital malformations associated with antiepilepsy drugs

Distal digital hypoplasia
Distal nail hypoplasia
Ocular hypertelorism
Broad nasal bridge
Short, upturned nose
Altered lips
Altered epicanthal folds
Abnormal ears
Low hairline

Women who have epilepsy also should be counseled regarding the risk of seizure disorders for their offspring. Children of women who have idiopathic epilepsy have an increased incidence of seizure disorders; the risk of seizure disorders among these children is approximately 2.0% to 4.0%. Paternal epilepsy is not implicated in an increased rate of epilepsy among offspring [56].

Folic acid supplementation has been implicated in decreased efficacy of phenytoin during pregnancy [57]. The decrease in efficacy may be the result of decreased plasma levels of phenytoin during folic acid supplementation; however, the changes in plasma levels are seen without folic acid supplementation and may precede the initiation of supplementation [58,59]. Folic acid also has been shown to have epileptogenic properties in experimental conditions [60]. Despite this, it is extremely important that women who have epilepsy take folic acid supplements during pregnancy, particularly because of the increased incidence of neural tube defects that is associated with valproate and carbamazepine. The usual recommended dosage of folic acid for women who do not have an increased risk of neural tube defect is 0.4 mg/d, whereas the dosage for those who are at increased risk of neural tube defect because of a family history is 4.0 mg/d [61]. The American College of Obstetricians and Gynecologists recommends that women who have epilepsy and are being treated with antiepilepsy medications that are associated with an increased risk of neural tube defect (valproate and carbamazepine) receive 4.0 mg/d of folic acid [11]. No studies have examined the risk reduction of neural tube defect with folic acid in women who have epilepsy; however, some investigators suggested that 0.4 mg/d is sufficient [62].

All pregnant women, including women who have epilepsy, should be offered antenatal screening for neural tube defects through maternal serum α-fetoprotein screening (MS-AFP). The sensitivity of MS-AFP for detecting an open neural tube defect is 85%, thus 15% will remain undiagnosed when MS-AFP is used as the only screening tool [63]. Optimally, MS-AFP screening is performed between 16 and 18 weeks' estimated gestational age, but can be performed at between 15 and 22 weeks' gestation. A targeted ultrasound also should be performed between 18 and 20 weeks' gestation to screen for neural tube defects and other anomalies. The targeted sonogram has a sensitivity of 80% to 90% for detecting neural tube defects, and, in some specialized centers, can approach 95% sensitivity [64]. If indicated, amniocentesis should be offered for evaluation of amniotic fluid α-fetoprotein (AF-AFP) and acetylcholinesterase (AchE) levels, as well as karyotyping. The sensitivity of AF-AFP and AchE for detection of neural tube defects has been reported to be greater than 99% [63].

Most women do not seek preconception counseling. Therefore, one often is confronted with a woman who is at or near the end of the first trimester who is on antiepileptic medication. There is no evidence to support changing medications after the tenth completed week of gestation because the major fetal organ systems are formed completely at that time (Table 2). Changing medical therapy runs the risk of increasing the patient's seizure frequency, and, thus, should be avoided if the first trimester has passed. The American Academy of Neurology

Table 2
Timing of embryonic organogenisis

Organ system	Defect	Postconception age
Central nervous system	Neural tube defect	28 d
Face	Cleft lip	36 d
	Cleft palate	70 d
Cardiovascular system	Ventricular septal defect	42 d
Urogenital system	Hypospadius	56 d

Data from Moore KL. The developing human: clinically oriented embryology. 4th edition. Philadelphia: W.B. Saunders Company; 1988.

states that ''changing to an alternate antiepilepsy drug should not be undertaken during pregnancy for the sole purpose of reducing teratogenic risk''[2]. Monotherapy, using the lowest efficacious dosage, is a goal for all women of reproductive age. Weaning to a single anticonvulsant medication is best performed before conception.

If a woman has been seizure-free for 2 to 5 years, is not pregnant, and is willing to postpone conception for 6 to 9 months, it is possible to attempt to wean her off all medication. She must be counseled that this may precipitate a recurrence of seizures that may necessitate resumption of her anticonvulsant therapy. We recommend that this be done in consultation with a neurologist.

Monitoring drug levels during pregnancy is controversial. In general, if the patient is seizure-free on the current medication regimen, then she can be managed clinically [65]. If the woman is not seizure-free, then we recommend checking free serum levels and adjusting medication dosages as needed, keeping in mind that the dosaging may need to be readjusted postpartum. One should continue to use free serum levels until the sixth to eighth week postpartum. In doing so, one may be able to avoid symptoms of toxicity that result from the changes in pharmacokinetics postpartum. The American Academy of Neurologists recommends that a nonprotein bound level should be obtained during the preconception visit if possible, as well as once each trimester and during the last month of pregnancy [2].

The outcome of pregnancy in women who have epilepsy has been addressed in many studies, often with conflicting results. Reports of increased incidence of preeclampsia, vaginal hemorrhage, preterm labor, preterm delivery, operative deliveries, and fetal/neonatal death can be found in the older literature [66–69]. Other studies failed to replicate these findings [70–72].

Breastfeeding is safe for women who are being treated with any of several antiepilepsy drugs [2]. If excessive infant sedation is encountered, as may be seen with phenobarbital or primidone, the infant should be weaned slowly and monitored for signs and symptoms of withdrawal [73]. Despite the fact that the benefits of breastfeeding may outweigh the risks of exposure to small amounts of antiepilepsy drugs in breast milk (Table 3), patients and physicians are reluctant to promote breastfeeding [74]. It was recommended that infants be monitored for adverse effects if a woman is being treated with phenobarbital, clobazam,

Table 3
Breast milk: maternal plasma ratio of common antiepilepsy drugs

Medication	Breast milk:plasma ratio*	Possible adverse effects
Carbamazepine	0.69	Sedation, poor sucking
Gabapentin	0.73	None reported
Lamotrigine	0.6	None reported
Levetriacetam	Not known	Not known
Oxcarbazepine	0.5	Not known
Phenobarbital	0.4–0.6	Sedation, withdrawal
Phenytoin	0.45	Methemoglobinemia[a], sedation, poor sucking
Primidone	0.72	Sedation
Valproate	0.42	Thrombocytopenic purpura[a]

[a] One reported case.

* The breast milk to plasma ratio is the concentration of drug in the mother's milk divided by the concentration in the mother's plasma. A milk to plasma ratio that is less than 1.0 is considered low, (ie, there is minimal sequestration of the drug in breast milk). A high milk to plasma ratio (>1–5) indicates a drug that readily transfers to breast milk.

Summary data from Hale T. Medication and mother's milk. 10th edition. Pharmasoft Medical Publishing; 2002.

gabapentin, lamotrigine, or oxcarbazepine and consideration should be given to monitoring infant drug levels [65]. Additionally, further data are needed regarding the newer antiseizure medications, as well as the long-term effects on cognition and behavior after exposure to antiepilepsy medications in breast milk [38,75].

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Asthma in pregnancy

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Asthma is a chronic inflammatory disease of the airways. It is a significant medical problem and public health concern in the United States; more than 11 million people reported an asthma attack in the year 2000 [1]. In the United States more than 31 million people, including nearly 9.2 million children, have been told by a health care professional that they have asthma [2,3]. In 1999, 2 million emergency department visits, 478,000 hospitalizations, and 4426 deaths were attributed to asthma [1]. Asthma affects all ages but is a special concern in children; approximately 5% of all children who were younger than 18 experienced asthma attacks in the year 2000 [3]. Children who were younger than 15 was the only group that had an increase in the rate of hospitalizations for asthma. Since 1995 mortality rates have declined overall, but a disparity among ethnic groups remains. Asthma mortality is nearly three times higher in black men than in white men and 2.5 times higher in black women than in white women.

Asthma costs the American public billions of dollars annually. In 1998, the total cost of the disease was estimated to be in excess of $12 billion. Direct medical expenses (medications, hospitalizations, emergency-department visits, and physician services) accounted for nearly $7.4 billion and a reduced quality of life, loss of productivity at work or school, and other indirect costs accounted for the balance [2]. The cost of asthma treatment is related closely to the severity of the illness; a small cohort of patients consume 80% of all asthma-related health care resources.

Asthma remains a challenge for health care professionals. Management of this chronic condition is complicated by the nature of the disease, the presence of

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comorbid conditions, widespread variation in the implementation of treatment guidelines, the improper used of medications, the incorrect used of asthma devices, adverse drug events, poor patient compliance, and acceptance by patients of a substandard quality of life.

Given the high prevalence of asthma in the general population, it is not surprising that asthma is one of the most common complications of pregnancy; it occurs in 0.5% to 8% of gravid women [1,3–8]. Studies that report asthma severity during pregnancy show widely differing results. Data from the U.S. National Health Surveys demonstrated that the prevalence of asthma during pregnancy currently is between 3.7% and 8.4% [4]. The prevalence seems to be increasing, as indicated by increasing prevalence among younger pregnant women in these data, as well as increasing trends over time in women of childbearing age [4]. In about 0.05% to 2% of the cases, asthma occurs as a life-threatening event. Overall, the data suggest that the clinical severity of asthma during pregnancy improves in about one third of women, remains stable in about one third of women, and worsens in about one third of women [5,8]. Moreover, there is a tendency for the course of asthma to be concordant in subsequent pregnancies [5].

The global strategies of asthma management are similar to those in nonpregnant patients: (1) objective evaluation of maternal/fetal clinical conditions, (2) control asthma symptoms and prevent exacerbations by avoidance/control of triggering, (3) maximize lung function with pharmacologic treatment and minimize drug side effects, and (4) educational and psychologic support [8,9]. Objective assessment of pulmonary function includes encouraging women to perform peak expiratory flow rate (PEFR) recordings at home to assess symptoms, predict exacerbations, and adjust asthma therapy. Tests of fetal status, such as ultrasound measurements, and antepartum fetal assessment should be used as needed to evaluate the fetus. To manage patients optimally, health professionals need to appreciate the effects of asthma on pregnancy, the influence of pregnancy on asthma control, and the efficacy and safety of asthma treatment in pregnant women.

Normal physiology

Pregnancy results in anatomic and physiologic changes. Anatomic changes include a flaring of the lower ribs and an increase in the subcostal angle because the transverse diameter of the chest increases by approximately 2 cm [5]. The diaphragm is elevated approximately 4 cm [10]. Changes in the chest wall configuration peak at about 37 weeks' gestation and slowly return to normal after delivery [5]. The upper airway is affected by the increased vasodilatation of pregnancy which results in mucosal edema, nasal stuffiness, increased secretions, and possible nose bleeds. Total airway resistance is unchanged or slightly decreased during pregnancy as a result of progesterone relaxation of airway smooth muscle. Lung compliance is not changed during pregnancy; however, chest wall

compliance is decreased, which results in a decrease in total respiratory compliance in late gestation. The chest wall compliance effect is greater than that of decreased airway resistance effect. The result is an increase in the total work of breathing which contributes to the total 50% increase in oxygen consumption during pregnancy (Table 1) [10].

Physiologic changes that are mediated by placentally-produced progesterone include stimulation of the respiratory centers in the brain to produce hyperventilation and a sensation of dyspnea [5,8,11]. This hyperventilation decreases alveolar CO_2 tension and arterial P_{CO_2} and produces a state of respiratory alkalosis. The hypocarbia results in decreased plasma bicarbonate, which, in turn, results in minimal change in pH. Thus, normal pregnancy is a state of compensated respiratory alkalosis [11,12].

During pregnancy, oxygen consumption increases by 32 to 58 mL/min and the maximum oxygen consumption at rest varies between 249 and 331 mL/min. The "extra" consumption can be accounted for as follows: term fetus 12 mL/min; placenta 4 mL/min; increased cardiac output and ventilation 7 and 2 mL/min, respectively; kidneys 7 mL/min; and extra breast and uterine tissue 5 mL/min for a total of 37 mL/min [12].

The physiologic respiratory changes that occur during pregnancy may affect asthma control. Dyspnea is experienced by 60% to 70% of women at some time during their pregnancy, most commonly in the first or second trimester [5,8,10,12,13]. In early pregnancy, dyspnea may be caused by increasing circulating maternal progesterone levels, which result in a progressive increase in minute ventilation of up to 40% by the end of the first trimester, largely as a result of increases in tidal volume [5]. In late pregnancy, dyspnea is most likely to be caused by a combination of the hyperventilation of pregnancy and restriction that is due to uterine enlargement [5]. The latter leads to a small reduction in residual volume and functional residual capacity, whereas total lung capacity is maintained by an increase in inspiratory capacity [5]. Changes in peak flow rates and forced expiratory volume in one second (FEV_1) are small and of no clinical significance (Fig. 1).

Maternal gas exchange is disordered mildly as a result of the increase in minute ventilation [5,10,12]. A slight increase in arterial oxygen tension, a change in carbon dioxide tension, and pH changes are common and indicate a mild respiratory alkalosis [5,12]. The changes in arterial blood gas tensions occur despite increases in oxygen consumption and carbon dioxide production in the last few months of pregnancy [12]. Arterial blood gas levels in pregnancy were reported to be affected by maternal position and altitude of residence [10].

Pathophysiology

Asthma is one of several specific disease entities that is included in the general category of obstructive lung disease, which is characterized by limitation of airflow that generally is marked more during expiration than inspiration and

Table 1
Pulmonary values in pregnancy

Pulmonary function	Definition	Nonpregnant normal	Normal value in pregnancy	Other
Total lung capacity	Volume of air in lungs following maximal inspiration = VC + RV			
Vital capacity (VC)	Maximal volume of air exhaled from the lungs following maximal inspiration = IC + FRC		Unchanged	
Functional residual capacity (FRC)	Volume of air in the lungs at the end of expiration during normal breathing = ERV + RV		Decreased by 18% at term	3 techniques to measure: 1. closed-circuit helium dilution 2. open-circuit nitrogen washout 3. body plethysmography
Inspiratory capacity (IC)	Maximal volume of air that can be inhaled from FRC = V_T + IRV		Increases 5–10%	
Inspiratory reserve volume (IRV)				
Tidal volume (V_T)	Volume of air that enters the lungs during inspiration and leaves the lungs during expiration in normal breathing	450 mL	600 mL (increase of 40%)	
Expiratory reserve volume (ERV)	Maximal additional volume of air that can be exhaled following a normal expiration to FRC		Decreased by 15% at term	

Residual volume (RV)	Volume of air remaining in the lungs at the end of a maximal exhalation FRC − ERV	1000 mL	800 mL. Decreased by 20%.	Improves gas transfer from alveoli to blood
FEV_1	Volume of gas exhaled in 1 second by a forced exhalation after a full inspiration	Approximately 80–85% of vital capacity	No change	Measured with spirometry. Abnormal in patients who have lung disease.
FVC	Maximum amount of air that can be moved from maximum inspiration to maximum expiration	3.5 L	No change	If > 1 L, pregnancy usually is well tolerated.
FEV_1/FVC				Measured with spirometry. Determine degree obstruction/ monitor efficacy of treatment
PEFR			No change	Measure with flow meter. Requires patient cooperation/ effort dependent.
Minute ventilation	Volume of air moved per minute = RR × V_T	7.2 L	9.6 L (increase of 40% due to increase in V_T)	Increases oxygen available to fetus
Alveolar ventilation	Volume of air available for gas exchange each minute			$V_E - V_A$ represents gas in anatomic dead space
Respiratory rate (RR)	Number of respirations per minute	16/min	Minimal change	

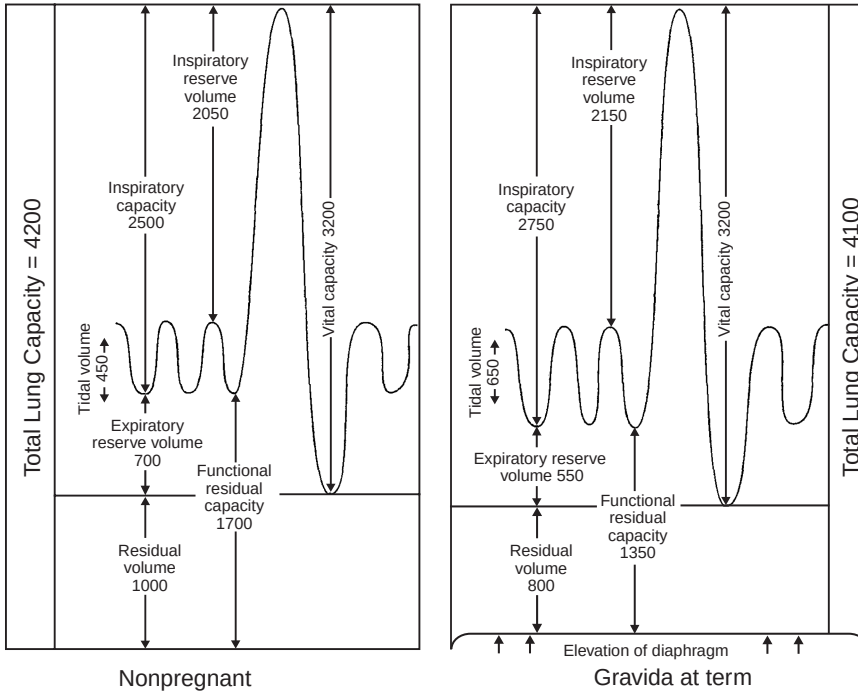

Fig. 1. Lung volume changes in pregnancy (units in milliliters).

results in a prolonged expiratory phase [5]. Asthma has varying degrees of airway obstruction, bronchial hyperresponsiveness, and airway edema that are accompanied by eosinophilic and lymphocytic inflammation [2,8]. It involves a complex interplay of inflammatory cells, cellular mediators, and external triggers [8]. It is a chronic disease with acute exacerbations that are characterized by recurrent bouts of wheezing and dyspnea that result from airway obstruction. The airway of an asthmatic person is hyperresponsive to stimuli such as allergens, viral infections, air pollutants, exercise, and cold air.

Airway inflammation is found in virtually all individuals who have asthma symptoms [2,11]. Endobronchial biopsies of asthmatic patients demonstrate hyperplasia and hypertrophy of the airway epithelial cell layer wall. Within the epithelial layer are increased numbers of surface secretory cells and mucus glands. In addition, the airway wall of asthmatics is infiltrated by many inflammatory cells (including eosinophils, neutrophils, monocytes, and lymphocytes) that produce epithelial injury, mucosal edema, abnormalities in neural mechanisms, increases in airway smooth muscle responsiveness, and airflow obstruction [8]. These cells can produce a series of cytokines that include interleukin (IL)-3, IL-4, and IL-5 and granulocyte-macrophage colony-stimulating factor. The synthesis of IgE occurs when these factors are released or stimulated [2,14]. The presence of IgE and eosinophils seems to have a major role in the

inflammatory response that is seen in asthma [2,6,11,14]. In addition to the cellular components that contribute to airway thickening, a thickening of the airway occurs that is not cellular in nature. The basement membrane is increased in thickness and shows alterations in its collagen components that contribute to airway obstruction and hyperresponsiveness [2,14].

