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Gestational Hypertension and Preeclampsia

Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide. It has been estimated that preeclampsia complicates 2–8% of pregnancies globally (1). In Latin America and the Caribbean, hypertensive disorders are responsible for almost 26% of maternal deaths, whereas in Africa and Asia they contribute to 9% of deaths. Although maternal mortality is much lower in high-income countries than in developing countries, 16% of maternal deaths can be attributed to hypertensive disorders (1, 2). In the United States, the rate of preeclampsia increased by 25% between 1987 and 2004 (3). Moreover, in comparison with women giving birth in 1980, those giving birth in 2003 were at 6.7-fold increased risk of severe preeclampsia (4). This complication is costly: one study reported that in 2012 in the United States, the estimated cost of preeclampsia within the first 12 months of delivery was $2.18 billion ($1.03 billion for women and $1.15 billion for infants), which was disproportionately borne by premature births (5). This Practice Bulletin will provide guidelines for the diagnosis and management of gestational hypertension and preeclampsia.

Background

Risk Factors

A variety of risk factors have been associated with increased probability of preeclampsia (Box 1) (6–12). Nonetheless, it is important to remember that most cases of preeclampsia occur in healthy nulliparous women with no obvious risk factors. Although the precise role of genetic–environmental interactions on the risk and incidence of preeclampsia is unclear, emerging data suggest the tendency to develop preeclampsia may have some genetic component (13–16).

Definitions and Diagnostic Criteria for Hypertensive Disorders of Pregnancy

Preeclampsia (With and Without Severe Features)

Preeclampsia is a disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term. Although often accompanied by new-onset proteinuria, hypertension and other signs or symptoms of preeclampsia may present in some women in the absence of proteinuria (17). Reliance on maternal symptoms may be occasionally problematic in clinical practice. Right upper quadrant or epigastric pain is thought to be due to periportal and focal parenchymal necrosis, hepatic cell edema, or Glisson's capsule distension, or a combination. However, there is not always a good correlation between the hepatic histopathology and laboratory abnormalities (18). Similarly, studies have found that using headache as a diagnostic criterion for preeclampsia with severe features is unreliable and nonspecific. Thus, an astute and circumspect diagnostic approach is required when other corroborating signs and symptoms indicative of severe preeclampsia are missing (19, 20). Of note, in the setting of a clinical presentation similar to preeclampsia, but at gestational ages earlier than 20 weeks, alternative diagnoses should to be considered, including but

Box 1. Risk Factors for Preeclampsia

Nulliparity
Multifetal gestations
Preeclampsia in a previous pregnancy
Chronic hypertension
Pregestational diabetes
Gestational diabetes
Thrombophilia
Systemic lupus erythematosus
Prepregnancy body mass index greater than 30
Antiphospholipid antibody syndrome
Maternal age 35 years or older
Kidney disease
Assisted reproductive technology
Obstructive sleep apnea

not limited to thrombotic thrombocytopenic purpura, hemolytic–uremic syndrome, molar pregnancy, renal disease or autoimmune disease.

Although hypertension and proteinuria are considered to be the classical criteria to diagnose preeclampsia, other criteria are also important. In this context, it is recommended that women with gestational hypertension in the absence of proteinuria are diagnosed with preeclampsia if they present with any of the following severe features: thrombocytopenia (platelet count less than $100{,}000 \times 10^9$/L); impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit of normal concentration); severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); pulmonary edema; or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances (Box 2). *Gestational hypertension* is defined as a systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure (21). Women with gestational hypertension with severe range blood pressures (a systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher) should be diagnosed with preeclampsia with severe features. These severe ranges of blood pressure or any of the severe features listed in Box 3 increase the risk of morbidity and mortality (22).

Box 2. Diagnostic Criteria for Preeclampsia

Blood pressure

- Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
- Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).

and

Proteinuria

- 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or
- Protein/creatinine ratio of 0.3 mg/dL or more or
- Dipstick reading of 2+ (used only if other quantitative methods not available)

Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia: Platelet count less than $100{,}000 \times 10^9$/L
- Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Proteinuria during pregnancy is defined as 300 mg/dL of protein or more in a 24-hour urine collection (21, 23) or a protein-to-creatinine ratio of 0.30 or more (24). When quantitative methods are not available or rapid decisions are required, a urine protein dipstick reading can be substituted. However, dipstick urinalysis has high false-positive and false-negative test results. A test result of 1+ proteinuria is false-positive in 71% of cases compared with the 300 mg cutoff on 24-hour urine collection, and even 3+ proteinuria test results may be false-positive in 7% of cases. Using the same 24-hour urine collection standard, the false-negative rate for dipstick urinalysis is 9% (25). If urinalysis is the only available means of

Box 3. Severe Features

- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than $100{,}000 \times 10^9$/L)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit normal concentration), and severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

assessing proteinuria then overall accuracy is better using 2+ as the discriminant value (25, 26).

Gestational Hypertension

Gestational hypertension is defined as a systolic blood pressure 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure (21). Gestational hypertension is considered severe when the systolic level reaches 160 mm Hg or the diastolic level reaches 110 mm Hg, or both. On occasion, especially when faced with severe hypertension, the diagnosis may need to be confirmed within a shorter interval (minutes) than 4 hours to facilitate timely antihypertensive therapy (27). Gestational hypertension occurs when hypertension without proteinuria or severe features develops after 20 weeks of gestation and blood pressure levels return to normal in the postpartum period (21). It appears that this diagnosis is more of an exercise of nomenclature than a pragmatic one because the management of gestational hypertension and that of preeclampsia without severe features is similar in many aspects, and both require enhanced surveillance. Outcomes in women with gestational hypertension usually are good, but the notion that gestational hypertension is intrinsically less concerning than preeclampsia is incorrect. Gestational hypertension is associated with adverse pregnancy outcomes (17) and may not represent a separate entity from preeclampsia (28). Up to 50% of women with gestational hypertension will eventually develop proteinuria or other end-organ dysfunction consistent with the diagnosis of preeclampsia, and this progression is more likely when the hypertension is diagnosed before 32 weeks of gestation (29, 30). Although investigators have reported a higher perinatal mortality rate in women with nonproteinuric hypertension compared with proteinuric preeclampsia (31), in a cohort of 1,348 hypertensive pregnant patients, the women with proteinuria progressed more frequently to severe hypertension and had higher rates of preterm birth and perinatal mortality; however, women without proteinuria had a higher frequency of thrombocytopenia or liver dysfunction (17). Women with gestational hypertension who present with severe-range blood pressures should be managed with the same approach as for women with severe preeclampsia. Gestational hypertension and preeclampsia may also be undistinguishable in terms of long-term cardiovascular risks, including chronic hypertension (32).