Susceptibility to asthma seems to be established during infancy [15,16]; its course has been attributed to genetic features, such as atopy (the predisposition to form antibodies and to acquire allergies), and environmental factors, including viruses, allergens, and occupational exposures [2,15,16]. Immune mechanisms seem to be related causally to the development of asthma in more than 90% of patients who are younger than 16 years of age, in more than 70% of patients between 17 and 30 years of age, and in more than 50% of patients who are older than 30 years of age [2]. In addition, patients who have elevated serum IgE levels show a high incidence of self-reported asthma [2]. Asthma prevalence was shown to be associated with increased levels of total IgE, even in subjects who tested negative for specific IgE to common allergens and in nonatopic (nonhypersensitive) patients. Persistent wheezing, early sensitization, and bronchial hyperresponsiveness are associated with high serum levels at all ages. It was reported that patients who have nonatopic asthma produce IgE throughout the airways.

IgE-dependent mechanisms are involved in many of the allergic responses at the level of the airway [2]. After IgE antibodies are produced, mast cells and other airway cells are sensitized and become activated when specific antigens are encountered. Following sensitization, a two-phase reaction occurs upon exposure to an allergen.

Early phase

Early phase peaks at about 30 minutes after the allergen challenge and is mediated primarily by IgE-dependent processes. This response is initiated when IgE that is bound to receptors on the surface of effector cells is cross-linked subsequently by an allergen. This interaction causes the release of stored inflammatory mediators from the effector cell. The early response is associated closely with the level of free IgE.

Late phase

A later response—4 to 8 hours—may occur after allergen exposure. This later response is caused by inflammation that develops over time. The hyperactivity is manifested by bronchospasm, mucosal edema, and mucus plugging that results in air trapping and hyperinflation of the lungs [5,8,11]. Clinically, exacerbations of asthma produce acute episodes of progressive worsening of shortness of breath, sneezing, or chest tightness [8]. As airway obstruction progresses, expiratory airflow decreases and functional residual capacity increases. During pregnancy, these changes, if left untreated, may lead to hypoxemia in the mother, and subsequently in the fetus, especially if maternal P_{AO_2} decreases to less than 60 to 70 mm Hg [5,11]. The airway response to these stimuli includes contraction of

bronchial smooth muscle, mucus hypersecretion, and mucosal edema, all of which contribute to the pathophysiology of reversible airway obstruction that is characteristic of this disease. Inflammatory changes are present in the submucosa of airways in all cases of asthma; this fact has led to new thinking about the optimal treatment of asthma.

Severity of asthma

It is difficult to predict which women will experience worsening of their asthma during pregnancy; however, the severity of the condition before pregnancy and an absence of the expected decrease in IgE concentration during pregnancy should alert the clinician to this possibility. If asthma is going to worsen, it usually does so between 24 and 36 weeks' gestation. In most women, asthma severity returns to the prepregnant state within 3 months of delivery [17–19].

The National Asthma Education and Prevention Program (NAEPP) has classified asthma as: (1) mild intermittent, (2) mild persistent, (3) moderate persistent, or (4) severe persistent; recommended patients are treated accordingly. Mild asthma has the following symptoms: (1) episodes of asthma that are not more frequent than one to two times per week, (2) near-normal pulmonary function and peak expiratory flow variability, (3) nocturnal awakening because of symptoms not more than one to two times per month, and (4) no interference with normal daily activities. Moderate asthma is characterized by: (1) more than two episodes of asthma per week, (2) a pulmonary function test at 60% to 80% of predicted values with peak expiratory flow variability of 20% to 30%, (3) nocturnal awakening up to two to three times per week, and (4) some interference with normal activities but rare severe exacerbation. Severe asthma is characterized by: (1) daily asthma symptoms, (2) a pulmonary function test less than 60% of predicted values with greater than 30% variability in the PEFR, (3) nightly awakenings because of asthma symptoms, and (4) limitations of daily activities with frequent severe asthma exacerbation [8].

Patients are assigned to the grade of asthma that is consistent with their most severe symptoms. Because the natural course of asthma is highly variable, there are overlaps between classifications and classifications are likely to vary with time. Patients at any level of severity can have mild, moderate, or severe exacerbations. Mild asthma includes those who have a FEV_1 of at least 80%; mild persistent FEV_1 of at least 70%. Moderate asthma includes those who have an FEV_1 of at least 60% or who do not respond to bronchodilators. Pregnant women who do not respond to maximal doses of inhaled corticosteroids and bronchodilators are considered to have severe asthma ($FEV_1 \leq 60\%$).

Changes in blood gases that are secondary to acute asthma are superimposed on the physiologic respiratory alkalosis or pregnancy. Therefore, a normal or elevated P_{CO_2} level that is associated with acute asthma indicate respiratory compromise of greater severity in pregnancy than in the nonpregnant state. The dyspnea of pregnancy must be differentiated from dyspnea that is caused by asthma.

Effects of asthma on pregnancy/fetal outcomes

The fetus depends on its oxygen supply from the maternal arterial oxygen content, venous return and cardiac output, and uterine artery and placental bloodflow. The fetus is particularly prone to maternal respiratory changes. The placenta acts as a simple concurrent oxygen exchanger (ie, maternal and fetal blood run parallel to each other as they pass through the placenta) [14]. In the presence of maternal critical illness, such as with an acute exacerbation of asthma, maternal arterial Po_2 may decrease from its normal value of near 106 mm Hg. Any decrease in maternal Pao_2 may result in decreased fetal Pao_2 and fetal hypoxia. Administration of oxygen to the mother may produce only small increases in fetal Pao_2, but this may increase fetal oxygen saturation significantly [8]. There also are fetal adaptations to compensate for the low oxygen tension. Fetal hemoglobin has greater affinity for oxygen than does adult hemoglobin and fetal hemoglobin levels are higher than adult levels. Nevertheless, in asthma in which the mother is prone to respiratory alkalosis, the fetus may develop hypoxemia well before there is maternal perception of respiratory compromise [8]. With significant maternal respiratory compromise, fetal hypoxemia is suspected to result from decreased uterine blood flow, decreased maternal venous return, and a left shift of the oxyhemoglobin dissociation curve. These maternal changes ultimately produce changes in the fetus that include decreased umbilical blood flow, increased systemic and pulmonary vascular resistance, and decreased cardiac output. According to this scenario, the fetus may demonstrate compromise before the pregnant woman's perception of the seriousness of the asthma. Poorly-controlled asthma or severe asthma attacks further threaten the fetus because of increased maternal hypoxemia and diminution of uterine artery bloodflow secondary to hypocapnic vasoconstriction.

Clark [20], at the National Asthma Education Program Working Group on Asthma During Pregnancy, reported on the increased potential adverse effects of asthma on pregnancy. These adverse outcomes were collected from multiple epidemiologic studies and included an increased incidence of preterm labor, low birth weight infants, pre-eclampsia, and perinatal morbidity [8]. An increased incidence of low birth weight and premature babies, neonatal hypoxia, complications of labor, and perinatal and maternal mortality have been reported in poorly-controlled pregnant asthmatics. Pregnancies that are affected by asthma are at increased risk for hyperemesis gravidarum, preterm birth, pre-eclampsia, gestational diabetes, intrauterine growth retardation (IUGR), and neonatal mortality [11].

Asthmatic women are almost three times more likely than those who do not have asthma to have hyperemesis gravidarum [9,21,22]. Maternal hemorrhage is twice as common in asthmatics with a greater risk in those who take corticosteroids [9,21]. A large retrospective study of pregnant women who had asthma found longer hospital stays and an almost twofold increase in pre-eclampsia, placenta previa, and cesarean sections [1,3,9]. Together with other studies, this study suggests that pregnancy-induced hypertension is two to three times more common in women who have asthma [1,3,9]. Premature labor was reported to be

more common in asthmatics, especially in the corticosteroid-dependent patient [1,14,21]. A recent prospective cohort study of 873 pregnant patients who had mild asthma, 814 pregnant patients who had moderate asthma, and 52 pregnant patients who had severe asthma found no increase in preterm delivery as compared with 881 nonasthmatic controls [6]. There was increased rate of cesarean delivery in the asthmatic group. Bracken et al [7] reported that IUGR was associated with asthma severity, possibly as the result of hypoxic fetal effect. They also found that women who had asthma symptoms but no diagnosis were at particular risk of undermedication and delivering IUGR infants. Perhaps because of some of the aforementioned complications, women who have asthma are more likely to undergo induction of labor.

Maternal outcomes in those who have mild asthma are no different from those in women who did not have asthma [6]. Maternal mortality from asthma seems to be low. Although maternal death from asthma is uncommon, it usually occurs in patients who have status asthmaticus. Of the 16 women who had severe asthma in the Collaborative Perinatal Project, 4 women died [14]. Potentially life-threatening complications of severe asthma include pneumothorax, pneumomediastinum, acute cor pulmonale, and respiratory arrest. Maternal mortality rates approach 40% when a pregnant asthmatic requires mechanical ventilation.

Effects of pregnancy on asthma

The effects of pregnancy on asthma are unpredictable [21]. A review of nine studies with more than 1000 pregnancies that were complicated by asthma found that 50% of asthmatic patients remained stable, 30% improved, and 20% had worsening of their disease [14]. Another prospective study reported that slightly more than one third of pregnant asthmatics had deterioration in their condition and required more intensive therapy during their pregnancy [9].

Prediction of who will have worsening of their asthma during pregnancy is difficult; however, those who have more severe disease before conception are at greater risk of deterioration than those who have mild disease [18]. Up to 40% of pregnant asthmatics experience an exacerbation during labor and delivery [23]. Postpartum may also prove dangerous for asthmatics; 26% to 42% of women experience an exacerbation of asthma after delivery [24].

Fetal gender may influence asthma. In one study of 34 pregnant women who had asthma and were unaware of their child's sex, those who gave birth to boys were more likely to report improved asthma symptoms during pregnancy. Another study found that the use of drugs to treat asthma was less common among mothers of boys [9].

Suggested causes of asthma deterioration in pregnancy include refractoriness to cortisol, prostaglandin F2 α-mediated bronchoconstriction, viral or bacterial respiratory infections, gastroesophageal reflux, stress, increased inflammatory mediators (eg, placental major basic protein) reaching the lungs, and reduced functional residual capacity.

Goals for the pregnant woman who has asthma

A pregnant woman who has asthma should be able to carry on her normal daily activities. A goal of good control with near normal pulmonary function rates should be sought. Good control includes that the expectant mother is active without experiencing any asthma symptoms. She should be sleeping comfortably through the night and not be awoken by asthma symptoms. Finally, she should give birth to a healthy baby.

Asthma guidelines

The National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program (NAEPP) in an effort to help health care professional bridge the gap between current knowledge and practice convened expert panels and published their first set of guidelines in 1991 [25]. Six specific components were included in the guidelines: (1) a definition of asthma and criteria for its diagnosis, (2) a classification of asthma by severity, (3) a section on the use of objective measures to assess the severity of asthma, (4) a section on patient education, (5) a history of environment control measures and stress factors that trigger asthma exacerbations, and (6) recommendations for pharmacologic approach that is designed to treat exacerbations [2,25].

Recommendations for the treatment of asthma during pregnancy were organized around the following four components of effective asthma management [8]:

- Use of objective measures of lung function to assess the severity of asthma and to monitor the course of therapy
- Patient education that fosters a partnership among the patient, his or her family, and clinicians
- Environmental control measures to avoid or eliminate factors that contribute to asthma severity
- Comprehensive pharmacologic therapy for long-term management that is designed to reverse and prevent the airway inflammation that is characteristic of asthma, as well as pharmacologic therapy to manage asthma exacerbations [2,25]

Objective measures of lung function

Pulmonary function testing is necessary to establish the diagnosis of asthma [21]. The single best measure of pulmonary function for making the assessment of asthma severity is the FEV_1 [21]. Subdivisions of lung volume can be determined by means of a spirometer. A spirometer is a simple gas volume recorder. The commonly-used water-filled spirometer consists of a double-walled drum into which a bell is fitted. The bell is attached by a pulley to a pen that writes on a second rotating drum. As air enters the spirometer, the drum rises and, because of

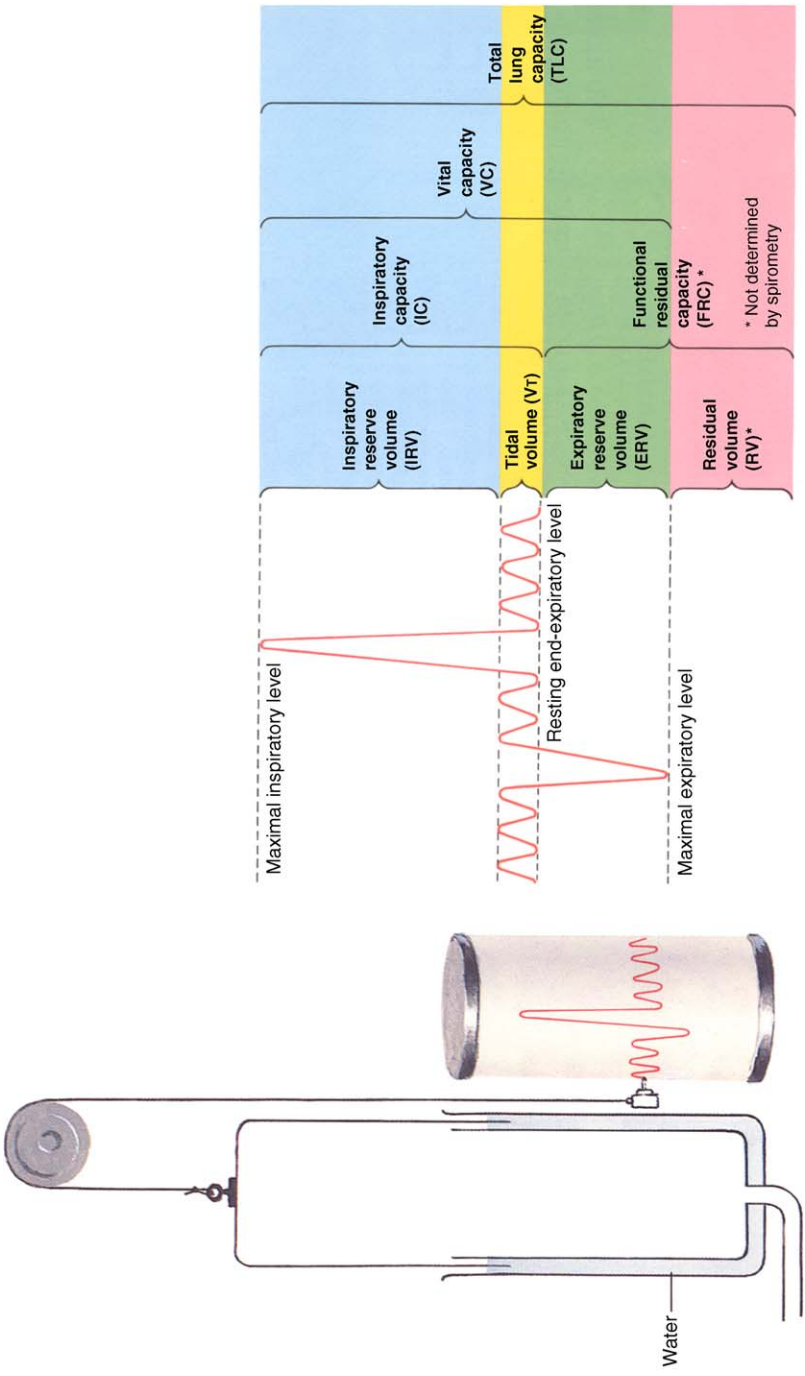

Fig. 2. Spirometry measure of lung volumes.

Fig. 3. Peak flow meter.

the pulley, the pen is lowered (Fig. 2). To determine lung volumes and capacities, the patient is seated and breathes quietly from the spirometer. After several breaths to establish the resting end-expiratory level, a maximal inspiration is taken followed by a slow complete expiration.

By convention, all lung volumes are expressed in terms of a body temperature, ambient pressure, and saturation with water vapor. Because gas volumes that are measured in a spirometer are at ambient temperature, rather than body temperature, appropriate corrections must be made. Forced vital capacity (FVC) and FEV_1 are measured using a spirometer.

PEFR is the greatest flow velocity that is achieved during a forced expiration. This measurement correlates well with the FEV_1 [26] and is easy to measure by the patient herself with a peak flow meter (Fig. 3), an inexpensive, hand-held flow meter. It allows home monitoring of PEFR and provides a daily assessment of lung function and response to ongoing therapy [8,27]. Ideally, pregnant women who have asthma should take daily PEFR measurements at home with a portable hand-held peak flow meter. The measurements should be taken twice a day, once upon arising in the morning and again roughly 12 hours later [8] and should be recorded in a diary. The patient should bring this diary and it should be reviewed with the obstetrician at each prenatal visit. Predicted values of PEFR are in the range of 380 to 550 L/min for women, and show little or no change with pregnancy. Although predicted values offer valuable parameters, it is best to make management decisions of the patient's "personal best" PEFR, which is established during a symptom-free period.

Patient education

Patient education should begin at the time of diagnosis, be integrated with continuing care, and involve all members of the health care team. A partnership

among the patient, her family, and the health care providers should be sought through open communication and joint development of a treatment plan. Educational components should include the nature of asthma, an understanding of the different medications that are prescribed for its treatment, instruction regarding the proper technique in the use of devices for administering medications and monitoring air flow obstruction, and written guidelines for maintenance therapy and rescue therapy for exacerbations.

Episode prevention

Prevention is the key for asthmatic episodes. Some ways this can be done include avoidance of the environment triggers that result in bronchoconstriction of the airways, avoidance of the causes or inducers that result in inflammation of the airways, and continuing regularly scheduled medications during pregnancy, labor, and delivery. Measures such as changing filters in the home heating and cooling systems, avoiding smokers, moving pets outside, and avoiding the home for 1 hour after vacuuming or dusting may help to prevent exacerbations [28]. Most asthmatics benefit from encasing their mattresses and pillows in airtight covers, washing bed linens weekly in 130° F water, lowering home humidity to 50% or less, avoiding vacuuming or wearing a mask while vacuuming, closing windows and using air conditioning, and avoiding mid-day outdoor activities when allergen concentration or air pollution may be at their highest levels.

Triggers irritate the airways and result in bronchoconstriction [28]. They do not cause inflammation, and, therefore, do not cause asthma. Triggers result in symptoms that are immediate, short-lived, and rapidly reversible. The effect of triggers is worse if inflammation is already present in the airways. Examples of triggers include cold air; dust; strong fumes; exercise; inhaled irritants; emotional stress; food additives, such as sulfites; some drugs, such as aspirin and β-blockers, and smoke [8]. Cigarette smoke may be the most common environmental irritant to trigger asthma. Second-hand smoke is particularly aggravating to children and pregnant women who have asthma and should be avoided.