Hemolysis, Elevated Liver Enzymes and Low Platelet Count Syndrome

The clinical presentation of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is one of the more severe forms of preeclampsia because it has been associated with increased rates of maternal morbidity and mortality (33). Although different diagnostic benchmarks have been proposed (34), many clinicians use the following criteria (35) to make the diagnosis: lactate dehydrogenase (LDH) elevated to 600 IU/L or more, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated more than twice the upper limit of normal, and the platelets count less than 100,000 x 10^9/L. Although HELLP syndrome is mostly a third-trimester condition, in 30% of cases it is first expressed or progresses postpartum. Furthermore, HELLP syndrome may have an insidious and atypical onset, with up to 15% of the patients lacking either hypertension or proteinuria (36). In HELLP syndrome, the main presenting symptoms are right upper quadrant pain and generalized malaise in up to 90% of cases and nausea and vomiting in 50% of cases (35, 37).

Eclampsia

Eclampsia is the convulsive manifestation of the hypertensive disorders of pregnancy and is among the more severe manifestations of the disease. Eclampsia is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use. Some of these

alternative diagnoses may be more likely in cases in which new-onset seizures occur after 48–72 hours postpartum (38) or when seizures occur during administration of magnesium sulfate.

Eclampsia is a significant cause of maternal death, particularly in low-resource settings. Seizures may lead to severe maternal hypoxia, trauma, and aspiration pneumonia. Although residual neurologic damage is rare, some women may have short-term and long-term consequences such as impaired memory and cognitive function, especially after recurrent seizures or uncorrected severe hypertension leading to cytotoxic edema or infarction (39). Permanent white matter loss has been documented on magnetic resonance imaging after eclampsia in up to one fourth of women, however, this does not translate into significant neurologic deficits (39).

Eclampsia often (78–83% of cases) is preceded by premonitory signs of cerebral irritation such as severe and persistent occipital or frontal headaches, blurred vision, photophobia, and altered mental status. However, eclampsia can occur in the absence of warning signs or symptoms (40, 41). Eclampsia can occur before, during, or after labor. Of note, a significant proportion of women (20–38%) do not demonstrate the classic signs of preeclampsia (hypertension or proteinuria) before the seizure episode (42). Headaches are believed to reflect the development of elevated cerebral perfusion pressure, cerebral edema, and hypertensive encephalopathy (43).

The term preeclampsia implies that the natural history of patients with persistent hypertension and significant proteinuria during pregnancy is to have tonic–clonic seizures if no prophylaxis if instituted. However, the results of two randomized placebo-controlled trials indicate that seizure occurred in only a small proportion of patients with preeclampsia (1.9%) (44) or severe preeclampsia (3.2%) (45) allocated to the placebo arm of both studies. It is also noteworthy that there is a significant proportion of patients who had abrupt-onset eclampsia without warning signs or symptoms (40). In a nationwide analysis of cases of eclampsia in the United Kingdom, it was noted that in 38% of eclamptic cases the seizure occurred without any prior documentation of either hypertension or proteinuria in the hospital setting (46). Thus, the notion that preeclampsia has a natural linear progression from preeclampsia without severe features to preeclampsia with severe features and eventually to eclamptic convulsions is inaccurate.

Nervous system manifestations frequently encountered in preeclampsia are headache, blurred vision, scotomata, and hyperreflexia. Although uncommon, temporary blindness (lasting a few hours to as long as a week) also may accompany preeclampsia with severe features and eclampsia (47). Posterior reversible encephalopathy syndrome (PRES) is a constellation of a range of clinical neurologic signs and symptoms such as vision loss or deficit, seizure, headache, and altered sensorium or confusion (48). Although suspicion for PRES is increased in the setting of these clinical features, the diagnosis of PRES is made by the presence of vasogenic edema and hyperintensities in the posterior aspects of the brain on magnetic resonance imaging. Women are particularly at risk of PRES in the settings of eclampsia and preeclampsia with headache, altered consciousness, or visual abnormalities (49). Another condition that may be confused with eclampsia or preeclampsia is reversible cerebral vasoconstriction syndrome (50). Reversible cerebral vasoconstriction syndrome is characterized by reversible multifocal narrowing of the arteries of the brain with signs and symptoms that typically include thunderclap headache and, less commonly, focal neurologic deficits related to brain edema, stroke, or seizure. Treatment of women with PRES and reversible cerebral vasoconstriction syndrome may include medical control of hypertension, antiepileptic medication, and long-term neurologic follow-up.

Pathophysiology

Several mechanisms of disease have been proposed in preeclampsia (1, 51, 52), including the following: chronic uteroplacental ischemia (53), immune maladaptation (53), very low-density lipoprotein toxicity (53), genetic imprinting (53), increased trophoblast apoptosis or necrosis (54, 55), and an exaggerated maternal inflammatory response to deported trophoblasts (56, 57). More recent observations suggest a possible role for imbalances of angiogenic factors in the pathogenesis of preeclampsia (58). It is possible that a combination of some of these purported mechanisms may be responsible for triggering the clinical spectrum of preeclampsia. For example, there is clinical (59, 60) and experimental evidence (61, 62) suggesting that uteroplacental ischemia leads to increased circulating concentrations of antiangiogenic factors and angiogenic imbalances (63).

Vascular Changes

In addition to hypertension, women with preeclampsia or eclampsia typically lack the hypervolemia associated with normal pregnancy; thus, hemoconcentration is a frequent finding (64). In addition, the interaction of various vasoactive agents, such as prostacyclin (vasodilator), thromboxane A_2 (potent vasoconstrictor), nitric oxide (potent vasodilator), and endothelins (potent vasoconstrictors) results in another significant change

described in preeclampsia: intense vasospasm. Attempts to correct the contraction of the intravascular space in preeclampsia with vigorous fluid therapy are likely to be ineffective and could be dangerous because of the frequent capillary leak and decreased colloid oncotic pressure often associated with preeclampsia. Aggressive fluid therapy may result in elevation of the pulmonary capillary wedge pressure and increased risk of pulmonary edema. A study using invasive hemodynamic monitoring in women with preeclampsia found that before intravenous fluid therapy, women with preeclampsia had hyperdynamic ventricular function with low pulmonary capillary wedge pressure (65). However, after aggressive fluid therapy, the pulmonary capillary wedge pressure increased significantly above normal levels (65) with increased risk of pulmonary edema.

Hematologic Changes

Various hematologic changes also may occur in women with preeclampsia, especially in preeclampsia with severe features. Thrombocytopenia and hemolysis may occur and may reach severe levels as part of HELLP syndrome. Thrombocytopenia results from increased platelet activation, aggregation, and consumption (66) and is a marker of disease severity. A platelet count less than 150,000 x 10^9/L is found in approximately 20% of patients with preeclampsia, varying from 7% in cases without severe manifestations to 50% in cases with severe manifestations (67). However, reduced platelet counts are not found in all cases of preeclampsia or eclampsia (68). Interpretation of hematocrit levels in preeclampsia should take into consideration that hemolysis and hemoconcentration may occur (69). In some cases, the hematocrit may not appear decreased despite hemolysis because of baseline hemoconcentration. Lactate dehydrogenase is present in erythrocytes in high concentration. High serum concentrations of LDH (more than 600 IU/L) may be a sign of hemolysis (34, 35).

Hepatic Changes

Hepatic function may be significantly altered in women with preeclampsia with severe features. Alanine aminotransferase and AST may be elevated. Aspartate aminotransferase is the dominant transaminase released into the peripheral circulation in liver dysfunction due to preeclampsia and is related to periportal necrosis. The fact that AST is increased to a greater extent than ALT, at least initially, may help in distinguishing preeclampsia from other potential causes of parenchymal liver disease in which ALT usually is higher than AST. Increased serum levels of LDH in preeclampsia are caused by hepatic dysfunction (LDH derived from ischemic, or necrotic tissues, or both) and hemolysis (LDH from red blood cell destruction). Increase in bilirubin secondary to significant hemolysis may develop only in the late stages of the disease. Similarly, alterations in hepatic synthetic function, as reflected by abnormalities of prothrombin time, partial prothrombin time, and fibrinogen, usually develop in advanced preeclampsia. Evaluation of these coagulation parameters is probably only useful when the platelet count is below 150,000 x 10^9/L, there is significant liver dysfunction, or there is suspected placental abruption (70).

Renal Changes

The histopathologic renal changes classically described in preeclampsia as glomerular endotheliosis consist of swollen, vacuolated endothelial cells with fibrils, swollen mesangial cells, subendothelial deposits of protein reabsorbed from the glomerular filtrate, and tubular casts (71, 72). Proteinuria in preeclampsia is nonselective, as a result of increased tubular permeability to most large-molecular-weight proteins (albumin, globulin, transferrin, and hemoglobin). Urinary calcium decreases because of an increased tubular reabsorption of calcium.

In women with preeclampsia, contraction of the intravascular space secondary to vasospasm leads to worsening renal sodium and water retention (73). The normal increase in renal blood flow and glomerular filtration rate and the expected decrease in serum creatinine may not occur in women with preeclampsia, especially if the disease is severe. Preeclampsia with severe features may include acute renal deterioration as part of the clinical spectrum. Oliguria in severe preeclampsia is a consequence of intrarenal vasospasm with an approximate 25% reduction in glomerular filtration rate. In these patients, transient oliguria (less than 100 mL over 4 hours) is a common observation in labor or the first 24 hours of the postpartum period. Plasma concentrations of uric acid normally increase in late pregnancy, and this is thought to be due to increased rates of fetal or placental production, or both, decreased binding to albumin, and a decrease in uric acid clearance. The serum uric acid concentration increases to a greater extent in preeclampsia (74). The most commonly accepted explanation for hyperuricemia in preeclampsia, besides increased production, is the increased reabsorption and decreased excretion of uric acid in the proximal renal tubules.

Fetal Consequences

As a result of impaired uteroplacental blood flow secondary to failure of physiologic transformation of the spiral arteries or placental vascular insults, or both, manifestations of preeclampsia also may be seen in the

fetal–placental unit (63). Abnormalities in the placental bed and subsequent failure of physiologic transformation of the spiral arteries in the first or early second trimester (75, 76) limit the blood flow to the uteroplacental unit. Additional mechanisms for chronic uteroplacental ischemia include placental vascular insults (77, 78). Among women with preeclampsia, clinical manifestations that follow from this uteroplacental ischemia include fetal growth restriction, oligohydramnios, placental abruption, and nonreassuring fetal status demonstrated on antepartum surveillance. Consequently, fetuses of women with preeclampsia are at increased risk of spontaneous or indicated preterm delivery.

Clinical Considerations and Recommendations

▶ ***Are there screening methods that are useful to identify women at risk of developing hypertensive disorders of pregnancy?***

Several studies have evaluated the role of biochemical markers or a combination of biochemical and biophysical markers in the prediction of preeclampsia in the first and second trimesters of pregnancy (79). Regardless of the parameters used, screening for preeclampsia in low-risk women is associated with very low positive predictive values ranging from 8% to 33% (79). Thus, most screen-positive patients will not develop the disease and any prophylactic intervention in the screen-positive group would unnecessarily expose a large number of patients who would not benefit from these interventions.

In general, the sensitivity and specificity for the prediction of early-onset preeclampsia using first-trimester (80–82) and second-trimester biochemical (81, 83) or biophysical parameters (84–87) are better than for late-onset preeclampsia. The reason for this is still unclear but it is possible that the timing of the insults to the fetal supply line or the fetal response to these insults may be different between early-onset and late-onset preeclampsia. Even so, there is limited evidence that an accurate prediction of early-onset preeclampsia can be followed by interventions that improve maternal or fetal outcome.

Regardless of the index or combinations of indices used, uterine artery Doppler studies alone have a low predictive value for the development of early-onset preeclampsia and an even lower value for late-onset preeclampsia (88). Extensive work has identified some angiogenic factors (soluble fms-like tyrosine kinase-[sFlt-1], placental growth factor [PlGF], and soluble endoglin) in the second trimester as likely tools for the prediction of early-onset preeclampsia. However, no single test reliably predicts preeclampsia and further prospective investigation is required to demonstrate clinical utility. In the first trimester of pregnancy, it has been reported that a combination of low maternal serum concentrations of PlGF, high uterine artery pulsatility index, and other maternal parameters, identified 93.1% of patients who would develop preeclampsia requiring delivery before 34 weeks of gestation (82). However, the results of this study are based on mathematical modeling derived from a nested case−control study applied to a large cohort of almost 7,800 patients in which PlGF was measured only in the case−control group. The calculated positive predictive value was only 21.2%, indicating that approximately 79% of the women in the screen-positive group would not develop hypertensive disorders during pregnancy (82). Of note, a similar algorithm underperformed in a subsequent randomized trial performed by the same research group (89). Thus, biomarkers and ultrasonography cannot accurately predict preeclampsia and should remain investigational.

▶ ***Are there prevention strategies for reducing the risk of hypertensive disorders of pregnancy?***

Strategies to prevent preeclampsia have been studied extensively over the past 30 years. To date, no intervention has been proved unequivocally effective at eliminating the risk of preeclampsia. With regard to nutritional interventions, evidence is insufficient to demonstrate effectiveness for vitamins C and E (90), fish oil (91), garlic supplementation (92), vitamin D (93), folic acid, (94) or sodium restriction (95) for reducing the risk of preeclampsia. A meta-analysis of 13 trials (15,730 women) reported a significant reduction in preeclampsia with calcium supplementation, with the greatest effect among women with low-baseline calcium intake (96). Yet, this is not the case in the United States or other developed countries. Likewise, data do not support effectiveness of bed rest and, thus, it should not routinely be recommended (97).