Vigorous exercise may cause bronchospasm. Pregnant women who have asthma may exercise under the supervision of their obstetrician. Prevention of exercise-induced asthma includes taking medication, such as albuterol, before exercise; properly warming up and cooling down; and wearing a scarf or mask over the nose and mouth if exercising in the cold or on high-pollen days [28].

Causes or inducers of asthma, in contrast to triggers, cause airway inflammation and airway hyperresponsiveness. Inducers result in symptoms that last longer, are delayed, and are less easily reversible than those that are caused by triggers [28]. Allergens and respiratory viral infections are the most common example of inducers.

Inhaled allergens are the most important cause of asthma. Seventy-five percent to 85% of patients who have asthma are reported to have positive immediate skin test reactions to common inhalant allergens. The most common inhaled allergens include pollen (grasses, trees, and weeds), animal (cat and horse) secretions (urine and saliva), molds, and house dust mites.

Immunotherapy may prevent allergic inflammation and was shown to reduce asthma symptoms that were provoked by allergens, such as house dust mites, animal dander, and grass pollen. Immunotherapy may be considered for patients when avoiding allergens or irritants is not possible and when appropriate medications fail to control asthma. The principal concern with the use of allergy immunotherapy during pregnancy has been the occurrence of anaphylaxis, which may induce uterine contractions or cause fetal morbidity or mortality. Women who are at increased risk for anaphylaxis include those who are receiving increased doses of antigen, who have extreme sensitivity, and who are exposed to high levels of environmental allergens [8]. As a consequence, the initiation of immunotherapy is not recommended during pregnancy. Ongoing immunotherapy may be continued at the current dosage unless immunotherapy was started recently or the patient experiences frequent reactions.

Respiratory viral infections, particularly in children, may evoke an asthmatic reaction. The influenza vaccine is indicated for all patients who have moderate or severe asthma [8]. This may help to prevent complications that result from influenza; however, this vaccine is contraindicated in patients who have a known allergy to eggs.

Treatment/maintenance

Asthma should be integrated into regular obstetric care. If possible, the same provider should be managing both aspects of the patient's care. If more than one clinician is involved, a team approach should be mandated. Pregnant women who have asthma should be reassured that their asthma medication carries less risk to the fetus than a severe asthma attack. Inadequately-treated or poorly-controlled asthma can cause maternal and fetal hypoxemia, which, in turn, can lead to pregnancy complications and poor birth outcomes. Several factors influence the control of the asthmatic patient, including the dynamic nature of the disease, poor patient adherence to therapy, ignorance of the effect of comorbid conditions on treatment outcomes, poor access to care, and the cost of health care.

Management of an asthma exacerbation requires assessment of its severity. Treatment decisions are based on matching therapy to the intensity of symptoms. Hence, planning effective and safe strategies for managing asthma depends on the correct diagnosis of disease severity. Preconception optimalization of asthma is ideal. The aim of good control relies, therefore, on a continuum. When necessary, the number of medications and frequency of administration should be adjusted to maintain control.

Measurements of PEFR are used to formulate a management plan for asthma treatment. Three zones of measurement—green, yellow, and red—are used commonly to interpret peak flow rates. The ''green zone'' is 80% to 100% of the patient's ''normal'' peak flow rate. A reading in this zone signals that asthma is under reasonably good control and the patient should continue on her prescribed program of management. The ''yellow zone'' represents 50% to 80% of the patient's ''normal'' peak flow rate and signifies caution. It implies that the airways are narrowing and extra treatment may be required. The patient's symptoms may get better or are on the way to worsening, depending on response to treatment. The patient should be instructed that values in the yellow zone necessitate a phone call to the physician. The ''red zone'' is equal to less than 50% of ''normal'' peak flow rate and signifies a medical alert. Immediate actions need to be taken that include contacting the physician and treatment with rescue medications. An office or emergency room visit is recommended if the patient does not respond to rescue medications. A management plan for each zone should be developed by the physician and asthmatic patient. This plan should be clear, agreed upon by physician and patient, written down, and readily available to the patient and her family in case of an asthma attack. The underlying rationale for the use of the PEFR monitoring is to detect exacerbations that many asthmatics fail to perceive. This poor perception of the severity of the condition is a major cause for delay in the treatment of symptoms.

Asthma status should be monitored at every prenatal visit using objective lung testing. Subjective assessments are notoriously inaccurate. Consequently, objective measures of lung function are necessary to assess the severity of disease and to tailor appropriate therapy for ongoing symptoms. The best measure of lung function for assessing the severity of asthma is FEV_1. Another objective measure is the PEFR. The PEFR correlates with FEV_1 and can be measured with an inexpensive, hand-held flow meter. The peak expiratory flow meter is a user-friendly objective method of testing patient status. A ''personal best'' should be established during an asymptomatic period. Home monitoring of peak expiratory flow rate provides a daily assessment of lung function and response to ongoing therapy. Patients should be encouraged to keep a written log of their PEFR and bring these to their clinic appointments—similar to blood sugar records for diabetic patients. Adjustments of asthma therapy and interventions are based on reductions from the patient's personal best benchmark. PEFR and FEV_1 are indicators of airway obstruction and do not change during pregnancy. A goal of therapy is normal to near normal pulmonary function.

First-trimester ultrasound confirmation of gestational age allows comparison for eventual fetal growth. Additional ultrasound examinations may be needed if IUGR is suspected. In the third trimester, the need for fetal surveillance, through assessment of fetal movement or fetal heart rate monitoring, should be based on the severity of asthma. Routine obstetric monitoring for the pregnant patient who has asthma should include ultrasound for fetal growth, Doppler assessment of fetal heart tones, and daily kick counts. Biweekly biophysical profiles or nonstress tests may be instituted beginning at 28 weeks' gestation.

Pharmacotherapy

Pharmacologic therapy for pregnant women who have asthma should be individualized and based on the severity of disease [29]. Patients who have mild intermittent disease (exhibit daytime and nocturnal symptoms less than twice a week and infrequent exacerbations) should be taking daily scheduled medications. Inhaled medications are preferred because they deliver the medications directly to the bronchial tree, thus decreasing the potential for systemic side effects. For patients who have difficulty with the proper coordination of inspiration and actuation of the inhaler, use of a spacer may be helpful. The possible occurrence of severe exacerbation should be treated with a course of systemic corticosteroids. Medications should be taken daily on a regular schedule, not just when symptoms arise. Women who do not respond to maximal doses of inhaled corticosteroids and bronchodilators are considered to have severe asthma and usually require systemic corticosteroids. Chronic mild asthma results in brief, intermittent symptoms that occur up to twice a week. Generally, the PEFR is greater than 80% of expected or even 80% of the patient's personal best value. Therapy for these patients consists of an inhaled β2-agonist, two puffs every 3 to 4 hours for the duration of symptoms.

Patients who have moderate asthma have symptoms more often than twice a week; symptoms may last several days, affect sleep, or require emergency care. The PEFR is usually 60% to 80% of baseline. Inhaled anti-inflammatory agents (cromolyn sodium or corticosteroids) should be added to the regimen of patients who have moderate asthma or who do not respond to bronchodilators. Therapy consists of inhaled corticosteroid or inhaled cromolyn to reduce inflammation and an inhaled β2-agonist for bronchodilation.

Patients who have severe chronic asthma have continuous symptoms, limited activity, and frequent nocturnal symptoms and exacerbations that may require emergency treatment and hospitalization. The PEFR may be less than 60% of normal. Regular use of inhaled corticosteroids, inhaled cromolyn, and inhaled β2-agonist is recommended. Oral corticosteroids in a short burst (40 mg daily for 7 days followed by tapering for 7 days) may be necessary to relieve symptoms.

β2-Agonists

Generally, inhaled bronchodilators (β2-agonists) are first-line therapy for patients who have mild disease. These agents activate adenyl cyclase, and, therefore, increase intracellular cyclic adenosine monophosphate, which has a bronchodilator effect by way of action on airway smooth muscle cells and an inhibitory effect on release of mediators from mast cells. The inhaled β-agonists that are used most frequently are those that are β2-selective, such as albuterol and terbutaline.

The safety of inhaled β2-agonist bronchodilators was reported from a prospective study of 259 pregnant asthmatics who used β2 agonists compared with 101 pregnant asthmatics who did not using bronchodilators, and 295 pregnant

control subjects [21]. Overall, the inhaled β2-agonists were not associated with an increased frequency of malformations or other unwanted effects in newborns [9,21]. Although data are limited to indicate which specific β2-agonist is preferable, albuterol, terbutaline, and metaproterenol are considered short-acting β2 agonists of first choice; they have been used for decades without any reported significant side effect in humans. Generally, the inhalatory route is well-tolerated. Oral/parenteral administration of β2-agonists to asthmatic pregnant women is not recommended because of the lack of safety data in the first trimester, potential inhibitory effect on the delivery, and the higher rate of side effects compared with the inhalatory route. Limited data are available on the safety of long-acting β2-agonists, salmeterol and formoterol, because of their recent commercial availability. One report on 33 patients who took formoterol during pregnancy showed no adverse side effects [25]. It was shown that when asthma symptoms are not controlled by inhaled corticosteroids, the addition of salmeterol is more effective than doubling the dose of steroids [30]. Therefore, long-acting βB2-agonists can be prescribed to pregnant patients, after evaluation of the risk/benefit ratio, if they had been treated successfully with these agents before pregnancy or are suffering from recurrent nocturnal asthma.

Cromones

Cromolyn sodium is considered safe in pregnancy because of its virtually complete absence of systemic side effects [11,21]. In vitro and in vivo animal studies showed that cromolyn sodium inhibited the release of mediators from sensitized mast cells. Cromolyn sodium acts by inhibiting the release of histamine and leukotrienes slow reacting substance of anaphylaxis (SRSA) from the mast cell. Cromolyn sodium has no intrinsic vasoconstrictor, antihistamine, or glucocorticoid activity. It is poorly absorbed from the gastrointestinal tract; therefore, the inhalation route is recommended. It has been assigned U.S. Food and Drug Administration (FDA) category B with no evidence of fetal malformations in animal studies; however, no adequate and well-controlled studies have been done in pregnant women [21].

Nedocromil (alocril) is the newer cromone sodium. It is a mast cell stabilizer. Nedocromil inhibits the release of mediators from cells that are involved in hypersensitivity reactions. Decreased chemotaxis and decreased activation of eosinophils also were demonstrated. In vitro studies with adult human bronchoalveolar cells showed that nedocromil sodium inhibited histamine release, from a population of mast cells that have been defined as belonging to the mucosal subtype, and β-glucuronidase release from macrophages. It also carries an FDA pregnancy category B rating. Although no human data are available, teratogenic events have not been shown in animal studies.

Inhaled corticosteroids

Inhaled corticosteroids (ICSs) are the cornerstone of long-term therapy for bronchial asthma because they effectively control inflammation and reduce

asthma exacerbations and the need for on-demand bronchodilators [20]. The precise mechanism of corticosteroid action on inflammation in asthma is not known. Corticosteroids have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) that are involved in allergic- and nonallergic-mediated inflammation [11]. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Limited data are available on the safety of ICS use in pregnancy. All ICSs, with the exception of budesonide, are pregnancy category C. The FDA recently upgraded budesonide to pregnancy risk category B based on data from three Swedish registries that covered more than 2000 births from 1995 to 1997 [21]. These studies showed no increased risk of congenital malformations for women who took budesonide. Fluticasone (advair, flonase, flovent) carries a category C risk because of unfavorable animal study reports following subcutaneous administration; however, human studies have not reported adverse outcomes. Beclomethasone was recommended in the past because the greatest amount of published data was available regarding its use in pregnancy [20]. Beconase is available as a nasal spray for allergic rhinitis. Flunisolide (aerobid) is another popular ICS.

Ipratropium bromide

Ipratropium bromide (atrovent) is an anticholinergic (parasympatholytic) agent that, based on animal studies, seems to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent that is released from the vagus nerve. Anticholinergics prevent the increases in intracellular concentrations of cyclic GMP that are caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. The bronchodilation following inhalation of atrovent primarily is a local, site-specific effect, not a systemic one. Ipratropium is used largely for the treatment of chronic obstructive pulmonary diseases. It is a pregnancy category B drug; however, no adequate or well-controlled studies have been conducted in pregnant women. Because it does not offer significant advantages over β2-agonists, it is not considered a first-line therapy in pregnancy [21].

Theophylline

Theophylline (theo-dur) is a bronchodilator that is classified structurally as a methylxanthine. Theophylline has two distinct actions in the airways of patients who have reversible obstruction: smooth muscle relaxation (ie, bronchodilation) and suppression of the response of the airways to stimuli (ie, nonbronchodilator prophylactic effects) [26]. Although the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase (phosphodiesterase III and, to a lesser extent, phosphodiesterase IV), whereas nonbronchodi-

lator prophylactic actions probably are mediated through one or more direct molecular mechanism that do not involve inhibition of phosphodiesterase III or antagonism of adenosine receptors. Serum concentrations between 10 and 15 μg/mL achieve most of the drug's potential therapeutic benefit while minimizing the risk of serious adverse events.

Theophylline was shown to cause birth defects in animals when given in dosages that were many times higher than the normal human dosage. Many drugs are known to have significant drug interactions with theophylline. A high-carbohydrate/low protein diet can decrease the clearance and prolong the half-life of theophylline. It has several side effects, including nausea, gastroesophageal reflux, and hypertension, and, therefore, may not be well-tolerated in pregnancy. Furthermore, it readily crosses the placenta and the ability to clear theophylline from the body may decrease in later pregnancy [29]. Serum levels are recommended for monitoring. For all of these reasons, it is not a first-line treatment for asthma in pregnancy.

Leukotriene modifiers

Montelukast (singulair) and zafirlukast (accolate) are widely available for the treatment of asthma. The cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene receptors (CysLT) that are found in the human airway. Cysteinyl leukotrienes and leukotriene receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity that is associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Montelukast is an orally-active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically-important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity. It is a pregnancy category B drug with no adverse outcomes from animal studies. Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women.

Zafirlukast is a selective and competitive receptor antagonist of LTD4 and LTE4, components of SRS-A. In humans, zafirlukast inhibited bronchoconstriction that was caused by several kinds of inhalation challenges. Pretreatment with single oral doses of zafirlukast inhibited the bronchoconstriction that was caused by sulfur dioxide and cold air in patients who had asthma. Pretreatment with single doses of zafirlukast attenuated the early- and late-phase reactions that are caused by inhalation of various antigens, such as grass, cat dander, ragweed, and missed antigens in patients who had asthma. It also attenuated the increase in bronchial hyperresponsiveness to inhaled histamine that followed inhaled allergen challenge. It is a pregnancy category B drug with no adequate well-controlled studies in humans.

IgE blockers

Omalizumab, a humanized murine monoclonal antibody, inhibits the binding of IgE to mast cells by forming complexes with circulating free IgE [3]. This agent binds to the C3 domain of the IgE, the region where IgE binds to the mast cell and FceRI receptor [2]. It forms complexes only with free IgE and cannot displace or cross-link mast cell–bound IgE. Further, by removing free IgE from the circulation, omalizumab indirectly down-regulates FceRI expression. This is an important feature because down-regulation of IgE receptors further reduces the potential for basophil/mast cell activation by IgE molecules. It has been advocated for patients who have severe persistent asthma; however, it has not been studied in pregnancy.

Systemic corticosteroids

In some cases of severe asthma, systemic corticosteroids may be required [9,11]. Chronic use of oral corticosteroids or even assumption of high-dosage systemic steroid during pregnancy carries some risk. Perlow and coworkers [24] reported an increased incidence of diabetes mellitus, preterm labor, premature rupture of membranes, preterm delivery, and low-birthweight infants in 31 steroid-dependent pregnant asthmatics. An association with pre-eclampsia was reported. Also, an increased incidence of pregnancy-induced hypertension in pregnant asthmatic women who took corticosteroids was described.

Animal studies have reported an association of cleft palate, placental insufficiency, spontaneous abortion, and growth retardation with systemic corticosteroid use. In humans, data that were derived from the Spanish Collaborative Study of Congenital Malformations showed a relationship between exposure to corticosteroids during the first trimester of pregnancy and an increased risk of cleft lip (with or without cleft palate) in newborns [32]. This study design suffered from recall bias, highly variable exposure, and lack of logistic regression analysis for confounding variables, such as maternal illness or smoking. Furthermore, only 4 of the 1184 infants who had oral clefts had a history of corticosteroid exposure; one's mother was given only two dosages of prednisone, 40 mg. Two other case-control studies associated first trimester maternal use of systemic corticosteroids with an increased risk of oral clefts [33,34]. Another population-based control study demonstrated no association between cleft palate or other congenital anomalies and corticosteroid use [35]. Furthermore, many normal infants have been born to women who received systemic corticosteroids throughout pregnancy. The risk/benefit ratio suggests that women who require systemic corticosteroids for asthma control should take them because the risk of poor outcomes from uncontrolled asthma outweighs the potential harm from corticosteroid use.

Treatment/acute episode

Exposure to an allergen may cause an immediate response, such as coughing or wheezing. Hyperresponsive airways react by tightening. These symptoms

usually are relieved by a bronchodilator, such as ventolin. A later response—4 to 8 hours—may occur after allergen exposure and is caused by inflammation that develops over time.

An attack of bronchial asthma, if not treated immediately, can progress to a severe attack or status asthmaticus. Status asthmaticus is a medical emergency [36]. Severe asthma of any type that does not respond after 30 to 60 minutes of intensive therapy is termed status asthmaticus [37]. During pregnancy, consideration for early intubation with mechanical ventilation that is indicated by fatigue, carbon dioxide retention, or hypoxemia should be considered. Consultation with a maternal fetal medicine specialist and pulmonologist is highly recommended for management of these cases. Hypoxia may put the mother and fetus at risk. A brief history, including events that preceded the attack, other illness, present medications, associated cardiac or pulmonary disease, allergies, the presence of productive cough, and presence and characteristics of sputum should be obtained. Information should be obtained that includes the history of similar attacks and their management. Onset and duration of current symptoms and events that led up to the symptoms should be documented. Current medications should be reviewed.

Physical examination should include general appearance of the patient: Is she cyanotic? Can she speak in complete sentences? Is she using accessory respiratory muscles? Attention should be paid to underlying or complicating cardiopulmonary disease, respiratory malfunction, or cyanosis and to the state of consciousness. Vital signs should be obtained immediately upon arrival and recorded. Special attention should be paid to temperature and respiratory rate. If febrile, the patient should be admitted for work-up and treatment. A radiograph of the chest should be obtained on all febrile patients to rule out bronchopneumonia. Continuous pulse oximetry should be obtained. Laboratory analysis should include complete blood count, spirometry with FEV_1 or PEFR by flow meter, chest radiograph, serum electrolytes, arterial blood gases, and sputum gram stain and culture. Oxygenation, as measured by arterial blood gas, monitors patient status. Initially, the P_{CO_2} decreases, but as the patient hyperventilates, the P_{O_2} increases. An increasing P_{CO_2} (>35 mm Hg) in the presence of hypoxia suggests imminent respiratory collapse and the need for intubation.

Medication dosages for the treatment of acute exacerbations of asthma in pregnancy are listed in Table 2. Inhaled β-agonists have become the primary treatment for acute exacerbations of asthma. Bronchodilation begins within 5 minutes of therapy. Treatments can be repeated every 20 to 30 minutes as needed. Inhaled epinephrine or isoproterenol is not recommended because of the higher incidence of cardiovascular side effects that result from β1 stimulation. Subcutaneous terbutaline can be used in place of the inhaled agents at a dosage of 0.25 mg every 20 to 30 minutes for three dosages; however, current practice favors inhalation therapy. Oxygen should be given to all pregnant women who have an asthma episode to maintain the P_{O_2} at greater than 70 mm Hg or O_2 saturation at greater than 95%.

For women who have rapid response (an FEV_1 or PEFR greater than 70% of predicted) to bronchodilator therapy, follow-up may be on an outpatient basis. Patients who have an incomplete response to β2-agonist bronchodilator therapy may be treated for up to 4 hours to determine whether admission to the hospital is required. Most patients who have an FEV_1 or PEFR that is less than 40% after 1 hour of bronchodilator therapy or less than 70% after 4 hours of therapy require hospitalization.

Methylxanthine use, including theophylline or aminophylline, is discouraged in acute asthma cases. β2-Agonists are more effective and do not require the serum level monitoring.

Intravenous corticosteroids should be given if the exacerbation is severe, if the exacerbation occurs while the patient is taking oral steroids, or if the response to bronchodilator therapy is incomplete or poor after 1 hour of bronchodilator therapy. Incomplete response includes an FEV_1 or PEFR of 40% to 70% of the predicted value; a poor response is an FEV_1 or PEFR that is less than 40%.

Antibiotics are reserved for patients who present with fever, elevated leukocyte count, or purulent sputum [26]. They are not given routinely. Hydration should be given to patients who demonstrate dehydration by the state of mucous membranes, urine output, urine specific gravity, or electrolyte disturbances. Sedatives, mucolytics, anticholinergics, and chest physical therapy do not improve acute asthma symptoms and may cause harm.

Fetal status should be monitored continuously during treatment of the acute asthma exacerbation.

Asthma and labor and delivery

Continuous monitoring of mother and fetus is especially important for the pregnant woman who has asthma. Intravenous access should be obtained upon admission. A peak flow rate should be taken upon admission to the labor suite and then every 12 hours. If asthma symptoms develop, peak flows should be measured after treatments. The mother's asthma medications should be continued during labor and delivery. Women whose asthma is well-controlled may continue to take their usual medications. Intravenous hydrocortisone (100 mg, every 8 hours for 24 hours) should be given to women who have received systemic corticosteroids during the pregnancy [26].

The fetus should be monitored beginning at admission and throughout labor. In almost all cases, continuous electronic monitoring is indicated during active labor.

Pain management for the asthmatic women in labor requires special attention. Adequate pain management decreases the mother's risk of bronchospasm during labor. Narcotics, such as morphine and meperidine, should be avoided because of their actions on smooth muscle and the potential for respiratory depression [8]. A nonhistamine-release narcotic, such as fentanyl, is preferred over morphine or meperidine if needed [8,21]. Lumbar epidural is probably the anesthetic of

Table 2
Asthma medications

Drug class	Drug name	Uses	Pregnancy risk	Lactation risk	Dosage	Drug interactions/concerns
β-2 agonist Short-acting	Albuterol	Bronchodilator in ambulatory management of chronic asthma	C	L1	2–4 mg tid or qid	Albuterol effects are reduced when used with β-blockers cardiovascular (CV) effects are potentiated when used with monoamine oxidase inhibitor (MAO) inhibitors, tricyclic antidepressants, amphetamines, and inhaled anesthetics (enflurane).
β-2 agonist Short-acting	Albuterol	Acute exacerbations	C	L1	2.5 mg (0.5 mL of a 0.5% solution, diluted with 2–3 mL of normal saline)	
β-2 agonist Short-acting	Metaproterenol	Acute exacerbation	C	L3	15 mg (0.3 mL of a 5% solution, diluted with 2–3 mL of normal saline)	
Corticosteroid	Methylprednisolone	Acute exacerbation	C	L3	60–80 mg IV bolus q 6–8	
Corticosteroid	Hydrocortisone	Acute exacerbation	C	L3	2.0 mg/kg IV bolus q 4 hours or 2.0 mg/kg IV bolus, then 0.5 mg/kg/h continuous IV infusion	

Corticosteroid	Prednisone or methlyprednisolone	Acute exacerbation	C	L3	60 mg given immediately, then 60–120 mg/d in divided doses, tapered over several days at the discretion of the physician	With improvement in patient's condition, tapered to a single daily dosage of oral prednisone or methlyprednisolone (e.g. 60 mg/d) or divided dosages (e.g., 20 mg three times daily), then gradually further reduced over 7–14 days. If patient requires a prolonged course or oral corticosteroids, side effects may be minimized by a single dosage given on alternate mornings.
Corticosteroid	Prednisone	Ambulatory management of chronic asthma	C	L3	40 mg/d, single or divided dosage for 1 week, then taper for 1 week	
Corticosteroid	Beclamethasone	Ambulatory management of chronic asthma	C	L3	2–5 puffs bid-qid (inhalation) or 2 sprays in each nostril bid (intranasally for allergic rhinitis)	
Anti-inflammatory	Cromolyn sodium	Ambulatory management of chronic asthma	B	L1	2 puffs qid inhalations or 2 sprays in each nostril bid – qid (intranasally for nasal symptoms)	

(continued on next page)

Table 2 (*continued*)

Drug class	Drug name	Uses	Pregnancy risk	Lactation risk	Dosage	Drug interactions/concerns
Long-acting β-adrenergic bonchodilator	Salmeterol	Ambulatory management of chronic asthma	C	L2	50 μg bid	
Leukotriene inhibitor for asthma	Zafirlukast	Ambulatory management of chronic asthma	B	L3		Receptor antagonist of leukotriene D4 and other components of slow-reacting substance on anaphylaxis which are mediators of bronchoconstriction in asthmatic patients. Not a bronchodilator. Not for acute asthma attacks.
β-2 adrenergic	Terbutaline	Acute exacerbation	B	L2	0.25 mg subcutaneous	
Methylzanthine bronchodilator	Theophylline	Ambulatory management of chronic asthma	C	L3	3mg/kg q 8 h needed to reach serum concentration level of 8–12 μg/mL	
	Ipratropium bromide		B			
IgE blocker	Omalizumab		C	unknown		

choice for women who have asthma [8]. Propofol is the agent of choice for asthmatics who require general anesthesia for cesarean section [21].

Labor induction with oxytocin or prostaglandin E2 may be performed. Oxytocin or intrarectal prostaglandin E2 suppositories may be used in the treatment of uterine atony with postpartum hemorrhage; however, the use of 15-methyl prostaglandin F2-α (hemabate) may worsen asthma, was reported to cause status asthmaticus, and should be avoided [12].

Asthma and postpartum/breastfeeding

Breastfeeding should be encouraged in women who have asthma because breast milk confers some immunity to infection to the baby, especially to respiratory and gastrointestinal infections, and was proposed as a protective mechanism for allergic conditions and asthma [16,31].

Breast milk may contain small amounts of the drugs that are used to treat asthma; however, in general, these are not known to be harmful to the infant [16,31]. Corticosteroids are approximately 90% protein bound in the blood and are not secreted into breast milk in any significant quantity [31]. Inhaled β2-agonist medication (metaproterenol, terbutaline, albuterol) by metered dosage delivers the least amount of drug to the infant. Theophylline, as with caffeine, can cause irritability and wakefulness in the infant and is no longer considered to be the primary treatment [31].

Summary

Asthma continues to impose a significant clinical and economic burden on patients and society. Asthma is a comorbid condition in approximately 4% of all pregnancies; the incidences of asthma itself and asthma in pregnancy seem to be rising. In pregnancy, approximately one third of women who have asthma experience worsening of their condition, one third remains the same, and one third improves [38]. Objective testing is key for the evaluation of asthma because patients and physicians tend to underestimate the severity of the disease. Testing may include office spirometry which measures FEV_1 or peak flow meter which correlates with FEV_1 measures. Patients should have optimal measurement of FEV_1 or peak flow meter in a symptom-free period. This optimal value should be used to guide therapy treatment throughout the pregnancy.

For patients who have mild disease, daily long-acting β-agonists are the first-line therapy. For patients who have moderate persistent asthma, the preferred treatment includes the daily use of a combination of low-dose inhaled corticosteroids and long-acting β-agonists. For patients who have severe persistent asthma, the currently recommended treatment is combination therapy with high-dosage ICSs and long-acting β-agonists. If needed, corticosteroid tablets or syrup (2 mg/kg/d, not to exceed 60 mg/d) can be added to maintain control; however,

all attempts should be made to reduce the use of systemic corticosteroids and to maintain control with high dosages of ICSs.

The most important aspect may be prevention. Avoidance of triggers, such as cigarette smoke, pets, dust, and stress, is vital. Another key point is that women should take medications daily, on a regular schedule, not just when symptoms arise. Peak flow should be done daily at home and recorded by the patient. These values should be brought to the regular appointments and reviewed with the patient. Medications should be adjusted based on the objective lung tests of peak flow and spirometry. It should be emphasized to the patient that her asthma medications pose less risk to the infant than a serious asthma attack. Furthermore, daily medications are more effective than medications that are begun after an attack has started.

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Pregnancy after organ transplant

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The frequency and variety of solid organ transplantation in reproductive-age women increases each year. A transplanted organ, in many cases, restores fertility and reproductive function in women of childbearing age as reported following renal and liver transplants [1–5]. The first reported pregnancy in a renal transplant recipient occurred in 1958 in a woman who received a kidney from her identical twin [6]. Since that time, pregnancies in female recipients of solid organ transplants have become increasingly common as reported by single center experiences, case reports, and registry data in the United States and Europe [7–9]. Successful pregnancies have been reported after a variety of organ transplants, including kidney, liver, liver–kidney, pancreas–kidney, heart, heart–lung, and lung [7]. It is difficult to ascertain outcome data in pregnancies following solid organ transplantation from case reports and small series. In 1991, the National Transplantation Pregnancy Registry (NTPR) was established at Thomas Jefferson University to study the safety and outcomes of pregnancies in female transplant recipients and male transplant recipients who fathered pregnancies [7]. The NTPR is an ongoing database with steady follow-up of recipients and their offspring. Questionnaires, telephone interviews, and review of parental and newborn medical records are performed. Pregnancy outcomes are analyzed and the long-term follow-up of parents and offspring is reported. The number of female transplant recipient entries into the NTPR as of October 2002 is listed in Table 1 [7].

Patients and clinicians are concerned about pregnancy outcomes and graft function in pregnant transplant recipients. Pregnancy does not seem to affect graft function adversely if it was functioning well before pregnancy [10]. Outcomes are not always similar among transplanted organs. Three areas must be considered when discussing the safety of pregnancy in a transplant recipient: maternal

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Table 1
Pregnancies in female transplant recipients from the National Transplantation in Pregnancy Registry 2002

Organ	Recipients	Pregnancies	Pregnancy outcomes[a]
Kidney	667	1030	1060
Liver	102	173	174
Liver–kidney	3	5	6
Pancreas–kidney	34	47	49
Heart	31	52	52
Heart–lung	3	3	3
Lung	13	14	14
TOTALS	853	1324	1358

[a] Includes twins and triplets.

Data from Armenti VT, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. In: Cecka JM, Terasaki PI, editors. Clinical Transplants 2002. Los Angeles (CA): UCLA Immunogenetics Center; 2003. p. 121–30.

outcome, neonatal outcome, and continued graft function [11]. When discussing childbearing plans, patients may have questions about pregnancy advisability, pregnancy complications, maternal complications, fetal malformations, effects of immunosuppressive agents, risk of infection, effects of pregnancy on graft function, and neonatal complications [2,3]. In this article, immunosuppressive agents, preconception counseling, contraceptive options, pregnancy outcome, and delivery options are reviewed in pregnancies after solid organ transplantation.

Immunosuppressive agents

Immunosuppressive agents are necessary to maintain graft function and maternal survival. Outcomes in transplant recipients have improved steadily because of the enhanced ability to suppress the immune system to avoid rejection [12]. The main goal of immunosuppressive agents is to prevent acute rejection. No specific combination of agents is superior; generally, if working well, a woman will continue on the same immunosuppressive regimen during her pregnancy. Good maternal and graft outcome with the lowest risk of fetal toxicity are additional aims of immunosuppressive therapy [13]. With the advances and modifications in immunosuppressive therapy, there are concerns about malformations or derangements in the fetus. A combination of various agents allows for synergistic effects and decreases the risk of drug toxicities [13]. Clinicians must stress to their patients the importance of continuing immunosuppressive agents during pregnancy to preserve graft function. Pregnant recipients may be inclined to discontinue medications or decrease the amount of agents taken because they are concerned about their effect on the developing fetus. Additionally, women may harbor feelings of guilt about exposing their fetus to pharmacologic agents; the care provider should address these feelings.

Immunosuppressive drugs are studied for teratogenic, mutagenic, and carcinogenic effects; these data are provided by animal experimentation [14]. Immunosuppressants are not carcinogenic as shown in animal studies. Certain agents, however, may be teratogenic (azathioprine, prednisone, mycophenolate, tacrolimus) and mutagenic (azathioprine) in animal models [14]. In the United States, the background birth defect rate is 3% to 5%; most defects have an unknown etiology and it is estimated that only 2% to 3% are classified as teratogen-induced malformations [13]. The incidence of structural malformations in transplant recipients is not increased compared with the background risk of 3%, although newer regimens are being evaluated [13,15]. Susceptibilities and thresholds to particular regimens are patient-specific. Specific patterns or an increased incidence of malformations have not been observed in newborns of transplant recipients in published case reports or registries [13].

There are three types of immunosuppressive regimens: (1) induction regimens are used in the first weeks after transplant to avoid rejections and establish good graft function. Biologic agents, including antilymphocyte sera (polyclonal or monoclonal antibodies) or interleukin-2 receptor blockade are used; (2) antirejection regimens use high-dose, short-term treatments (less than 3 weeks) that usually consist of corticosteroids (methylprednisolone) or antilymphocyte sera to treat episodes of rejection and (3) maintenance therapy provides long-term immunosuppression to prevent rejection. In maintenance regimens, drug dosages are tapered over the first posttransplant year to a baseline level that continues indefinitely [13,16]. Usually, pregnant posttransplant recipients will be on maintenance therapy. Most immunosuppressive agents are United States Food and Drug Administration (FDA) Category C for safety (animal studies show an adverse effect and there are no controlled studies in pregnant women or studies in animals and women are unavailable) which suggests the use of the agent only if potential benefit justifies potential fetal risk [4,13,15]. The other FDA categories include: (1) Category A—controlled studies in humans fail to demonstrate risk with first trimester exposure, possibility of fetal harm is remote; (2) Category B—animal studies do not demonstrate fetal risk and there are no controlled studies in pregnant women or animal studies show an adverse effect that was not confirmed in controlled studied in the first trimester; (3) Category D—positive evidence of human fetal risk, but benefits may be acceptable despite the risk; and (4) Category X—positive evidence of fetal risk and the use of the drug in pregnant women clearly outweighs any possible benefit [4]. Pregnancy affects drug absorption, distribution, and elimination. In pregnancy, gut motility is slowed, but drug transfer is enhanced through the gastrointestinal membranes as the result of increased local blood flow. Distribution of drugs into tissues is modified by the increase in maternal blood volume and fat stores. Additionally, transplacental transfer of certain drugs occurs. Immunosuppressive agents that are cleared through the kidney are affected by the increased glomerular filtration rate in pregnancy. As a result of the changes in pregnancy, serum levels of immunosuppressive agents should be monitored closely and dosage adjustments should be made accordingly [14–16]. Common

Table 2
Common immunosuppressive agents in transplant recipients and their FDA category in pregnancy

Drug	Uses	FDA category
Corticosteroids	Maintenance/antirejection	
prednisone, prednisolone		B
methylprednisolone		B
Azathioprine	Maintenance	D
Imuran		
Cyclosporin A (CyA)	Maintenance	C
novartis formulations		
Sandimmune		
Cyclosporin capsules USP (mod)	Maintenance	C
generic microemulsion		
formulation of cyclosporin		
Neoral		
Tacrolimus or FK506	Maintenance/antirejection	C
Prograf		
Mycophenolate mofetil	Maintenance	C
CellCept		
Sirolimus	Maintenance	C
Rescue agents used for treatment of rejection or induction		
Muromonab-CD3 (OKT-3)		C
Orthoclone OKT3		
Antithymocyte globulin		C
Atgam, ATG		
Antithymocyte globulin		C
Thymoglobulin		

Data from Armenti VT, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Register (NTPR): Outcomes of pregnancy after transplantation. In: Cecka JM, Terasaki PI, editors. Clinical transplants 2002. Los Angeles (CA): UCLA Immunogenetics Center; 2003. p. 121–30; and Armenti VT, Moritz MJ, Davison JM. Renal transplantation and pregnancy. In: Gleicher N, editor. Principles and practice of medical therapy in pregnancy. 3rd edition. Stamford (CT): Appleton & Lange; 1998. p. 1081–91.

immunosuppressive agents and their FDA categories in pregnancy are listed in Table 2.

Corticosteroids

Corticosteroids (prednisone, prednisolone, and methylprednisolone) are used in almost all immunosuppressive therapies, have broad anti-inflammatory effects, inhibit all types of lymphocytes, and are classified as Category B drugs in pregnancy. Adverse effects of steroid therapy include accelerated bone loss, aseptic necrosis (usually of the hips), diabetes that requires insulin, peptic ulcer disease, and psychiatric disturbances [13,15,16]. Steroid use may predispose the pregnant transplant recipient to premature rupture of membranes and may

aggravate hypertension [13,15]. Stress dose steroids are needed at the time of delivery and for 24 to 48 hours after delivery.

Azathioprine

Azathioprine (Imuran) is an inhibitor of purine metabolism that inhibits clonal proliferation of T cells [13,16]. After absorption, azathioprine is converted rapidly in the liver to its active metabolite, 6-mercaptopurine. Azathioprine toxicity causes neutropenia. Teratogenicity has been noted in animal studies and azathioprine is an FDA Category D drug. Reports of problems in newborns include thymic atrophy, leukopenia, anemia, thrombocytopenia, chromosome aberrations, reduced immunoglobulin levels, infections, and sepsis. Transient newborn peripheral blood lymphocyte chromosome damage was reported in a kidney transplant recipient who was maintained on azathioprine and prednisone. This finding disappeared within several months; similar chromosomal aberrations were noted in the mother [13,16]. Preterm delivery and fetal growth restriction/small for gestational age has been noted, but no clear pattern of structural anomalies has been identified in newborns who are exposed to azathioprine in utero [13,15]. With the availability of newer agents, azathioprine use has decreased markedly [13].