Investigators hypothesized that an imbalance in prostacyclin and thromboxane A_2 metabolism was involved in the pathogenesis of preeclampsia, leading to the initial studies of aspirin for preeclampsia prevention because of its preferential inhibition of thromboxane A_2 at lower doses (98, 99). In a recent meta-analysis of aggregate data from 45 randomized trials, only a modest reduction in preeclampsia was noted when low-dose aspirin was started after 16 weeks of gestation (relative risk [RR], 0.81; 95% CI, 0.66–0.99) but a more significant reduction in severe preeclampsia (RR, 0.47; 95% CI, 0.26–0.83) and fetal growth restriction (RR, 0.56; 95% CI, 0.44–0.70) was demonstrated when low-dose aspirin

was started before 16 weeks of gestation (100). In contrast, in pooled individual data from 31 high-quality randomized trials, the beneficial effects of low-dose aspirin were consistent, whether treatment was started before or after 16 weeks of gestation (101). Women with any of the high-risk factors for preeclampsia (previous pregnancy with preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, and chronic hypertension) and those with more than one of the moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index [BMI; calculated as weight in kilograms divided by height in meters squared] of more than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors) should receive low-dose (81 mg/day) aspirin for preeclampsia prophylaxis initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continuing until delivery (Table 1).

In a recent multicenter, double blind, placebo-controlled trial, pregnant women at increased risk of preterm preeclampsia (less than 37 weeks of gestation) were randomly assigned to receive aspirin, at a higher dose (150 mg/day), or placebo from 11 weeks to 14 weeks of gestation until 36 weeks of gestation (89). Preterm preeclampsia occurred in 1.6% of the participants in the aspirin group, as compared with 4.3% in the placebo group (odds ratio, 0.38; 95% CI, 0.20−0.74; P=.004). The authors also reported that there were no significant differences in the incidence of neonatal adverse outcomes between groups. The authors concluded that low-dose aspirin in women at high risk of preeclampsia was associated with a lower incidence for preterm preeclampsia. However, there were no differences in the rates of term preeclampsia between study groups. Of note, as a possible study limitation, the prevalence of preterm preeclampsia in the placebo group was one half of that expected for

Table 1. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

*Includes only risk factors that can be obtained from the patient's medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.

†Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or more in a pregnant woman with one or more of these risk factors.

‡A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia. These risk factors are independently associated with moderate risk of preeclampsia, some more consistently than others.

§Moderate-risk factors vary in their association with increased risk of preeclampsia.

Modified from LeFevre, ML. U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2014;161(11):819–26.

a high-risk population based on first-trimester parameters (89).

The use of metformin for the prevention of preeclampsia has been suggested. In a meta-analysis of five randomized controlled trials comparing metformin treatment (n=611) with placebo and control (n=609), no difference in the risk of preeclampsia was found (combined/pooled risk ratio, 0.86; 95% CI, 0.33–2.26; $P=.76$; $I^2=66\%$) (102). Because preeclampsia was a secondary outcome in most studies in this meta-analysis, the effect of metformin needs to be assessed by a study designed to evaluate the reduction in the prevalence of preeclampsia as a primary endpoint. In the meantime, the use of metformin for the prevention of preeclampsia remains investigational, as is the use of sildenafil and statins (103–105). These drugs are not recommended for this indication outside of the context of clinical trials.

▶ ***What is the optimal treatment for women with gestational hypertension or preeclampsia?***

Delivery Versus Expectant Management

At the initial evaluation, a complete blood count with platelet estimate, serum creatinine, LDH, AST, ALT, and testing for proteinuria should be obtained in parallel with a comprehensive clinical maternal and fetal evaluation. In the settings of diagnostic dilemmas, such as in the evaluation of possible preeclampsia superimposed upon chronic hypertension, a uric acid test may be considered. Fetal evaluation should include ultrasonographic evaluation for estimated fetal weight and amount of amniotic fluid, as well as fetal antepartum testing. Subsequent management will depend on the results of the evaluation and gestational age. The decision to deliver must balance the maternal and fetal risks.

Continued observation is appropriate for a woman with a preterm fetus if she has gestational hypertension or preeclampsia without severe features (21). There are no randomized controlled trials in this population, but retrospective data suggest that without severe features, the balance should be in favor of continued monitoring until delivery at 37 0/7 weeks of gestation in the absence of abnormal antepartum testing, preterm labor, preterm prelabor rupture of membranes (also referred to as premature rupture of membranes) or vaginal bleeding, for neonatal benefit (106). The risks associated with expectant management in the late preterm period include the development of severe hypertension, eclampsia, HELLP syndrome, placental abruption, fetal growth restriction and fetal death; however, these risks are small and counterbalanced by the increased rates of admission to the neonatal intensive care unit, neonatal respiratory complications and neonatal death that would be associated with delivery before 37 0/7 weeks of gestation (39). In the HYPITAT trial, women with gestational hypertension and preeclampsia without severe features after 36 weeks of gestation were allocated to expectant management or induction of labor. The latter option was associated with a significant reduction in a composite of adverse maternal outcome including new-onset severe preeclampsia, HELLP syndrome, eclampsia, pulmonary edema, or placental abruption (RR, 0.71; 95% CI, 0.59–0.86) (107). In addition, no differences in rates of neonatal complications or cesarean delivery were reported by the authors (107).

Continued monitoring of women with gestational hypertension or preeclampsia without severe features consists of serial ultrasonography to determine fetal growth, weekly antepartum testing, close monitoring of blood pressure, and weekly laboratory tests for preeclampsia. The frequency of these tests may be modified based on clinical findings and patient symptoms. Following the initial documentation of proteinuria and the establishment of the diagnosis of preeclampsia, additional quantifications of proteinuria are no longer necessary. Although the amount of proteinuria is expected to increase over time with expectant management, this change is not predictive of perinatal outcome and should not influence the management of preeclampsia (108, 109). Women should be advised to immediately report any persistent, concerning, or unusual symptoms. In women with gestational hypertension without severe features, when there is progression to preeclampsia with severe features, this progression usually takes 1–3 weeks after diagnosis, whereas in women with preeclampsia without severe features, the progression to severe preeclampsia could happen within days (72). Gestational hypertension and preeclampsia are known risk factors for fetal death and antenatal testing is indicated. However, limited-to-no data exist regarding when to start testing, the frequency of testing, and which test to use. In women with gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery rather than expectant management upon diagnosis is recommended.

Preeclampsia with severe features can result in acute and long-term complications for the woman and her newborn. Maternal complications include pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome, coagulopathy, renal failure, and retinal injury. These complications are more likely to occur in the presence of preexistent medical disorders. The clinical course of preeclampsia with severe features is characterized by progressive deterioration of maternal and fetal condition. Therefore, delivery is recommended when gestational hypertension or preeclampsia with

Box 4. Conditions Precluding Expectant Management*

Maternal

- Uncontrolled severe-range blood pressures (persistent systolic blood pressure 160 mm Hg or more or diastolic blood pressure 110 mm Hg or more not responsive to antihypertensive medication
- Persistent headaches, refractory to treatment
- Epigastric pain or right upper pain unresponsive to repeat analgesics
- Visual disturbances, motor deficit or altered sensorium
- Stroke
- Myocardial infarction
- HELLP syndrome
- New or worsening renal dysfunction (serum creatinine greater than 1.1 mg/dL or twice baseline)
- Pulmonary edema
- Eclampsia
- Suspected acute placental abruption or vaginal bleeding in the absence of placenta previa

Fetal

- Abnormal fetal testing
- Fetal death
- Fetus without expectation for survival at the time of maternal diagnosis (eg, lethal anomaly, extreme prematurity)
- Persistent reversed end-diastolic flow in the umbilical artery

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.