Cyclosporin

Cyclosporin A (CyA) or Sandimmune has been the mainstay of immunosuppressive therapy since the early 1980s [16]. CyA is a calcineurin inhibitor that inhibits helper T-cell function by blocking the transcription of cytokine genes that are necessary for T-cell activation and proliferation [13]. CyA is fat soluble and depends on bile acids for absorption, thereby having variable bioavailability. Neoral is a newer formulation of CyA that is a microemulsion with improved bioavailability and more predictable pharmacokinetics [13,16]. Known toxicities of CyA therapy include nephrotoxicity, hypertension, tremor, hypertrichosis, and hyperlipidemia. CyA only affects lymphocytes without depressing bone marrow or leukocyte counts; therefore, it has a lower risk of infection than either corticosteroids or azathioprine [13]. CyA levels should be monitored closely throughout pregnancy and appropriate dosage adjustments should be made. CyA readily crosses the placenta; fetal toxicities and abnormalities were reported in animal studies that used higher dosages than that in clinical use. An increased incidence of congenital anomalies has not been reported in humans; CyA use is associated with a moderate risk for fetal growth restriction. CyA is a FDA Category C agent [13]. Several commonly-used medications and foods may increase (ketoconazole, erythromycin, verapamil, grapefruit food products) or decrease (phenytoin, phenobarbital, rifampin, carbamazepine) CyA levels; cau-

tion should be exercised when prescribing additional medications to a patient who is on immunosuppressive agents [15].

Tacrolimus

Tacrolimus (Prograf, FK506) is a macrolide antibiotic that has a mechanism of action that is similar to CyA (calcineurin inhibitor), but is more potent [13,16]. Common side effects are similar to CyA and include nephrotoxicity, hypertension, neurotoxicity, and diabetes mellitus [13]. Tacrolimus cannot be used with CyA because of synergistic nephrotoxicity [16]. A lower incidence of hypertension and hyperlipidemia is seen with tacrolimus use as compared with CyA. Neonatal adverse effects include a higher incidence of diabetes and transient perinatal hyperkalemia [13]. Tacrolimus blood concentration levels also are followed to assure adequate dosage. Tacrolimus is an FDA Category C drug in pregnancy with no predominant malformation pattern reported [15]. Plasma tacrolimus levels are reduced with the concomitant use of antiepileptics and are increased with macrolide antibiotic use [2].

Mycophenolate mofetil

Mycophenolate mofetil (MMF or CellCept) is a reversible inhibitor of inosine monophosphate dehydrogenase that blocks de novo purine synthesis on which lymphocytes are dependent [13]. This drug is more selective than azathioprine, seems to be synergistic with CyA and tacrolimus, and may be the first drug that is effective in reducing the rate of chronic rejection [16]. Toxicities of MMF include nausea, gastritis, diarrhea, and leukopenia [13,16]. Generally, MMF is used with a calcineurin inhibitor with or without corticosteroids for maintenance therapy in transplant recipients. MMF is an FDA Category C drug, but teratogenic risks are concerning because rats and rabbits exhibited developmental toxicity, malformations, and intrauterine death at dosages that coincide with recommended clinical dosages that are based on body surface area [13]. Because there is no safety margin based on reproductive toxicology studies in animals, there is a possibility of increased risk in humans. The risk of potential graft rejection when switching MMF because of pregnancy must be weighed against the potential risk for teratogenicity. Azathioprine has been replaced, to a large extent, by MMF in nonpregnant recipients because of MMF's greater selectivity [13,16]. MMF use in pregnancy is an unresolved issue in the transplant community; continued surveillance of the newer agents is ongoing [7].

Sirolimus

Sirolimus is another macrolide that was approved for use in the United States in 1999; it inhibits cytokine-driven T-cell proliferation and has no effect on

calcineurin activity. Less acute rejections and improved immunosuppression were noted in initial trials when sirolimus was used with CyA and prednisone. Decreased fetal weights and delayed skeletal ossification in animal studies were reported, but specific teratogenicity was not noted. When sirolimus was used with CyA (calcineurin inhibitor) in animal studies, decreased numbers of live fetuses, increased fetal mortality, and an increased number of resorptions were noted which implied that toxicity is increased with this combination. Sirolimus is classified as an FDA Category C agent in pregnancy, but no definitive clinical pregnancy outcome data are available [13].

Additional immunosuppressive agents that are used rarely in pregnant transplant recipients as a rescue to treat acute rejection and as induction agents include muromonab-CD3 (OKT-3), antithymocyte globulin (ATG, ATGAM), dacilizumab, and basiliximab [13].

Preconception counseling

When a woman of childbearing age is undergoing evaluation for organ transplantation, adequate counseling about the return of fertility and possibility of pregnancy is imperative. Adequate contraception before and after transplantation and optimal timing of pregnancy (if desired) are important issues to discuss. It is reasonable to advise female recipients to wait 1 or 2 years after transplant to become pregnant. This allows the woman to recover from surgery and allows time to ensure graft function, stability, and whether there is evidence of ongoing rejection. Additionally, delaying conception allows time for immunosuppressive agents to be at maintenance levels and for associated medical conditions (hypertension, diabetes) to be under good control [11,12,15]. Because of the need for life-long immunosuppression, recipients of organ transplants are at high risk for opportunistic infection. Active infection with cytomegalovirus (CMV) is common after organ transplantation and occurs most often in the first few months after transplantation and coincides with the period of maximal immunosuppression [12,17]. A specific time interval from transplant to conception allows for recipients to complete postoperative treatment of opportunistic infections [15].

Women who are age 35 or older may be referred for genetic counseling before conception to discuss the increased risk of karyotypic abnormalities in the fetus. An immunization history is essential. Specific laboratory evaluations, including titers for rubella, varicella, herpes simplex, CMV, and toxoplasmosis, as well as a hepatitis panel, HIV, and blood type with antibody screen must be evaluated. Live virus vaccines are contraindicated posttransplant; therefore, rubella and varicella vaccines should be administered to susceptible women of childbearing age before organ transplant [3]. Vaccination of an immunosuppressed patient could result in systemic sepsis, and, possibly, death [18]. Hepatitis B vaccination may be given before or during pregnancy. Cystic fibrosis carrier testing also is offered to women who desire future fertility. Tobacco, alcohol, and recreational

drug use is discouraged before and during pregnancy. Folic acid supplementation of at least 400 μg/d should be recommended at least 1 to 2 months before conception to reduce the occurrence of open neural tube defects in the fetus. Women of childbearing age who are Rhesus (Rh)D-negative and receive an RhD-positive solid organ should receive anti-D immunoglobulin (Rhogam) at the time of transplantation [19]. Women who did not receive anti-D prophylaxis should be monitored each trimester for increasing anti-D titers (indirect Coombs) if there is a possibility that the fetus is RhD-positive [15].

In preconception counseling sessions with members of the transplant team, obstetricians, and genetic counselors, specific risks of the needed immunosuppressive agents should be reviewed in detail. Specific pregnancy risks of a transplant recipient who has various associated medical problems can be discussed and a plan of management for pregnancy can be reviewed. Potential maternal and fetal risks during early pregnancy involve the woman's ability to tolerate immunosuppressants because of nausea. Early hospitalization, intravenous fluids, and antiemetics can allow for scheduled immunosuppressant therapy [1]. A woman should be cautioned to contact her transplant center if she becomes pregnant and not to stop or decrease current medications [3]. An additional area of discussion with the organ transplant recipient is the emotional stress that pregnancy may cause. Women are forced to deal with the possibility of not surviving to raise her child into adulthood and may have feelings of guilt about exposing her child to various medications in utero [20]. Counseling and appropriate antidepressant medications may be necessary. After adequate preconception counseling, a transplant recipient is empowered to make an informed decision about attempting or avoiding pregnancy [12].

Contraception

Contraceptive options should be discussed with transplant recipients before hospital discharge after transplantation. The choice of appropriate contraception should be individualized. If the woman is uninterested in future fertility, she should be counseled on permanent sterilization with tubal ligation that might be performed at the time of transplantation or male partner vasectomy. Vasectomy of the male partner is another option that lacks the increased risk of ectopic pregnancy that is associated with tubal ligation [4].

Barrier contraceptives

Barrier contraceptives (condoms, diaphragms) reduce the incidence of sexually transmitted diseases (STDs) and have the lowest risk of side effects. Spermicides have bactericidal properties and also reduce the transmission of STDs. These methods often produce local irritation and provide the least reliability for contraception. Patients must be motivated to use barrier contraception; "perfect" user failure rates are as high as 9% [4].

Oral contraceptive pills

Oral contraceptive pills (OCPs) reduce the incidence of STDs by altering cervical mucus. Menstrual flow also is reduced which decreases the available culture medium for bacterial growth. Low-dose combined OCPs contain estrogen and progesterone and afford excellent contraception when taken as prescribed. The potential interaction with CyA necessitates periodic monitoring of liver and renal function. Absolute contraindications to OCP use include previous thromboembolism, deep venous thrombosis, known thrombophilia, estrogen-dependent malignancy, pregnancy, and severe liver disease. Relative contraindications include hypertension, diabetes, smoking at age 35 and older, migraine headaches, and depression [4].

Progesterone-only contraception

Progesterone-only OCPs avoid the risk that is associated with estrogen-containing agents, but have a higher failure rate than combination OCPs. These agents may produce menstrual irregularities and need to be taken at the same time every day. Depomedroxyprogesterone acetate injections are administered at 3-month intervals and provide excellent contraception. In addition to menstrual irregularities, additional side effects of progesterone-only contraceptive methods include weight gain, altered lipid metabolism, hair loss, vaginal atrophy, and depression. Again, monitoring of CyA levels is prudent when using these agents because progestational agents may interfere with CyA metabolism. Ovulation may be delayed after discontinuation of depomedroxyprogesterone acetate injections; therefore, this is a poor contraceptive method for a woman who is planning a pregnancy in the near future [4].

Intrauterine device

The intrauterine device (IUD) is an effective form of longer-acting contraception. Prophylactic antibiotics must be used at the time of insertion. Because of the increased risk of infection in organ transplant recipients, this form of contraception is discouraged strongly [4]. In addition to the risk for infection, the efficacy of the IUD may be reduced in women who take immunosuppressive medications; patients on immunosuppressants may not mount an appropriate inflammatory response [2,15,16].

Pregnancy outcomes and general recommendations

Specific maternal and fetal risks are associated with pregnancy after organ transplant. Successful pregnancy outcomes are now the rule in this population without an apparent increase in either the incidence or type of malformations in newborns [13]. The NTPR continues to analyze the safety of pregnancy in female transplant recipients in addition to the outcomes of pregnancies that are fa-

thered by male transplant recipients [10]. According to the 2001 summary, pregnancy does not seem to affect graft function adversely if the function of the graft was stable before pregnancy [10]; however, a small percentage of recipients within each organ system may develop graft rejection, dysfunction, or loss that may occur in recipients who have prepregnancy graft dysfunction or it may occur unpredictably [10]. Waiting 1 to 2 years after transplantation before conception is reasonable to allow for stable graft function and stabilization of immunosuppressive agents [10,11]. Analysis of this recommendation should be made on a case-to-case basis because favorable outcomes have been reported with shorter and longer intervals [10]. Prematurity and a trend toward lower mean birth weight have been consistent outcomes in pregnancies after transplantation. It is reassuring that no specific pattern of malformation in newborns or increase in the incidence of small-for-gestational age newborns has been noted. Outcome data of pregnancies that were fathered by transplant recipients has not been as well studied; however, outcomes have been favorable and seem to be similar to the general population [11].

Much of the experience in organ transplantation stems from the renal transplant population. Davison and Bailey [2], in reviewing the management of pregnancies following renal transplant, recorded the effects of renal transplantation in pregnancy, counseling issues, and management schemes. They echo that pregnancy is not contraindicated in renal transplant recipients who have stable renal function. Poorer outcomes were observed in women who had graft dysfunction or hypertension before conception. The investigators concluded that pregnancy does not compromise long-term graft function.

Fetal growth restriction (20%–30%), preterm labor, preterm premature rupture of membranes (PPROM), and pre-eclampsia (25%–30%) are common pregnancy complications in the renal transplant recipient [2,16]. Davison and Bailey's [2] guidelines for prepregnancy counseling in renal transplant recipients included: good general health for 2 years posttransplantation; no (or minimal) proteinuria; no (or minimal, well-controlled) hypertension; no evidence of graft rejection; no pelvi-calyceal dilatation on a recent intravenous urogram; stable renal function; and immunosuppressive drugs that are reduced to maintenance levels.

Additionally, the European Best Practice Guidelines for pregnancy in renal transplant recipients concisely states their summary of recommendations for this group. The investigators concluded that in women who have normal graft function, pregnancy usually has no adverse effect on graft function and survival [21].

The first known pregnancy in a liver transplant recipient occurred in 1978 [22]. Casele and Laifer [12], reported that with optimal management, successful pregnancies occur for most liver transplant recipients. Armenti and colleagues [2] also reported that pregnancies in the liver transplant recipient are well-tolerated if the graft function was stable and adequate before pregnancy. In Casele and Laifer's [12] review, pregnancy did not seem to alter hepatic allograft function. Certain pregnancy complications may occur more frequently in this group and

include worsening hypertension, pre-eclampsia, PPROM, anemia, small-for-gestational-age fetuses, cesarean delivery, infection, and first trimester abortion. Renal dysfunction from long-term use of CyA may predispose transplant patients to pre-eclampsia.

2002 National Transplant Pregnancy Registry summary

The NTPR maintains an ongoing database to study the outcomes of pregnancies in female transplant recipients and those that were fathered by male transplant recipients. The latest NTPR synopsis from 2002 (published in 2003) reviews data that were collected and analyzed over the previous 12 years and is included below [7].

Kidney

Only a small percentage of pregnancies in female kidney recipients experienced graft rejection and poorer outcomes were noted with respect to maternal graft function and their neonate. In addition to their usual analyses, a focused review on outcomes of recipients who had systemic lupus erythematosus (SLE) or multiple gestations (no reports higher than triplets) was performed. Patients who had SLE with a kidney transplant maintained their pregnancies with outcome similar to other diagnoses. Multiple gestations in female kidney recipients who were maintained on calcineurin inhibitors were reported and successful outcomes were noted [7].

Other organs

Analysis of female liver recipients revealed no specific graft or newborn outcome differences when a comparison was made between different calcineurin inhibitor regimens. Pregnancies following pancreas–kidney transplantation are well-tolerated with respect to graft function and no diagnoses of gestational diabetes was reported. Fewer data are available for thoracic recipients (heart, heart-lung, lung). Poorer maternal survival following delivery in recipients of lung transplants was noted and may be related to risk factors that are inherent in this population [7].

Other issues

Data published on transplant recipients who were treated with azathioprine and CyA reveal a pattern of prematurity but no increase in the incidence or pattern of specific malformations in the newborn. Less information is available with newer agents, such as sirolimus and MMF. Birth defect patterns have not been specific to a particular immunosuppressive regimen; no regimen has been identified as superior to another for use in pregnancy [7].

Pregnancy management

A multidisciplinary team approach that involves the obstetrician/maternal–fetal specialist, transplant team, anesthesiologist, and neonatologist best achieves optimal management of a pregnancy following solid organ transplant. During the initial obstetric visits, a complete history and physical examination are performed. After fetal viability is assured by ultrasound, prenatal laboratory studies include complete blood count; blood type and antibody screen; rubella titer; chemistries to evaluate liver and kidney function; CMV, herpes, and toxoplasmosis titers; cervical and urine cultures; screens for HIV; hepatitis panel; and evaluation for syphilis. Of importance is the well-known association between immunosuppressive agents and the increased risk of malignancy in renal transplant patients [4]. Human papillomavirus and cervical neoplasia rates are higher in immunocompromised and transplant recipients; therefore, cervical cytology is obtained [4,12]. Immunosuppressive agents are continued and levels are drawn to maintain therapeutic concentrations; adjustments are made as needed [5,12].

Serum screening for open neural tube defects and chromosome abnormalities may be offered in the second trimester to women who are younger than age 35. Women who are older than age 35 are offered genetic counseling and the option of genetic amniocentesis. Targeted sonography is offered at 20 weeks' gestation to assess for structural fetal anomalies. Beginning at about 24 to 26 weeks' gestation, serial sonography is performed every 4 weeks to monitor fetal growth because of the association of immunosuppressive medications with alterations in fetal growth [5]. Weekly fetal surveillance with nonstress tests, biophysical profiles, or both should be performed beginning at about 26 weeks' gestation, because of the increased risk for fetal growth restriction and pre-eclampsia in some transplant recipients [12]. Corticosteroids, CyA, and tacrolimus may alter glucose metabolism; first trimester screening for gestational diabetes should be performed. Diabetes screening is repeated at 24 to 28 weeks' gestation [5,12]. Lower vagina/perineal/rectal swabs for group B *Streptococcus* colonization are obtained at 35 to 37 weeks' gestation.

Delivery options

In many cases, the timing of delivery is determined by maternal or fetal condition. Some centers recommend delivery at 40 weeks' gestation or when fetal lung maturity is confirmed to minimize continued fetal exposure to immunosuppressive agents [12]. The mode of delivery should be determined by standard obstetric indications. Pelvic osteodystrophy may occur in renal transplant recipients or women who have had a prolonged use of corticosteroids and may necessitate a cesarean delivery [4]. In case of a cesarean delivery, the exact location of the graft should be known. Women who are maintained on corticosteroid therapy will require stress dose steroids for delivery and for the first 24 to

48 hours postpartum. Transplant recipients who are maintained on immunosuppressive therapy are at risk for infection; therefore, antibiotic prophylaxis is recommended for vaginal and abdominal deliveries [12].

Breast-feeding

Breast-feeding offers many recognized benefits for the neonate and mother. There is little information available on the risks that are associated with immunosuppressive agents in human milk [4]. Differing views exist about the safety of breast-feeding with regard to drug exposure to the infant; this issue remains unresolved [7].

Summary

Successful pregnancy outcomes are possible after all types of solid organ transplants. In most pregnancies studied posttransplant, pregnancy does not seem to affect graft function adversely if function was stable before pregnancy. Immunosuppressive agents are required to prevent graft rejection; no specific combination is superior. Clinicians must be vigilant in watching the levels of immunosuppressive agents and must make appropriate adjustments to keep medications in a therapeutic range to prevent graft rejection. Favorable pregnancy outcomes are observed without an apparent increase in the type or incidence of malformations. Risks of preterm birth, pre-eclampsia, fetal growth restriction, and infection are increased in the transplant recipient. Cautious prenatal care, using a multidisciplinary approach with communication among specialists, may help to ensure the safety of the mother and infant.