*In some cases, a course of antenatal steroids can be considered depending on gestational age and maternal severity of illness.

Data from Balogun OA, Sibai BM. Counseling, management, and outcome in women with severe preeclampsia at 23 to 28 weeks' gestation. Clin Obstet Gynecol 2017;60:183–9.

severe features (Box 3) is diagnosed at or beyond 34 0/7 weeks of gestation, after maternal stabilization or with labor or prelabor rupture of membranes. Delivery should not be delayed for the administration of steroids in the late preterm period.

In women with preeclampsia with severe features at less than 34 0/7 weeks of gestation, with stable maternal and fetal condition, expectant management may be considered. Two randomized controlled trials of delivery versus expectant management of preterm preeclampsia with severe features demonstrated that expectant management is associated with higher gestational age at delivery and improved neonatal outcomes (110, 111). These observations were reiterated by a Cochrane systematic review (112). The limited available randomized data are consistent with observational evidence suggesting that expectant management of early preeclampsia with severe features prolongs pregnancy by 1–2 weeks, has low maternal risk, and improves neonatal outcomes (113). In contrast, in a multicenter randomized controlled trial in Latin America, the authors found no neonatal benefit with expectant management of preeclampsia with severe features from 28 weeks to 34 weeks of gestation (114). These different results may reflect the limitations in neonatal intensive care in low-resource settings.

Embarking on a course of expectant management necessitates adherence to principles of shared decision making with discussions of maternal and fetal risks and benefits, appropriate resources (levels of care), and ongoing vigilant surveillance. Close maternal and fetal clinical monitoring is necessary, and laboratory testing (complete blood count including platelets, liver enzymes, and serum creatinine) should be performed serially (115).

The expectant management of preeclampsia with severe features before 34 0/7 weeks of gestation is based on strict selection criteria of those appropriate candidates and is best accomplished in a setting with resources appropriate for maternal and neonatal care (116). Because expectant management is intended to provide neonatal benefit at the expense of maternal risk, expectant management is not advised when neonatal survival is not anticipated. During expectant management, delivery is recommended at any time in the case of deterioration of maternal or fetal condition, which may include some of the criteria in Box 4. Indications for expedited delivery irrespective of gestational age after maternal stabilization are described in Box 4 (115).

If delivery is indicated at less than 34 0/7 weeks of gestation, administration of corticosteroids for fetal lung maturation is recommended (115); however, delaying delivery for optimal corticosteroid exposure may not always be advisable. Maternal or fetal deterioration may preclude completion of the course of steroid treatment. Previously, fetal growth restriction was considered an indication for delivery. In the setting of normal fetal parameters (eg, amniotic fluid volume, Doppler findings, antenatal fetal testing), continuation of expectant management may be reasonable in the absence of other, aforementioned maternal and fetal criteria.

Inpatient Versus Outpatient Management

Ambulatory management at home is an option only for women with gestational hypertension or preeclampsia without severe features and requires frequent fetal and maternal evaluation. Hospitalization is appropriate for women with severe features and for women in whom adherence to frequent monitoring is a concern. Because assessment of blood pressure is essential for this clinical condition, health care providers are encouraged to follow the recommendations from regulatory bodies regarding the proper technique for blood pressure measurement. Having a blood pressure cuff that is too small or too large may result in erroneous evaluations. To reduce inaccurate readings, an appropriate size cuff should be used (length 1.5 times upper arm circumference or a cuff with a bladder that encircles 80% or more of the arm). The blood pressure level should be taken with an appropriately-sized cuff with the patient in an upright position after a 10-minute or longer rest period. For patients in the hospital, the blood pressure can be taken with either the patient sitting up or in the left lateral recumbent position with the patient's arm at the level of the heart (117). The patient should not use tobacco or caffeine for 30 minutes preceding the measurement because these agents can temporarily lead to increased blood pressure (118).

If home management is selected, frequent fetal and maternal evaluation are required. No randomized trials have determined the best tests for fetal or maternal evaluation. Among women with gestational hypertension or preeclampsia without severe features, expectant management up to 37 0/7 weeks of gestation is recommended, during which frequent fetal and maternal evaluation is recommended. Fetal monitoring consists of ultrasonography to determine fetal growth every 3–4 weeks of gestation and amniotic fluid volume assessment at least once weekly. In addition, an antenatal test one-to-two times per week for patients with gestational hypertension or preeclampsia without severe features is recommended.

Maternal evaluation consists primarily of frequent evaluation for either the development of or worsening of preeclampsia. In women with gestational hypertension or preeclampsia without severe features, weekly evaluation of platelet count, serum creatinine, and liver enzyme levels is recommended. In addition, for women with gestational hypertension, once weekly assessment of proteinuria is recommended. However, these tests should be repeated sooner if disease progression is a concern. In addition, women should be asked about symptoms of preeclampsia with severe features (eg, severe headaches, visual changes, epigastric pain, and shortness of breath). Blood pressure measurements and symptom assessment are recommended serially, using a combination of in-clinic and ambulatory approaches, with at least one visit per week in-clinic.

Intrapartum Management

In addition to appropriate management of labor and delivery, the two main goals of management of women with preeclampsia during labor and delivery are 1) prevention of seizures and 2) control of hypertension.

Seizure Prophylaxis

The prevention of eclampsia is empirically based on the concept of timely delivery, as previously discussed, once preeclampsia has been diagnosed. A significant body of evidence attests to the efficacy of magnesium sulfate to prevent seizures in women with preeclampsia with severe features and eclampsia. In the Magpie study, a randomized placebo-controlled trial with 10,110 participants (two thirds originating from developing countries), the seizure rate was reduced overall by more than one half with this treatment. It is interesting to note that the reduction in the rate of eclampsia was not statistically significant in the subset of women enrolled in high-resource countries in the Western world (RR, 0.67; 95% CI, 0.19–2.37) (44). In a subsequent systematic review that included the Magpie study and five other studies, magnesium sulfate compared with placebo more than halved the risk of eclampsia (RR, 0.41; 95% CI, 0.29–0.58), reduced the risk of placental abruption (RR, 0.64; 95% CI, 0.50–0.83), and reduced the risk of maternal mortality albeit nonsignificantly (RR, 0.54; 95% CI, 0.26–1.10). There were no differences in maternal morbidity or perinatal mortality. A quarter of women reported adverse effects with magnesium sulfate, primarily hot flushes, and the rate of cesarean delivery was increased by 5% when magnesium sulfate was used (119).

There is no consensus regarding the prophylactic use of magnesium sulfate for the prevention of seizures in women with gestational hypertension or preeclampsia without severe features. Two small randomized trials (total n=357) allocated women with preeclampsia without severe features to either placebo or magnesium sulfate and reported no cases of eclampsia among women allocated to placebo and no significant differences in the proportion of women that progressed to severe preeclampsia (120, 121). However, given the small sample size, the results of these studies cannot be used for clinical guidance (122, 123).

The rate of seizures in preeclampsia with severe features without magnesium sulfate prophylaxis is four

times higher than in those without severe features (4 in 200 versus 1 in 200). It has been calculated that 129 women need to be treated to prevent one case of eclampsia in asymptomatic cases, whereas in symptomatic cases (severe headache, blurred vision, photophobia, hyperreflexia, epigastric pain), the number needed to treat is 36 (124). The evidence regarding the benefit-to-risk ratio of magnesium sulfate prophylaxis is less supportive of routine use in preeclampsia without severe features (122). The clinical decision of whether to use magnesium sulfate for seizure prophylaxis in patients with preeclampsia without severe features should be determined by the physician or institution, considering patient values or preferences, and the unique risk-benefit trade-off of each strategy. Although the benefit-to-risk ratio for routine prophylaxis is less compelling for patients in high resource settings, it is recommended that magnesium sulfate should be used for the prevention and treatment of seizures in women with gestational hypertension and preeclampsia with severe features or eclampsia (124, 125).

Magnesium sulfate is more effective than phenytoin, diazepam, or nimodipine (a calcium-channel blocker used in clinical neurology to reduce cerebral vasospasm) in reducing eclampsia and should be considered the drug of choice in the prevention of eclampsia in the intrapartum and postpartum periods (119, 126, 127). Benzodiazepines and phenytoin are justified only in the context of antiepileptic treatment or when magnesium sulfate is contraindicated or unavailable (myasthenia gravis, hypocalcemia, moderate-to-severe renal failure, cardiac ischemia, heart block, or myocarditis).

There are still sparse data regarding the ideal dosage of magnesium sulfate. Even the therapeutic range of 4.8–9.6 mg/dL (4–8 mEq/L) quoted in the literature is questionable (128, 129). Although there is a relationship between toxicity and plasma concentration of magnesium, with higher infusion rates increasing the potential for toxicity, the accurate magnesium concentration clinically effective in prevention of eclampsia has not been established. Seizures occur even with magnesium at a therapeutic level, whereas several trials using infusion rates of 1 g/hour, frequently associated with subtherapeutic magnesium levels, were able to significantly reduce the rate of eclampsia or recurrent convulsions (44, 130). Further complicating aspects are that steady magnesium levels are reached more slowly during the antepartum period than postpartum period. Larger volume of distribution and higher BMI also affect the dosage and duration needed to reach adequate circulating levels. It has been reported in patients with a high BMI (especially greater than 35) that the antepartum level of magnesium may remain subtherapeutic for as long as 18 hours after infusion initiation when an intravenous loading dose of 4.5 g followed by 1.8 g/hour is used (131). However, infusion rates in excess of 2 g/hour have been associated with increased perinatal mortality in a systematic review of randomized studies of magnesium sulfate used for tocolysis (132). These data may be considered supportive for the regimen generally preferred in the United States (intravenous [IV] administration of a 4–6 g loading dose over 20–30 minutes, followed by a maintenance dose of 1–2 g/hour). For women requiring cesarean delivery (before onset of labor), the infusion should ideally begin before surgery and continue during surgery, as well as for 24 hours afterwards. For women who deliver vaginally, the infusion should continue for 24 hours after delivery. In case of difficulties with establishing venous access, magnesium sulfate can be administered by intramuscular (IM) injection, 10 g initially as a loading dose (5 g IM in each buttock), followed by 5 g every 4 hours. The medication can be mixed with 1 mL of xylocaine 2% solution because the intramuscular administration is painful. The rate of adverse effects is also higher with the intramuscular administration (44). The adverse effects of magnesium sulfate (respiratory depression and cardiac arrest) come largely from its action as a smooth muscle relaxant. Deep tendon reflexes are lost at a serum magnesium level of 9 mg/dL (7 mEq/L), respiratory depression occurs at 12 mg/dL (10 mEq/L), and cardiac arrest at 30 mg/dL (25 mEq/L). Accordingly, provided deep tendon reflexes are present, more serious toxicity is avoided. (Table 2) Because magnesium sulfate is excreted almost exclusively in the urine, measuring urine output should be part of the clinical monitoring, in addition to monitoring of respiration status and tendon reflexes. If renal function is impaired, serum magnesium levels will increase quickly, which places the patient at risk of significant adverse effects. In patients with mild renal failure (serum creatinine 1.0–1.5 mg/dL) or oliguria (less than 30 mL urine output per hour for more than 4 hours), the loading dose of 4–6 g should be followed by a maintenance dose of only 1 gm/hour. Using a lower loading dose, such as 4 g, may be associated with subtherapeutic levels for at least 4 hours after loading (133). In cases with renal dysfunction, laboratory determination of serum magnesium levels every 4 hours becomes necessary. If the serum level exceeds 9.6 mg/dL (8 mEq/L), the infusion should be stopped and serum magnesium levels should be determined at 2-hour intervals. The infusion can be restarted at a lower rate when the serum level decreases to less than 8.4 mg/dL (7 mEq/L) (133). The serum concentration of magnesium is related to the occurrence of adverse effects and toxicities (see Table 2) (128, 134). Patients at risk of impending respiratory depression may require tracheal intubation and

Table 2. Serum Magnesium Concentration and Toxicities

Serum Magnesium Concentration			
mmol/L	mEq/L	mg/dL	Effect
2–3.5	4–7	5–9	Therapeutic range
>3.5	>7	>9	Loss of patellar reflexes
>5	>10	>12	Respiratory paralysis
>12.5	>25	>30	Cardiac arrest

Data from Duley L. Magnesium sulphate regimens for women with eclampsia: messages from the Collaborative Eclampsia Trial. Br J Obstet Gynaecol 1996;103:103–5 and Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and preeclampsia: pharmacokinetic principles. Clin Pharmacokinet 2000;38:305–14.

emergency correction with calcium gluconate 10% solution, 10 mL IV over 3 minutes, along with furosemide intravenously to accelerate the rate of urinary excretion.

Antihypertensive Approach: Drugs and Thresholds for Treatment

The objectives of treating severe hypertension are to prevent congestive heart failure, myocardial ischemia, renal injury or failure, and ischemic or hemorrhagic stroke. Antihypertensive treatment should be initiated expeditiously for acute-onset severe hypertension (systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more, or both) that is confirmed as persistent (15 minutes or more). The available literature suggests that antihypertensive agents should be administered within 30–60 minutes. However, it is recommended to administer antihypertensive therapy as soon as reasonably possible after the criteria for acute-onset severe hypertension are met. Intravenous hydralazine or labetalol and oral nifedipine are the three agents most commonly used for this purpose (see Table 3). A recent Cochrane systematic review that involved 3,573 women found no significant differences regarding either efficacy or safety between hydralazine and labetalol or between hydralazine and calcium channel blockers (135). Thus, any of these agents can be used to treat acute severe hypertension in pregnancy (135, 136). Although parenteral antihypertensive therapy may be needed initially for acute control of blood pressure, oral medications can be used as expectant management is continued. Oral labetalol and calcium channel blockers have been commonly used. One approach is to begin an initial regimen of labetalol at 200 mg orally every 12 hours and increase the dose up to 800 mg orally every 8–12 hours as needed (maximum total 2,400 mg/d). If the maximum dose is inadequate to achieve the desired blood pressure goal, or the dosage is limited by adverse effect, then short-acting oral nifedipine can be added gradually.