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Cardiac disease in pregnancy

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In the 1930s, it was estimated that 1% to 2% of all pregnancies were complicated by maternal cardiac disease and that 6% of these women died during pregnancy [1–4]. The current estimated prevalence of clinically-significant cardiac disease during pregnancy is similar (0.1%–1.4%) [5–7]; however the maternal mortality rate for these patients during pregnancy has decreased to 0.5% to 2.7% [5–8]. Nevertheless, cardiac disease still accounts for 15% of pregnancy-related mortality [9]. Although patients who had significant cardiac disease were discouraged strongly from becoming pregnant in the past, the vast improvements in cardiac care and advances in reproductive technology may result in more women who have these diagnoses planning pregnancies. Because pregnancy represents a unique hemodynamic state with profound implications for cardiac function, obstetricians and cardiologists must be prepared to provide optimal care to these patients.

Cardiovascular changes of normal pregnancy

Antepartum changes

The growing fetus demands a nearly ten-fold increase in uterine blood flow—from 2% of cardiac output in the nonpregnant state to 17% of cardiac output at term [10]. This requires an immense alteration in maternal hemodynamics, beginning as early as five weeks gestation [11]. Plasma volume increases by 45% and red blood cell mass increases by 20% to 30% [12,13]. This discrepancy leads to hemodilution and the physiologic anemia of pregnancy.

Increases in heart rate and stroke volume lead to a 30% to 50% increase in cardiac output during pregnancy [14–16]. Stroke volume begins to increase at

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5 weeks gestation, peaks at approximately 31 weeks' gestation, and then gradually declines until term [14]. At approximately 32 weeks gestation, the maximal heart rate of 15 to 20 beats/min above nonpregnant values is achieved and remains stable until delivery. This relative tachycardia counteracts the declining stroke volume; cardiac output declines only a small amount during the last 6 weeks of pregnancy [11,14]. Placing a patient in the supine position can cause a decrease in cardiac output of 25% to 30%, secondary to compression of the vena cava and decreased preload [17]. Thus, maternal positioning can be of critical importance during labor and delivery.

Systemic vascular resistance decreases by approximately 20%, with the greatest decrease at 16 to 24 weeks. This parallels the decrease of arterial blood pressure in the second trimester with a gradual increase at term [18,19].

Multiple EKG changes in pregnant women have been described. The most common is sinus tachycardia with a consequent decrease in PR, QRS, and QT intervals. Uterine enlargement can change the QRS axis, most commonly shifting it to the left, but right axis deviation also has been described. Rotation of the heart also can cause a small q-wave and negative p-wave in lead III. Precordial T wave flattening and small ST depressions also may be seen in asymptomatic pregnant women [20–22]. Echocardiography during pregnancy may reveal trivial tricuspid, pulmonary, or mitral regurgitation as well as increased size of the left atrium and ventricle [20].

Intrapartum changes

Cardiac output increases even further during labor—by 12% to 31% during the first stage and up to 49% during the second stage. Part of this increase is due to pain that causes increased sympathetic stimulation, tachycardia, increased blood pressure, and increased myocardial oxygen consumption [23,24]. This presents an opportunity for appropriate anesthesia to decrease cardiac work and improve outcomes for patients who have cardiac disease. A less modifiable contribution to the increased cardiac output is the autotransfusion of 300 to 500 mL of blood from the uterus to the systemic circulation with every contraction [25].

During the second stage of labor with maternal pushing efforts, the Valsalva maneuver produces even wider fluctuations in maternal hemodynamics. During the straining period, increased intrathoracic pressure results in decreased venous return to the heart, whereas systemic vascular resistance (SVR) increases and mean arterial pressure remains constant or slightly elevated. Initially, there is a transient reflex bradycardia; after a few seconds, sympathetic stimulation occurs to increase heart rate and contractility to maintain cardiac output in this setting of decreased preload and increased afterload. After the strain is completed, a rapid increase in venous return causes increased stroke volume and markedly increased blood pressure, which again is associated with reflex bradycardia [26]. Shortening the second stage of labor with assisted vaginal delivery is beneficial to patients who have certain cardiac conditions.

Postpartum changes

Immediately after delivery, relief of vena cava compression by the gravid uterus and autotransfusion of uteroplacental blood causes cardiac output to increase even further for a brief period. Within 1 hour of delivery, cardiac output returns to third trimester values [27,28]. The postpartum period is characterized by mobilization of extravascular fluid and diuresis, which has implications for certain cardiac conditions.

Recommendations for specific cardiac conditions

Valvular heart disease

In general, regurgitant valvular lesions are well-tolerated during pregnancy, whereas stenotic lesions have greater potential for decompensation. When valvular lesions are studied in aggregate, 62% of patients can expect to have a worsening of their New York Heart Association (NYHA) functional class (Box 1) during pregnancy, 38% will develop congestive heart failure, and up to 23% will have adverse fetal outcomes, such as preterm birth, intrauterine growth restriction, or stillbirth [29]. In estimating risk for an individual patient, it is much more helpful to examine the data on specific valvular lesions. Boxes 2 and 3 summarize high- and low-risk valvular lesions.

Mitral stenosis

Mitral stenosis occurs most commonly as a consequence of rheumatic heart disease. Although the incidence of rheumatic heart disease is decreasing in developed countries secondary to appropriate use of penicillin, immigrants to the United States from underdeveloped countries may still present with its sequelae [30]. Complications of mitral stenosis include pulmonary edema, right ventricular failure, and atrial arrhythmias with risk of embolization. Pregnancy is detrimental to cardiac function in the setting of mitral stenosis for several reasons. Expanded blood volume can increase the risk of pulmonary congestion and edema. The physiologic tachycardia of pregnancy decreases left ventricular filling time which

Box 1. NYHA functional status classification

Class I Asymptomatic
Class II Symptoms with greater than normal activity
Class III Symptoms with normal activity
Class IV Symptoms at rest

Box 2. Valvular heart lesions that are associated with high maternal risk or fetal risk during pregnancy

- Severe aortic stenosis (AS) with or without symptoms
- Aortic regurgitation (AR) with NYHA functional class III–IV symptoms
- Mitral stenosis (MS) with NYHA functional class II–IV symptoms
- Mitral regurgitation (MR) with NYHA functional class III–IV symptoms
- Aortic or mitral valve disease that results in severe pulmonary hypertension (pulmonary pressure > 75% of systemic pressure)
- Aortic or mitral valve disease with severe left ventricular (LV) dysfunction (ejection fraction (EF) < 40%)
- Mechanical prosthetic valve that requires anticoagulation
- AR in Marfan's syndrome

Adapted from Bonnows RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998; 32:1486–588; with permission.

leads to elevated left atrial pressures that cause pulmonary edema and decreased forward flow that causes hypotension, fatigue, and syncope.

The severity of mitral stenosis is classified based on the valve area: a valve area of >1.5 cm^2 is mild, 1.1 to 1.5 cm^2 is moderate, and $\leq$1 cm^2 is severe. Normal mitral valve area is 4 to 5 cm^2 [31]. In a prospective study of 80 pregnancies in 74 women who had mitral stenosis, the rate of maternal cardiac complications was 35% and the rate of adverse fetal or neonatal outcomes was 30%. The maternal cardiac complications consisted of pulmonary edema and arrhythmias; there were no cases of stroke, cardiac arrest, or death in this series nor was there any need for invasive interventions. The incidence of maternal and fetal complications was associated significantly with the degree of MS based on valve area (Fig. 1). The prepregnancy NYHA functional class did not correlate with maternal or fetal outcomes; however, all women in this series had class I or II disease [32]. With class III or IV disease, previous series reported maternal mortality rates of 5% to 7% and perinatal mortality rates of 12% to 31% [30,33].

Treatment of mitral stenosis in patients who have a history of rheumatic heart disease includes daily prophylactic penicillin, gentle diuresis to prevent pulmo-

Box 3. Valvular heart lesions that are associated with low maternal and fetal risk during pregnancy

- Asymptomatic AS with low mean gradient (<50 mm Hg) in presence of normal LV systolic function (EF>50%)
- NYHA functional class I or II AR with normal LV systolic function
- NYHA functional class I or II MR with normal LV systolic function
- Mitral valve prolapse (MVP) with no MR or with mild to moderate MR and normal LV systolic function
- Mild to moderate MS (mean valve area >1.5 cm^2, gradient <5 mm Hg) without severe pulmonary hypertension
- Mild to moderate pulmonic stenosis

Adapted from Bonnows RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998;32: 1486–588; with permission.

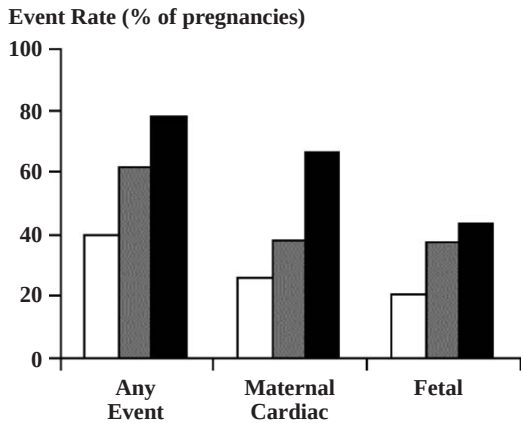

Fig. 1. Relation between severity of MS and frequency of adverse maternal cardiac, fetal, or neonatal events. Any event refers to cardiac, fetal, or neonatal events. White bars indicate pregnancies in women who have mild MS; gray bars indicate pregnancies in women who have moderate MS, and black bars indicate pregnancies in women who have severe MS. (*From* Silversides CK, Colman JM, Stermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. Am J Cardiol 2003;91:1382–5; with permission.)

nary edema without decreasing placental perfusion, and β-blockers as needed to prevent tachycardia. New onset atrial fibrillation can be treated with cardioversion; digoxin or β-blockers may be used for rate control in chronic atrial fibrillation. Patients who have atrial fibrillation should be anticoagulated to prevent systemic embolism [31,34]. The most common surgical treatment of mitral stenosis is percutaneous balloon mitral valvotomy. Ideally, this should be performed before conception in symptomatic women who have severe MS [31]. For women who have severe MS who have clinical deterioration to NYHA class III or IV disease during pregnancy, the procedure can be performed safely during pregnancy [35,36]. Balloon mitral valvotomy was shown to carry less fetal risk than open mitral valve commissurotomy [37].

During labor, adequate pain control is important to prevent tachycardia and its consequences. Epidural anesthesia in a patient who has mitral stenosis carries the risk of a rapid decrease in systemic vascular resistance in a patient who has decreased ability to increase her cardiac output to maintain blood pressure. If hypotension ensues, small doses of phenylephrine can increase SVR through pure α-effects without causing tachycardia, which results from combined α- and β-agonists, such as ephedrine. Intrathecal narcotics are the safest method of pain control during the first stage of labor because they avoid sympathetic blockade [38]. Additional antibiotics to prevent endocarditis during uncomplicated labor are given by many obstetricians; however, they are not recommended by the American College of Cardiology/American Heart Association (ACC/AHA) [31].

Aortic stenosis

The most common cause of AS in young women is a congenital bicuspid valve [31]. Rheumatic heart disease is a less common cause; some series of pregnant women who have AS also include a much smaller number of patients who have subaortic stenosis and hypertrophic cardiomyopathy [7]. The severity of AS can be described by the average valve area (AVA) or the peak pressure gradient across the valve. Severe AS is defined by the AHA as a peak gradient that is greater than 50 mm Hg; women who have severe stenosis or symptoms are advised to undergo surgical repair before attempting pregnancy [31]. Patients who have severe AS have difficulty achieving the increased cardiac output that is required by pregnancy. Their stroke volume is fixed by the obstructed valve, so heart rate is the key determinant of cardiac output. Bradycardia causes decreased cardiac output and hypotension; however, excessive tachycardia decreases ventricular filling time and again causes decreased cardiac output and the risk for myocardial ischemia [38].

In a Toronto study from 1986–2000 of 49 pregnancies in women who had AS, AS was defined as mild (AVA >1.5 cm^2 or peak gradient <36 mm Hg), moderate (AVA 1.0–1.5 cm^2 or peak gradient 36–63 mm Hg), or severe (AVA $\leq$1 cm^2 or peak gradient $\geq$64 mm Hg). All women had NYHA functional class I or II disease at the time of enrollment. Generally, pregnancy was well-tolerated. Ten percent of patients (3/29) who had severe AS experienced early cardiac com-

plications (pulmonary edema or atrial arrhythmias) during pregnancy; there were no early cardiac complications among the 20 patients who had mild or moderate AS. Twelve percent of pregnancies were complicated by preterm birth, respiratory distress syndrome, or intrauterine growth retardation (IUGR); this rate is similar to that seen in the general population [39]. Worse outcomes were found in a study of 1000 patients who had heart disease in pregnancy that were followed in Brazil between 1989 and 1999. The subset of patients who had moderate to severe AS experienced 68.5% maternal morbidity, including congestive heart failure (CHF), angina, the need for aortic valve replacement (2 patients), and sudden death (1 patient). [8]

Management of mild to moderate AS during pregnancy is conservative. For women who have severe symptomatic AS, balloon valvuloplasty has been reported during pregnancy without complications [40]; this procedure is contraindicated in the presence of significant aortic regurgitation (AR). Concomitant AR is found most often in patients who have congenital bicuspid aortic valves; these valves do not open or close properly. Open valve replacement is also an option for patients who have decompensation during pregnancy, but it is associated with up to 30% fetal mortality [41]. During labor, epidural anesthesia may be used cautiously, with generous fluid hydration to prevent hypotension and reflex tachycardia [38]. Assisted vaginal delivery is useful to shorten the second stage which is associated with the highest cardiac demands for these patients who have a fixed cardiac output. Because the acute decrease in preload that is associated with postpartum hemorrhage can be catastrophic for women who have AS, postpartum hemorrhage should be managed aggressively.

Pulmonic stenosis

Isolated pulmonic stenosis is a rare clinical entity, but it seems to be well-tolerated in pregnancy. A series of eight pregnancies in patients who had isolated pulmonic stenosis revealed no maternal complications and no increased risk of fetal complications compared with a control group [29]. Pulmonic stenosis, in association with cyanotic congenital heart disease, has a much worse prognosis (see later discussion).

Mitral regurgitation

Mitral regurgitation (MR) in pregnant women is most commonly due to mitral valve prolapse. The hemodynamic changes of pregnancy are beneficial to a patient who has MR, because a state of increased volume and decreased systemic vascular resistance promotes forward flow across the regurgitant valve. Pregnancy is generally well-tolerated. The small number of patients who have pulmonary congestion can be treated with diuretics; vasodilators, such as hydralazine, are beneficial for women who have associated systemic hypertension. Severe MR can lead to marked left atrial dilatation and consequent atrial

fibrillation. Epidural anesthesia can be used safely with adequate intravenous (IV) hydration [34,42].

Mitral valve prolapse

MVP is the most common cardiac condition that is encountered in obstetrics; it affects 4% of the general population and disproportionately affects women, with a reported prevalence of up to 12% to 17% in women of childbearing age [43]. Primary or idiopathic MVP is characterized by a redundant valve that prolapses into the ventricle during systole. It is a benign condition and most patients are asymptomatic; however, some have symptoms of chest pain, dyspnea, weakness, and palpitations. MVP also can be secondary and associated with atrial septal defects, endocarditis, mitral stenosis, or a calcified mitral annulus. A review of 28 pregnant patients who had mitral valve prolapse (10 of whom also had mitral regurgitation) revealed no cardiovascular complications, including no cases of endocarditis, whether antibiotic prophylaxis was given or not [44].

Aortic regurgitation

Causes of AR include a dilated aortic annulus, a bicuspid aortic valve, and previous endocarditis. Similarly to MR, pregnancy in the setting of AR generally is uncomplicated. Symptomatic patients can be treated with diuretics and vasodilators, if needed [31,34]. Left ventricular failure has been reported near term in severe cases [42]. Epidural anesthesia can be administered safely.

Mechanical heart valves

Pregnant patients who have mechanical heart valves present one of the greatest challenges to obstetricians and cardiologists; these patients have a maternal mortality rate of 1% to 4% secondary to valve thrombosis, despite anticoagulation [45,46]. Because of this high risk, women who have valvular heart disease who desire future childbearing should be considered for valve repair or replacement with a biologic, rather than a mechanical, valve, if possible [34].

Optimal anticoagulation for these women during pregnancy has become a subject of great controversy. Outside of pregnancy, warfarin is the preferred anticoagulant for patients who have mechanical heart valves; the addition of aspirin has been shown to provide added protection. The goal INR for most patients who have mechanical valves is 2.5 t o 3.5, which is higher than that which is recommended for the treatment of acute venous thromboembolism [31]. Newer bileaflet valves carry less risk of thrombosis than the older ball or disk valves; any type of aortic valve is less likely to thrombose than a prosthetic mitral valve. Therefore, patients who have bileaflet aortic valves but do not have atrial fibrillation may be managed with a slightly lower goal INR of 2.0 to 3.0 [31,46].

Generally, warfarin is considered to be contraindicated during pregnancy for several reasons. Exposure during embryogenesis may lead to warfarin embryopa-

thy, which consists of nasal and limb hypoplasia and epiphyseal stippling. It occurs in 5% to 10% of exposed fetuses, but this risk can be eliminated if heparin is substituted for warfarin from 6 to 12 weeks' gestation [45]. As warfarin crosses the placenta, it also causes fetal bleeding complications, the most dramatic of which is intracranial hemorrhage at the time of vaginal delivery. Central nervous system (CNS) abnormalities, such as microcephaly, mental retardation, optic atrophy, dorsal and ventral midline dysplasias, and midline cerebellar atrophy are believed to result from more subtle bleeding episodes at any time in gestation [45–47].

When unfractionated heparin has been substituted for warfarin throughout pregnancy, thromboembolism rates of 33% have been reported; this is equivalent to the rates of thromboembolism with no anticoagulation. When heparin was substituted for warfarin from 6 to 12 weeks' gestation only, the rate of thromboembolism was 9.2%, compared with 3.9% in patients who received warfarin throughout pregnancy [45]. High rates of thrombosis with heparin are suspected to be secondary to inadequate dosaging [46].

Low molecular weight heparin (LMWH) was believed to be a potentially useful anticoagulant for pregnant women who have mechanical valves because it does not cross the placenta; it has a longer half-life which would produce less fluctuation in drug levels. A study from New Zealand was encouraging; thrombosis occurred in only 1 of 12 pregnancies (8.3%) that were managed with enoxaparin (1 mg/kg, twice a day) and aspirin throughout gestation [48]. Aventis Pharmaceuticals, Bridgewater, New Jersey, the maker of enoxaparin, recently issued a warning which stated that enoxaparin is not recommended for anticoagulation of pregnant women who have mechanical heart valves. This warning was based on case reports of mechanical valve thrombosis and an unpublished trial from South Africa in which valve thrombosis and death occurred in two of seven patients who were treated with enoxaparin during pregnancy [46]. This manufacturer's warning may make it difficult to collect further data on this subject; however, the enoxaparin failures may have been secondary to inadequate levels of anticoagulation because anti-Xa levels were not maintained in a therapeutic range. Both peak and trough anti-Xa levels have been found to be lower in pregnant compared to nonpregnant women receiving LMWH [49].