Table 3. Antihypertensive Agents Used for Urgent Blood Pressure Control in Pregnancy

Drug	Dose	Comments	Onset of Action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV	Tachycardia is less common and fewer adverse effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.	1–2 minutes
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 minutes to a maximum cumulative dosage of 20 mg; or constant infusion of 0.5–10 mg/hr	Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings; may be more common than other agents.	10–20 minutes
Nifedipine (immediate release)	10–20 mg orally, repeat in 20 minutes if needed; then 10–20 mg every 2–6 hours; maximum daily dose is 180 mg	May observe reflex tachycardia and headaches	5–10 minutes

Abbreviations: IM, intramuscularly; IV, intravenously.

Monitoring for Disease Progression

Because the clinical course of gestational hypertension or preeclampsia without severe features can evolve during labor, all women with gestational hypertension or preeclampsia without severe features who are in labor must be monitored for early detection of progression to severe disease. This should include monitoring of blood pressure and symptoms during labor and delivery as well as immediately after delivery. Magnesium sulfate therapy should be initiated if there is progression to preeclampsia with severe features. The evidence regarding the benefit-to-risk ratio of magnesium sulfate prophylaxis is less supportive of routine use in preeclampsia without severe features (122). The clinical decision of whether to use magnesium sulfate for seizure prophylaxis in patients with preeclampsia without severe features should be determined by the physician or institution, considering patient values or preferences and the unique risk-benefit trade-off of each strategy.

Mode of Delivery

The mode of delivery in women with gestational hypertension or preeclampsia (with or without severe features) should be determined by routine obstetric considerations. Vaginal delivery often can be accomplished, but with labor induction in preeclampsia with severe features this is less likely with decreasing gestational age at diagnosis. The likelihood of cesarean delivery at less than 28 weeks of gestation could be as high as 97%, and at 28–32 weeks of gestation as high as 65% (137–139). For gestational hypertension or preeclampsia without severe features, vaginal delivery is preferred (137–139). Retrospective studies comparing induction of labor with cesarean delivery in women with preeclampsia with severe features remote from term concluded that induction of labor was reasonable and was not harmful to low-birth-weight infants (140, 141). The decision to perform cesarean delivery should be individualized, based on anticipated probability of vaginal delivery and on the nature and progression of preeclampsia disease state.

Anesthesia Considerations

With improved techniques over the past decades, regional anesthesia has become the preferred technique for women with preeclampsia with severe features and eclampsia for labor and delivery. A secondary analysis of women with preeclampsia with severe features in a randomized trial of low-dose aspirin reported that epidural anesthesia was not associated with an increased rate of cesarean delivery, pulmonary edema, or renal failure (142). Also, in a prospective study, the incidence and severity of hypotension did not appear to be increased with spinal anesthesia for cesarean delivery in women with preeclampsia with severe features (n = 65) compared with women without preeclampsia (143).

When the use of spinal or epidural anesthesia in women with preeclampsia with severe features was compared in a randomized trial (144), the incidence of hypotension was higher in the spinal group (51% versus 23%) but was easily treated and of short duration (less than 1 minute). General anesthesia carries more risk to pregnant women than regional anesthesia does because of the risk of aspiration, failed intubation because of pharyngolaryngeal edema, and stroke secondary to increased systemic and intracranial pressures during intubation and extubation (145, 146). However, neuraxial anesthesia and analgesia are contraindicated in the presence of a coagulopathy because of the potential for hemorrhagic complications (147). Thrombocytopenia also increases the risk of epidural hematoma. There is no consensus in regard to the safe lower-limit for platelet count and neuraxial anesthesia. The literature offers only limited and retrospective data to address this issue, but a recent retrospective cohort study of 84,471 obstetric patients from 19 institutions combined with a systematic review of the medical literature support the assertion that the risk of epidural hematoma from neuraxial anesthetics in a parturient patient with a platelet count of more than 70×10^9/L is exceptionally low (less than 0.2%) (148). Extrapolating this expanded data to previous recommendations (149) would suggest that epidural or spinal anesthesia is considered acceptable, and the risk of epidural hematoma is exceptionally low, in patients with platelet counts of 70×10^9/L or more provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not on any antiplatelet or anticoagulant therapy (148, 149).

Magnesium sulfate has significant anesthetic implications because it prolongs the duration of nondepolarizing muscle relaxants. However, women with preeclampsia who require cesarean delivery should continue magnesium sulfate infusion during the delivery. This recommendation is based on the observation that magnesium sulfate half-life is 5 hours and that discontinuation of the infusion of magnesium sulfate before cesarean delivery would only minimally reduce magnesium concentration at the time of delivery while possibly increasing the risk of seizure (150). Women with preeclampsia with severe features undergoing cesarean delivery remain at risk of developing eclampsia. The induction of general anesthesia and the stress of delivery may even reduce the seizure threshold and increase the likelihood of eclampsia in the immediate postpartum

period if the infusion of magnesium sulfate is stopped during delivery.

Postpartum Hypertension and Postpartum Headache

Postpartum hypertension and preeclampsia are either persistent or exacerbated hypertension in women with previous hypertensive disorders of pregnancy or a new-onset condition. It is important to increase the awareness among health care providers and to empower patients to seek medical advice if symptoms that precede eclampsia, hypertensive encephalopathy, pulmonary edema, or stroke are noted in the postpartum period. Most women who present with eclampsia and stroke in the postpartum period have these symptoms for hours or days before presentation (151–154). Some common medications and substances used in the postpartum period may potentially aggravate hypertension through three major mechanisms: volume retention, sympathomimetic activation, and direct vasoconstriction. Of particular interest are nonsteroidal antiinflammatory drugs (NSAIDs), which are frequently prescribed as postpartum analgesics. These medications decrease prostaglandins leading to a lack of vasodilation and increased sodium retention. Nonsteroidal anti-inflammatory medications should continue to be used preferentially over opioid analgesics; however, women with chronic hypertension may theoretically require intensification of blood pressure monitoring and regimen adjustments when on these medications. Overall, data support the safe use of NSAIDs in postpartum patients with blood pressure issues. In a randomized trial comparing use of ibuprofen to acetaminophen in postpartum patients with preeclampsia with severe features, ibuprofen did not lengthen the duration of severe-range blood pressures (155). In a cohort of 399 patients with preeclampsia with severe features, there was no association of NSAID use with postpartum blood pressure elevations (156). Further, another cohort study of postpartum patients on magnesium for seizure prophylaxis for preeclampsia did not show differences in blood pressure, antihypertensive requirements, or other adverse events for patients managed with NSAIDs in the postpartum period (157).