The current recommendations of the ACC/AHA for anticoagulation in pregnant women who have mechanical heart valves are summarized in Box 4 [31]. These guidelines were published in 1998, before there was data regarding the use of LMWH in pregnancy for cardiac valve prostheses. In addition, they were published before it was recognized that the usual dosaging for nonpregnant individuals who received thromboprophylaxis for other indications may be inadequate in pregnant women who have mechanical heart valves.

There are no anticoagulation alternatives that do not pose significant risks and all are unapproved in pregnancy. Warfarin is most likely to be the safest alternative for the mother but poses the greatest risk for the fetus. If possible, warfarin should be avoided in the first trimester and from 36 weeks gestation until delivery. Therefore, the pregnant woman must choose between one of

Box 4. ACC/AHA recommendations for anticoagulation during pregnancy in patients who have mechanical prosthetic valves

Weeks 1 through 35

- The decision whether to use heparin during the first trimester or to continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner. If she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her, with a higher risk of thrombosis and bleeding and that any risk to the mother also jeopardizes the baby.
- High-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) who choose NOT to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dosage to prolong the midinterval (6 hours after dosing) activated partial thromboplastin time (aPTT) to two to three times control. Transition to warfarin can occur thereafter.
- In patients who receive warfarin, international normalized ratio (INR) should be maintained between and 2.0 and 3.0 with the lowest possible dosage of warfarin and low-dose aspirin should be added.
- Women who are at low-risk (no history of thromboembolism, newer low-profile prosthesis) may be managed with adjusted-dosage subcutaneous heparin (17,500–20,000 U twice a day) to prolong the midinterval (6 hours after dosing) aPTT to two to three times control.

After the 36th week

- Warfarin should be stopped no later than Week 36 and heparin should be substituted in anticipation of labor.
- If labor begins during treatment with warfarin, a cesarian section should be performed.
- In the absence of significant bleeding, heparin can be resumed 4 to 6 hours after delivery and warfarin can be given orally.

Adapted from Bonnows RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998;32: 1486–588; with permission.

several problematic alternatives. At our institution, the pharmacy and therapeutics committee recommends the following three options:

(1) Unfractionated heparin throughout pregnancy, dosed every 8 to 12 hours to keep the midinterval partial thromboplastin time (PTT) two to three times normal or the peak PTT three times normal and the trough at least 1.5 times normal.
(2) LMWH throughout pregnancy to maintain peak anti-Xa levels at 0.8 to 1.5 and trough levels at least 0.7. Dalteparin may be preferable because of the medicolegal issues that surround the use of enoxaparin after the Aventis warning.
(3) Regimen 1 or 2 before 12 weeks' gestation and again from 36 weeks' gestation until delivery. Warfarin from 12 through 36 weeks' gestation with a goal INR of 2 to 3.5, depending on the thrombogenicity of the valve.

All three regimens should be given with a daily baby aspirin. Anti-Xa levels should be performed at least twice monthly and the dosages should be adjusted accordingly. Because there is no clear optimal regimen, informed consent is exceedingly important and must be documented carefully. If a patient presents with preterm labor before she has been switched from warfarin to heparin, cesarean delivery is recommended to decrease the risk of neonatal intracranial hemorrhage.

Congenital heart disease

Pregnancy in a patient who has congenital heart disease carries the risk of maternal cardiac decompensation and the transmission of specific defects to the fetus. Table 1 summarizes the estimated risks of transmission of specific cardiac defects. Ideally, these risks should be addressed with the patient in preconception

Table 1
Risk of transmission to offspring for women who have congenital cardiac defects

Condition	Risk to fetus
Pulmonary stenosis	7%
Aortic coarctation	6.5%
Aortic stenosis	17%
Patent ductus arteriosus	9%
Ventricular septal defect	17%
Atrial septal defect	6–12%
Cyanotic congenital heart disease	6%
Marfan's syndrome	50%

Data from Refs. [50–52].

counseling. During pregnancy, screening can be performed with fetal echocardiography or genetic testing in certain individuals.

Coarctation of the aorta

Coarctation of the aorta consists of a discrete narrowing of the descending aorta, most commonly distal to the left subclavian artery, with proximal hypertension and distal hypoperfusion [53,54]. Eighty percent of cases are detected in infancy or childhood; occasionally, the initial diagnosis is made in a young, pregnant woman [55], The severity of the lesion is described by gradient across the coarct, which is measured most easily by the arm–leg blood pressure gradient; a measurement that is greater than 20 mm Hg is considered to be significant. Treatment consists of open surgical repair or balloon angioplasty; after repair, there is a risk of restenosis and need for repeat interventions [56]. Coarctation of the aorta has been associated with intracranial aneurysms and an "intrinsic aortopathy" that predisposes patients to aortic dissection, aneurysm, and rupture.

Pregnancy in women who have a history of coarctation of the aorta was reported to carry a 9.5% mortality rate [57]; however a more recent series of 118 pregnancies in 50 women who had a history of coarctation (repaired and unrepaired) revealed only one maternal death of a 30-year-old woman at 36 weeks' gestation with a twin pregnancy who suffered an aortic dissection. Thirty percent of women had systemic hypertension during pregnancy; the incidence of hypertension was higher in women who had a significant coarctation gradient [54]. Wide fluctuations in blood pressure during labor, particularly the second stage, may increase the risk of intracranial aneurysm rupture or aortic dissection in patients who have coarctation of the aorta. This has led some obstetricians to recommend elective cesarean delivery; however, vaginal delivery is likely to be as safe with the use of epidural anesthesia to eliminate pain-related hypertension and assisted delivery to shorten the second stage.

Marfan's syndrome

Marfan's syndrome is an autosomal dominant condition that is caused by multiple family-specific mutations in the fibrillin gene that is located on chromosome 15. Its cardiovascular manifestations include MVP, MR, aortic root dilatation, AR, and a propensity toward dissection or rupture of the aortic root [58]. The mean age of death in patients who have Marfan's syndrome is 32 years; therefore, these catastrophic events may coincide with pregnancy and the hemodynamic changes of pregnancy may increase the risk of aortic complications [59]. Patients who have Marfan's syndrome are followed with aortic root diameter, because this may predict the risk of aortic dissection or rupture. Replacement of the ascending aorta in asymptomatic patients is recommended when the root diameter exceeds 5.5 cm [58].

Aortic root diameter also may predict maternal risk during pregnancy. The maternal mortality rate was reported to be as high as 50% in patients who had an aortic root diameter that was greater than 4.5 cm, AR, left ventricular dilatation or dysfunction, hypertension, or coarctation [60]. A prospective study of 45 pregnancies in 21 patients who had Marfan's syndrome found that the only two cases of aortic dissection during pregnancy occurred in patients who had predictable prepregnancy risk factors. One patient had a history of aortic dissection that required repair 6 months before conception; she also used cocaine during pregnancy. The second patient had AR and MVP prepregnancy. The remaining women had minimal cardiovascular complications during pregnancy; long-term follow-up revealed no worsening of disease compared with women who had Marfan's syndrome who did not become pregnant [61]. A subsequent review of 91 pregnancies in 36 women who had Marfan's syndrome was less encouraging; two women who had aortic root diameters that were less than 4.5 cm experienced aortic dissection during pregnancy [58].

Pregnant women who have Marfan's syndrome should have their aortic root diameter followed with monthly echocardiograms. Hypertension should be treated aggressively, typically with β-blockers. Patients who have aortic root diameters that are less than 4.5 cm and no associated cardiovascular complications may deliver vaginally with epidural anesthesia and an assisted second stage. Most investigators recommend elective cesarean section for high-risk patients who have Marfan's syndrome to minimize any episodes of hypertension that could precipitate aortic dissection. Patients should be counseled on the 50% transmission rate to their children and be offered prenatal diagnosis [58]. Patients who have Ehlers-Danlos syndrome type IV, which also is autosomal dominant, have a similar risk of aortic dissection; therefore, the same recommendations apply [62].

Left-to-right shunts

Generally, left-to-right shunts are well-tolerated in pregnancy. They are associated with a chronic state of volume expansion, which expands even further during pregnancy. Patients are at risk for stroke from paradoxic embolization across the shunt. Because pregnancy is a hypercoagulable state with a markedly increased risk of thromboembolism, the use of baby aspirin after the first trimester is advised [53]. Left-to-right shunts eventually can lead to pulmonary hypertension and reversal of the shunt with cyanosis. Echocardiography is recommended in pregnancy to evaluate for pulmonary hypertension; its presence is associated with a dramatically poorer prognosis for mother and fetus. Severe obstetric hemorrhage that leads to acute systemic hypotension also has been associated with transient reversal of the shunt [50,63].

Atrial septal defects

Ostium secundum defects are not encountered uncommonly in pregnancy; sometimes they are asymptomatic until the reproductive years and dispropor-

tionately affect females. Twenty to 30% of patients have coexisting mitral valve prolapse. Complications can include arrhythmias, pulmonary hypertension, and right ventricular failure; however, these typically develop after age 40 [56,63].

Ventricular septal defects

Ventricular septal defects (VSD) are encountered much less commonly in pregnancy because they typically are detectable in childhood and either close spontaneously or are surgically corrected by adulthood. If closure of a large VSD is delayed, irreversible pulmonary hypertension may develop. Membranous VSDs are the most common type and can be associated with AR [56]. A pregnant patient who has a history of corrected VSD and no pulmonary hypertension has no increased risk of adverse outcomes during pregnancy [50].

Patent ductus arteriosus

A persistent patent ductus arteriosus (PDA) also is encountered uncommonly in pregnancy because if it does not close spontaneously in infancy, typically it is repaired in childhood. Pregnancy outcomes are similarly related to the presence or absence of pulmonary hypertension.

Eisenmenger's syndrome

A long-standing left-to-right shunt produces chronically-increased pulmonary vascular blood flow. Over time, this can induce vascular remodeling and lead to increased pulmonary vascular resistance which meets or exceeds systemic vascular resistance. When the pressures are equal, flow across the shunt ceases, whereas when pulmonary vascular resistance exceeds systemic vascular resistance, reversal of flow and cyanosis occur. The most common cause of Eisenmenger's syndrome is a large VSD, followed by a large PDA, and, less commonly, an atrial septal defect (ASD). After Eisenmenger's pathophysiology is established, the pulmonary hypertension is permanent and surgical correction of the defect is unhelpful and may increase mortality [64].

Pregnancy in women who had Eisenmenger's syndrome from the 1940s to 1978 was associated with a 39% maternal mortality rate [65]. A more recent review of 73 patients who had Eisenmenger's syndrome from 1978 to 1996 revealed no improvement in maternal outcome. Three patients died during pregnancy and 23 patients died within 30 days postpartum for an overall maternal mortality of 36%. Causes of death included worsening pulmonary hypertension with heart failure, unspecified ''sudden death,'' pulmonary embolism, cerebral thromboembolism, and pulmonary artery rupture/dissection [66].

Management during pregnancy includes bed rest, supplemental oxygen, anticoagulation, and a low threshold for hospitalization if complications arise. Most patients who have Eisenmenger's syndrome have unreactive pulmonary vasculature that does not respond normally to vasodilators, such as prostacyclin [38,67]. Improvement of oxygenation with inhaled nitric oxide has been reported [68]. During labor, acute decreases in systemic vascular resistance, such as with

rapid administration of epidural anesthesia, may increase the right-to-left shunt fraction and increase hypoxia. Regional anesthesia with intrathecal narcotics or slow administration of epidural anesthetics may be administered safely. Acute postpartum hemorrhage similarly can cause systemic hypotension and increased shunt fraction and should be managed aggressively. A pulmonary artery catheter may provide useful information in some patients who have Eisenmenger's syndrome as a result of interatrial shunts; however, for patients who have interventricular shunts, it seems to be associated with an unacceptably high rate of complications, including embolization, pulmonary artery rupture, and arrhythmias [69].

Cyanotic congenital heart disease

This category of congenital heart disease includes any malformation that involves a right-to-left shunt that causes deoxygenated blood to pass into the systemic circulation with consequent cyanosis. It includes tetralogy of Fallot, transposition of the great arteries, tricuspid atresia, double-outlet right ventricle, single ventricle, and Ebstein's anomaly with ASD. Most of these conditions require repair in childhood or infancy to permit survival to childbearing age. Women who have a history of repair who are no longer cyanotic and whose ventricular function is normal may tolerate pregnancy well [70–72]; however, they may have residual problems, such as arrhythmias, progressive right ventricular failure (because the anatomic right ventricle may feed the systemic circulation after repair), thromboembolic risk, and recurrence of cyanosis [56]. Tetralogy of Fallot is the most common, uncorrected cyanotic congenital heart lesion that is seen in pregnant women. Generally, pregnancy is discouraged in these patients because the decreased systemic vascular resistance of pregnancy increases the volume of the right-to-left shunt and increases cyanosis. Further decreased venous return to the heart secondary to obstetric hemorrhage may be catastrophic [64].

Presbitero et al [73] reported on a series of 96 pregnancies in 44 patients who had cyanotic congenital heart disease (defined as central cyanosis at rest or with exertion, clubbing, documented systemic arterial desaturation, and cardiac anatomy to explain these findings). Thirty-two percent (14/44) of patients had cardiovascular complications during pregnancy or the puerperium, including heart failure, pulmonary embolism, stroke, supraventricular tachycardia, and endocarditis. One case of endocarditis resulted in maternal death 2 months' postpartum (maternal mortality 1%). Based on the 3% incidence of endocarditis in this study, the investigators disagreed with the ACC/AHA recommendations that endocarditis prophylaxis is not necessary for uncomplicated vaginal or cesarean delivery. After intentional pregnancy terminations were excluded, the live birth rate in this series was only 43% (41/96). Fifty-one percent of patients had spontaneous abortions and 6% had stillbirths after 26 weeks' gestation. Maternal prepregnancy arterial oxygen saturation and hemoglobin concentration were the best predictors of the chance of live birth. The live birth rate was 12% for women

with oxygen saturations less than or equal to 85% compared with 92% for women with oxygen saturations greater than or equal to 90%. A prepregnancy hemoglobin level of at least 20 g /dL was associated with an 8% rate of live birth [72].

Peripartum cardiomyopathy

The association between pregnancy and cardiomyopathy has been evident since as early as 1870; this condition has been referred to by several terms, including "toxic postpartal heart disease," "postpartum myocarditis," and "postpartum heart failure" [74,75]. The term "peripartum cardiomyopathy" (PPCM) was defined first in 1971 as symptoms of heart failure that become apparent in the last month of pregnancy or within 5 months postpartum in patients who have no pre-existing heart disease and no other obvious etiology for heart failure [76]. More recently, the following echocardiographic criteria for this diagnosis were established by Hibbard et al [75]: ejection fraction less than 45% or M-mode fractional shortening of less than 30%, and end-diastolic dimension that is greater than 2.72 cm/m^2 [75]. These criteria were created to allow for better characterization of this disease and better parameters upon which to enroll patients in research studies. The incidence of PPCM ranges from 1 in 2400 to 1 in 15,000 pregnancies [77,78]. It is more prevalent in patients who are older, multiparous, or of African descent, and in pregnancies that are complicated by multiple gestation, chronic hypertension, pre-eclampsia, or prolonged tocolytic therapy [74,78].

Treatment of PPCM is similar to that for congestive heart failure of any cause: preload reduction with sodium and fluid restriction, diuretics, and nitrates; afterload reduction; and positive inotropes, such as digoxin [74], In pregnant patients, a few modifications must be made. In nonpregnant individuals, angiotensin-converting enzyme inhibitors are the best agents for afterload reduction because they were shown to reduce mortality in patients who had CHF [79]. They are contraindicated in pregnancy secondary to association with fetal renal dysfunction that causes oligohydramnios and persistent neonatal anuria [80]. Hydralazine, nitroglycerin, or amlodipine are safe alternatives. Diuresis during pregnancy should be conservative so as to preserve uteroplacental perfusion [74].

Data on the prognosis of PPCM are limited and confounded by the inclusion of patients who had other causes of heart failure in older studies. The reported mortality rate ranges from 18% to 50% [75–78,81]. Witlin et al [78] followed 28 patients who were diagnosed with PPCM between 1986 and 1994. Five patients (18%) died of the disease, 3 patients (11%) required cardiac transplantation and subsequently did well, 18 patients (64%) had stabilization of their symptoms with medication, and 2 patients (7%) had complete clinical resolution of heart failure. Early studies reported a worse prognosis for women who had persistent cardiomegaly on chest radiograph 6 months after diagnosis [76]. More recent studies attempted to correlate echocardiographic features at the time of diagnosis with long-term prognosis but with inconsistent results [78,82,83].

Witlin et al [84] found that one of two patients who had mild myocardial dysfunction (LV end-diastolic dimension less than 60 mm plus fractional shortening of 22%–24%) had complete resolution of PPCM compared with none of seven patients who had severe myocardial dysfunction (LV end-diastolic dimension greater than 60 mm plus fractional shortening of up to 21%).

Another unresolved question is the risk of future pregnancies in women who survive the initial episode of PPCM. Older studies reported a recurrence risk of 50% to 100% [81]. Witlin et al [78] reported on six patients who had subsequent pregnancies. One patient who had complete resolution of PPCM had no recurrence with two future pregnancies. One patient who had stable heart failure that required digoxin and furosemide remained stable without decompensation during her next pregnancy. Four patients who had stable heart failure had worsening of functional status during subsequent pregnancies. A survey of cardiologists generated data on 60 subsequent pregnancies in 44 patients who had a history of PPCM. Twenty-eight patients who had normalization of LV function before their next pregnancy were defined as Group 1. During the next pregnancy, there were no deaths in this group and 21% had symptoms of heart failure. Group 2 consisted of 16 women who had persistent LV dysfunction before their next pregnancy. Three patients (19%) in this group died during the next pregnancy and 44% developed clinical CHF [85]. Sutton et al [86] reported good outcomes in four patients who had a history of PPCM who had echocardiograms that documented normal ventricular function before attempting subsequent pregnancies. These data suggest that echocardiography may be helpful in prognosticating for patients who are considering future pregnancies. An even more sensitive test may be the dobutamine stress echocardiogram. Lampert et al [87] demonstrated that women who had a history of PPCM with normal LV function at rest had decreased contractile reserve. These investigators postulated that this test may simulate some of the physiologic changes of pregnancy, particularly increased cardiac output, and could be helpful in predicting response to future pregnancy; this remains to be proven with prospective studies [75].

Ischemic heart disease

Acute myocardial infarction (MI) during pregnancy is a rare event that occurs in fewer than 1 in 10,000 pregnancies [88,89]. Although the overall risk is low, the hypercoagulable state and increased myocardial oxygen demands of pregnancy increase a young woman's risk of MI. Postpartum women have a six-fold higher rate of MI than age-matched nonpregnant women [88]. Medications that are used during pregnancy also may increase a woman's risk of MI. Case reports of coronary spasm and MI associated with administration of ergonovine (0.25 mg given IV for postpartum hemorrhage), prostaglandin E $(PGE)_1$, and PGE_2 have been published [90–92]. MI also has been reported in association with use of the combination of ritodrine and nifedipine for preterm labor [93]; most, but not all, of these cases involved women who had known cardiac risk factors. Compared

with the general obstetric population, patients who experience MI are more likely to be older than age 33 and multigravid [89,94].

A review of 125 cases of MI during pregnancy or within 3 months of delivery was performed by Roth and Elkayam [89]. Seventy-eight infarctions occurred antepartum (most in the third trimester), 17 were peripartum, and 30 were postpartum. The cause of MI seemed to be coronary atherosclerosis with or without thrombosis in 43%, coronary thrombus without atherosclerosis in 21%, coronary dissection in 16%, and coronary aneurysm in 4%. Including patients who had isolated thrombus, 29% had normal coronary arteries at the time of catheterization. Coronary spasm that caused acute thrombus formation was postulated as an explanation for this. Maternal mortality in this series was 21% and fetal mortality was 13% (usually associated with maternal death). Mode of delivery was not associated with maternal mortality [89]. Previous series found that death is most likely to occur acutely at the time of infarction or within the first 2 weeks. Delivery within 2 weeks of acute MI was associated with up to a 50% maternal mortality secondary to congestive heart failure or arrhythmias [21,94].

Treatment of myocardial infarction in pregnancy generally is unchanged from that of the nonpregnant patient. Thrombolytics, such as streptokinase and tissue plasminogen activator (t-PA), have been used with caution because of a few reports of placental abruption and neonatal intracranial hemorrhage [89]; however, maternal resuscitation is the most important factor for fetal well-being so if these agents are indicated then they should not be withheld. Successful use of t-PA for acute MI at 21 weeks' gestation with good maternal and fetal outcome has been reported [95]. Cardiac catheterization and interventional procedures are associated with fetal radiation exposures that range from less than 0.01 to 0.1 Gy, depending on the difficulty and extent of the procedure [89]. After organogenesis is completed, this risk is not significant enough to alter management.

Following acute MI, delivery should be delayed for at least 2 weeks, if possible, to allow myocardial healing. Vaginal delivery usually is preferred, with efforts to decrease myocardial oxygen demand, such as epidural anesthesia for pain control and an assisted second stage [89]. The risk of subsequent pregnancy in a woman who has a history of MI is unclear. Of 24 cases that were reported in the literature there were no maternal deaths and an approximately 20% incidence of CHF or angina during the subsequent pregnancy [96,97]. Avila et al [8] reported on pregnancy in an additional 14 patients who had significant coronary artery disease, 7 of whom had a history of MI. Although there were no maternal deaths, 50% of these patients had cardiovascular events during pregnancy, including unstable angina in 4 patients.

Maternal arrhythmias

The normal physiologic changes of pregnancy include an increase in heart rate by 10 to 20 beats/min. The presence of sinus tachycardia (defined as at least

100 beats/min) in an asymptomatic pregnant woman is not uncommon and often is not pathologic. Carson et al [98] found that 39% of healthy asymptomatic patients in the third trimester of pregnancy had sinus tachycardia in the seated position. The incidence of sinus tachycardia was even higher (58%) in obese patients (body mass index >30). Premature atrial and ventricular contractions are more common during pregnancy and the incidence of benign arrhythmias increases even further during labor. A study of EKGs of normal laboring women found that nearly all patients had some abnormalities, including premature atrial, ventricular, or nodal complexes; sinoatrial arrest; wandering atrial pacemaker; sinus tachycardia; and paroxysmal ventricular tachycardia [22,99].

Paroxysmal supraventricular tachycardia (SVT) is common in young women without structural heart disease and is not encountered uncommonly in pregnancy. Twenty-two percent of women who have SVT report an increased frequency of tachycardia events during pregnancy [100,101]. Treatment of SVT during pregnancy essentially is unchanged. To terminate acute episodes of SVT, vagal maneuvers should be attempted first, followed by IV adenosine. After viability, fetal monitoring should be performed during adenosine administration because fetal bradycardia has been reported [102]. For women who have frequent symptomatic episodes of SVT, β-blockers, calcium channel blockers, and digoxin may be used safely [103].

Typically, atrial fibrillation and atrial flutter occur in association with underlying conditions, such as hyperthyroidism, chronic obstructive pulmonary disease, pulmonary embolism, cardiomyopathy, or cardiac valvular lesions, such as mitral or aortic stenosis [42]. Treatment depends on the clinical scenario and generally is unaltered by pregnancy. New onset atrial fibrillation in patients who have mitral stenosis can lead to pulmonary edema and hemodynamic instability; cardioversion can be indicated in this setting. For patients who have stable atrial fibrillation, β-blockers, digoxin, and calcium channel blockers can be used for rate control [103,104]. Given the hypercoagulable state of pregnancy, anticoagulation is indicated for these patients to prevent left atrial thrombus formation and embolic events [103].

Ventricular tachycardia usually occurs in the setting of structural heart disease; however, there have been multiple reports of symptomatic ventricular tachycardia in pregnant women who do not have structural heart disease [42,104]. These episodes may be due to ''catecholamine sensitivity,'' sometimes were triggered by stress or exertion, and were suppressed with β-blockers [105]. In a hemodynamically-stable patient, pharmacologic cardioversion may be attempted with lidocaine followed by procainamide. Direct Current (DC) cardioversion is indicated for maternal or fetal hemodynamic instability. To suppress recurrence, β-blockers may be used. Amiodarone should be avoided if possible because of association with neonatal thyroid dysfunction, neurologic abnormalities, IUGR, and fetal bradycardia [42,106]. Patients who have life-threatening ventricular arrhythmias may require implantable cardioverter-defibrillators (ICDs). A series of 44 women who had ICDs placed either before or during pregnancy reported good maternal and fetal outcomes. The investigators concluded that in the

Table 2
American College of Cardiology/American Heart Association recommendations for antibiotic prophylaxis to prevent bacterial endocarditis

Cardiac lesion	Prophylaxis for uncomplicated delivery	Prophylaxis for suspected bacteremia[a]
High-risk category		
Prosthetic cardiac valves (homograft and bioprosthetic)	Optional	Recommended
Previous bacterial endocarditis	Optional	Recommended
Complex cyanotic congenital cardiac malformations	Optional	Recommended
Surgically-constructed systemic pulmonary shunts or conduits	Optional	Recommended
Moderate-risk category		
Congenital cardiac malformations (except repaired atrial septal defect, ventricular septal defect, or patent ductuc arteriosus, or isolated secundum atrial septal defect)	Not recommended	Recommended
Acquired valvular dysfunction (most commonly rheumatic heart disease)	Not recommended	Recommended
Hypertrophic cardiomyopathy	Not recommended	Recommended
Mitral valve prolapse with valvar regurgitation or thickened leaflets or both	Not recommended	Recommended
Negligible-risk category[b]		
Mitral valve prolapse without valvar regurgitation	Not recommended	Not recommended
Physiological, functional, or innocent heart murmurs	Not recommended	Not recommended
Previous Kawasaki disease without valvar dysfunction	Not recommended	Not recommended
Previous rheumatic fever without valvar dysfunction	Not recommended	Not recommended
Cardiac pacemakers and implanted defibrillators	Not recommended	Not recommended
Previous coronary bypass graft surgery	Not recommended	Not recommended

[a] Intra-amniotic infection, For example.
[b] Risk for developing endocarditis is not higher than in the general population.
Adapted from Prophylactic antibiotics in labor and delivery. ACOG Pract Bull 2003;47:639; with permission.

Table 3
Endocarditis prophylaxis regimens for genitourinary/gastrointestinal (excluding esophageal) procedures

Situation	Agents	Regimen
High-risk patients	Ampicillin plus gentamicin	Ampicillin 2.0 g IM/IV plus gentamicin 1.5 mg/kg (not to exceed 120 mg) within 30 minutes of starting the procedure. Six hours later, ampicillin 1.0 g IM/IV or amoxicillin 1.0 g po.
High-risk patients allergic to ampicillin	Vancomycin plus gentamicin	Vancomycin 1.0 g IV over 1–2 hours plus gentamicin 1.5 mg/kg (not to exceed 120 mg). Complete infusion within 30 minutes of starting the procedure.
Moderate-risk patients	Amoxicillin or ampicillin	Amoxicillin 2.0 g po 1 hour before procedure or ampicillin 2.0 g IM/IV within 30 minutes of starting the procedure.
Moderate-risk patients allergic to ampicillin	Vancomycin	Vancomycin 1.0 g IV over 1–2 hours. Complete infusion within 30 minutes of starting the procedure.

Adapted from Bonnow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease.) J Am Coll Cardiol 1998;32: 1486–588; with permission.

Table 4
Summary of maternal mortality associated with selected cardiac conditions

Condition	Maternal mortality	References
Mitral stenosis		
All mitral stenosis	0–1.6%	[8,32]
NYHA class III/IV	5–7%	[30,33]
Aortic stenosis		
All aortic stenosis	0–2.0%	[8,32]
Pulmonic stenosis	0	[5,8,29]
Mechanical heart valve	1–4%	[45,46]
Coarctation of the aorta	0–2%	[5,54]
Marfan's syndrome		
All Marfan's patients	0–1.1%	[58,61]
Patients with risk factors[a]	50%	[57,60]
Eisenmenger's syndrome	36%	[66]
Cyanotic congenital heart disease	1%	[73]
Peripartum cardiomyopathy		
In current pregnancy	18–50%	[74–78]
In previous pregnancy with persistent LV dysfunction	19%	[85]
Myocardial infarction within 2 weeks of delivery	50%	[21,94]

[a] Risk factors defined as aortic root diameter greater than 4.5 cm, aortic regurgitation, left ventricular dilatation or dysfunction, hypertension, or associated coarctation of the aorta.

Box 5. Key points

Preconception considerations

Optimization of maternal status:

Repair of structural defects should be performed before pregnancy if indicated.

Medications should be adjusted to optimize maternal functional capacity and minimize fetal effects.

Discussion of fetal risks:

Patients must be aware of the risk of transmission of congenital heart defects to their offspring (see Table 1).

Patients should understand the risk to fetus of maternal conditions or medications.

Antepartum considerations

Maternal risks vary greatly, depending on the specific lesion, severity of the lesion, and prepregnancy functional status (see Table 4).

Anticoagulation is indicated for patients who have mechanical heart valves, atrial arrhythmias, and cyanotic congenital heart defects.

For patients who require anticoagulation, consider a change from warfarin to heparin to minimize teratogenicity.

Intrapartum considerations

Labor is the most dangerous period for many patients who have cardiac disease; this is the period of the greatest increase in cardiac output.

Vaginal delivery is preferred over cesarean section for most patients because of less blood loss, fewer postpartum infections, and earlier ambulation with less risk of thrombosis and pulmonary complications.

An assisted second stage is recommended for patients who have significant cardiac disease to shorten labor and to decrease the dramatic fluid shifts that are associated with active pushing.

Endocarditis prophylaxis may be given to high-risk patients.

Telemetry is indicated during labor for patients who have arrhythmias.

Postpartum hemorrhage must be treated aggressively to prevent hypovolemia. This is particularly important for patients who are preload-dependent, such as those who have severe AS or MS.

Anesthetic considerations

Regional anesthesia is appropriate for most patients who have cardiac disease. Benefits of good pain control include:

- Avoidance of maternal tachycardia. This is particularly important for patients who have mitral stenosis whose left ventricle cannot fill properly if diastole is shortened.
- Decreased cardiac work
- The ability to perform an assisted vaginal delivery

Patients who have severe stenotic heart defects will not tolerate sudden decreases in systemic vascular resistance; epidural anesthesia must be administered slowly or intrathecal narcotics may be used. For cesarean delivery, these patients may require general anesthesia.

Postpartum considerations

Patients remain at high risk for thromboembolism during the postpartum period; prophylactic anticoagulation should be continued for at least 6 weeks.

Patients who have certain cardiac conditions (eg, Eisenmenger's syndrome) have a higher risk of death during the postpartum period than during pregnancy and may require prolonged hospitalization.

absence of severe underlying structural heart disease, the presence of an ICD should not be considered a contraindication to pregnancy [107].

Endocarditis prophylaxis

Many patients who have structural heart disease require antibiotics for endocarditis prophylaxis at the time of dental procedures and many patients and physicians assume that they also must need endocarditis prophylaxis at the time of delivery. Endocarditis is believed to occur from bacterial seeding of damaged heart valves and bacteremia has been found to occur after 60% to 90% of dental procedures [108,109] compared with only 1% to 5% of deliveries [110,111]. Based on these recommendations, the ACC/AHA does not recommend routine antibiotic prophylaxis for patients who have valvular heart disease who are undergoing routine vaginal or cesarean delivery. Clinical infection, such as chorioamnionitis, may be associated with bacteremia, and, therefore, endocarditis prophylaxis is warranted. Conveniently, the most common antibiotic regimen for chorioamnionitis (ampicillin and gentamicin) provides good coverage for endocarditis prophylaxis. In addition, the ACC/AHA allow for "optional" endocarditis prophylaxis for patients who have a history of endocarditis or high-risk

Table 5
Effects of cardiovascular drugs taken during pregnancy

Drug	Potential adverse effects in pregnancy	U.S. Food and Drug Administration pregnancy category	Breast-feeding category[a]
Warfarin	Crosses placental barrier, fetal hemorrhage in utero, warfarin embryopathy, CNS abnormalities	X	Compatible
Heparin	None reported. Does not cross placenta	C	Compatible
Digoxin	Low birth weight	C	Compatible
Quinidine	Toxic dose may induce preterm labor and cause damage to fetal eighth cranial nerve	C	Compatible
Procainamide	None reported	C	Compatible
Disopyramide	May initiate uterine contractions	C	Compatible
Lidocaine	High blood levels and fetal acidosis may cause CNS depression	B	Compatible
Mexiletine	Fetal bradycardia, IUGR, low Apgar scores, neonatal hypoglycemia, bradycardia, and hyperthyroidism	C	Compatible
Flecainide	One reported fetal death	C	Compatible
Propafenone	None reported	C	Unknown
Adenosine	None reported. Use during first trimester limited to a few patients.	C	Compatible

Amiodarone	IUGR, preterm birth, hypothyroidism	D	Incompatible
Calcium channel blockers	Fetal distress due to maternal hypotension	C	Compatible
β-Blockers	IUGR, apnea at birth, bradycardia, hypoglycemia, hyperbilirubinemia, β2-blockers may cause contractions	Atenolol D Solalol B Propranolol C Labetalol C	Use with caution Compatible Compatible Compatible
Hydralazine	None reported	C	Compatible
Sodium nitroprusside	Potential thiocyanate toxicity with high dose, fetal mortality in animal studies	C	Unknown
Nitroglycerin	Fetal heart rate decelerations and bradycardia	C	Unknown
ACE inhibitors	Skull ossification defect, IUGR, preterm birth, oligohydramnios, neonatal renal failure, anemia, and death, patent ductus arteriosus	C (1^{st} trimester) D (2^{nd} & 3^{rd} trimesters)	Enalapril, captopril compatible. Others unknown
Diuretics	Placental hypoperfusion, thrombocytopenia, jaundice, hyponatremia, bradycardia	Furosemide C HCTZ B[b]	Unknown Compatible but may suppress lactation

[a] Based on the American Academy of Pediatrics recommendations.

[b] HCTZ is classified as category B by the manufacturer based on teratogenic risk; however, based on its risks in the third trimester (neonatal jaundice, thrombocytopenia, hyponatremia) it is better classified as category D.

Data from Refs [31,115–117].

cardiac lesions, such as prosthetic valves, complex congenital heart disease, or a surgically-constructed systemic–pulmonary conduit [31]. These recommendations are summarized in Table 2. Specific antibiotic regimens for endocarditis prophylaxis are outlined in Table 3.

Despite these recommendations, many obstetricians administer endocarditis prophylaxis during labor or at the time of cesarean section. There are several reasonable explanations for this. The ACC/AHA guidelines discourage endocarditis prophylaxis for ''routine'' vaginal or cesarean delivery; however, in obstetrics it often is difficult to predict which deliveries will become complicated. Sugrue et al [111] collected serial blood cultures from 83 patients following vaginal deliveries (spontaneous and forceps). They found a 3.6% incidence of bacteremia but noted a possible increased risk with manual removal of the placenta. A concurrent series of 2165 patients who had cardiac disease revealed a 0.09% incidence of endocarditis following delivery, but both of these patients had manual removal of the placenta. This is a complication of delivery that cannot be predicted; the recommendations to give antibiotics before or within 30 minutes of starting the procedure make administration difficult after the fact. Therefore, many obstetricians liberalize the administration of prophylactic antibiotics at the time of delivery. This must be weighed against the risks of promoting bacterial resistance.

Cardiopulmonary bypass during pregnancy

The optimal time for cardiac surgery is before conception; however, patients who have structural heart disease who decompensate during pregnancy occasionally will require surgery. Cardiopulmonary bypass (CPB) represents a unique challenge to the pregnancy because of the profound alterations to systemic blood flow. Mortality rates for pregnant women who undergo CPB were similar to those for nonpregnant patients at 0% to 5%. Fetal mortality rates were reported to range from 4% to 33%, with the highest mortality rates reported in case series before 1970. Possible contributors to fetal loss include the severity of maternal cardiac disease in these patients who require surgery as well as the effects of CPB itself (altered coagulation, complement activation, risk of particulate or air embolism, hypotension, hypothermia, and nonpulsatile flow) [112,113].

Because there is no autoregulation of uterine blood flow, high flow rates (>2.5 L/m^2/min) and high pressures (mean arterial pressure (MAP) >70 mm Hg) are recommended to optimize placental perfusion. The fetal effects of hypothermia are controversial; some, but not all, series reported increased rates of fetal loss with hypothermia. Generally, mild hypothermia (such as 32°C) is believed to be safe. Intraoperative fetal monitoring is recommended after viability because fetal bradycardia may respond to interventions, such as increasing the flow rate. Fetal bradycardia often occurs during the initiation of CPB and then normalizes. The rewarming phase of cardiopulmonary CPB has been associated with uterine contractions [112,113].

Summary

Table 4 summarizes recent data on the maternal mortality that is associated with specific cardiac conditions. These risks are dramatically lower than those reported by Ueland [114] in a review article from 1978; this represents great progress in the treatment of these disorders and in obstetric care [112]. Maternal morbidity that is associated with pregnancy and neonatal morbidity from complications, such as preterm birth or IUGR, that are specific to each major maternal cardiac condition also must be considered. Key points are summarized in Box 5 (Table 5).

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