▶ ***What is the optimal treatment for eclampsia?***

The initial steps in the management of a woman with eclampsia are basic supportive measures such as calling for help, prevention of maternal injury, placement in lateral decubitus position, prevention of aspiration, administration of oxygen, and monitoring vital signs including oxygen saturation. Only subsequently is attention directed to the administration of magnesium sulfate. Most eclamptic seizures are self-limited. Magnesium sulfate is not necessary to arrest the seizure but to prevent recurrent convulsions.

During eclamptic seizures, there are usually prolonged fetal heart rate decelerations, even fetal bradycardia, and sometimes an increase in uterine contractility and baseline tone. After a seizure, because of maternal hypoxia and hypercarbia, the fetal heart rate tracing may show recurrent decelerations, tachycardia, and reduced variability. However, only after maternal hemodynamic stabilization should one proceed with delivery. Furthermore, maternal resuscitation is usually followed by normalization of the fetal tracing.

Cochrane reviews, including data originating from developing countries, indicate a significant reduction in recurrent seizures and eclampsia-related maternal mortality with the use of magnesium sulfate. Magnesium sulfate administered intramuscularly or intravenously is superior to phenytoin, diazepam, or lytic cocktail (usually chlorpromazine, promethazine, and pethidine) and also is associated with less maternal and neonatal morbidity (126, 158, 159). Thus, these data support the use of magnesium sulfate as the drug of choice to prevent recurrent seizures in women with eclampsia. In the rare cases of an extremely agitated patient, IV clonazepam 1 mg, diazepam 10 mg, or midazolam may be used for sedation to facilitate the placement of the IV lines and Foley catheter, and the collection of blood specimens. These drugs should be used cautiously and only if absolutely necessary because they inhibit laryngeal reflexes, increasing the risk of aspiration and also may depress the central respiratory centers leading to apnea.

Women with eclampsia should be delivered in a timely fashion. However, eclampsia by itself is not an indication for cesarean delivery. Once the patient is stabilized, the method of delivery should depend, in part, on factors such as gestational age, fetal presentation, and the findings of the cervical examination. A high rate of failure may be anticipated with induction or augmentation in pregnancies less than 30 weeks of gestation if the patient is not in active labor and the Bishop score is unfavorable. In these cases, it may be preferable to opt for cesarean delivery without further delay. However, patients that adequately progress in labor could be allowed to continue labor even after an eclamptic seizure.

It has been proposed that when convulsions recur, a further 2–4 grams of magnesium sulfate could be administered IV over 5 minutes (130). In cases refractory to magnesium sulfate (still seizing at 20 minutes after the bolus or more than two recurrences), a health care provider can use sodium amobarbital (250 mg IV in 3 minutes), thiopental, or phenytoin (1,250 mg IV at a rate of 50 mg/minute). Endotracheal intubation and assisted ventilation in the intensive care unit are appropriate in these

circumstances. Head imaging should also be considered because most of cases refractory to magnesium sulfate therapy may prove to have abnormal findings on brain imaging (160).

► ***What is the management of acute complications for preeclampsia with HELLP?***

The clinical course of HELLP syndrome often is characterized by progressive and sometimes sudden deterioration in maternal and fetal condition. Considering the serious nature of this entity, with increased rates of maternal morbidity and mortality, many authors have concluded that women with HELLP syndrome should be delivered regardless of their gestational age. Because the management of patients with HELLP syndrome requires the availability of neonatal and obstetric intensive care units and personnel with special expertise, patients with HELLP syndrome who are remote from term should receive care at a tertiary care center (116, 161).

It has been hypothesized that the antiinflammatory and immunosuppressive effects of corticosteroids may modify some of the proinflammatory features of preeclampsia with severe features and favorably affect the clinical course. Several randomized controlled trials of high-dose corticosteroid treatment for antepartum or postpartum stabilization of HELLP syndrome have been conducted. The use of corticoids in the management of HELLP syndrome compared with placebo or no treatment was reviewed in a Cochrane Database Systematic Review, which included 11 randomized trials (550 women) (162). There was no difference in the risk of maternal death, severe maternal morbidity, or perinatal or infant death. The only effect of treatment on individual outcomes was improved platelet count (standardized mean difference [SMD] 0.67; 95% CI, 0.24−1.10). The authors concluded that the evidence is insufficient to support the use of corticosteroids for attenuation of the disease process in HELLP syndrome (162).

Very close monitoring is required in HELLP syndrome until delivery and in the postpartum period, with laboratory testing at least at 12-hour intervals. Aspartate aminotransferase levels more than 2,000 IU/L or LDH more than 3,000 IU/L suggest an increased mortality risk. In the natural history of HELLP syndrome there is an inverse relationship between the trends in platelet values and liver enzymes level. During the aggravation slope in the disease evolution, platelet count usually decreases at an average rate of approximately 40% per day, whereas the liver enzymes values tend to increase. The lowest observed platelet count occurs at a mean of 23 hours after delivery. The disease may achieve peak intensity during the first 2 days after delivery, including a downward trend in hematocrit. If the platelet count continues to drop and liver enzymes to increase after 4 days postpartum, the validity of the initial diagnosis of HELLP syndrome should be reassessed. With supportive care alone, 90% of patients with HELLP syndrome will have platelet count more than $100{,}000 \times 10^9$/L and reversed trend (decrease) in liver enzymes values within 7 days after delivery. Not infrequently, a rebound phenomenon in platelet count follows reaching values of 400,000–$871{,}000 \times 10^9$/L (163). Women with HELLP syndrome are also at increased risk of pulmonary edema, acute respiratory distress syndrome and renal failure (164).

► ***What are the risks of subsequent cardiovascular disease among women with hypertensive disorders of pregnancy and are there prevention strategies that modify this risk?***

Women with a history of preeclampsia continue to have an elevated risk of cardiovascular disease in subsequent years. Several systematic reviews and meta-analyses have linked preeclampsia with an increased risk of cardiovascular disease (hypertension, myocardial infarction, congestive heart failure), cerebrovascular events (stroke), peripheral arterial disease, and cardiovascular mortality later in life, with an estimated doubling of odds compared with women unaffected by preeclampsia (165–167). Meta-regression analysis reveals a graded relationship between the severity of preeclampsia or eclampsia and the risk of cardiac disease (mild RR, 2.00; 95% CI, 1.83–2.19; moderate RR, 2.99; 95% CI, 2.51–3.58; severe RR, 5.36; 95% CI, 3.96–7.27, $P<.0001$) (168). The risk is even higher (4−8 times the risk for women with normal pregnancies) in women with recurrent preeclampsia (169) and women with early-onset preeclampsia or preeclampsia requiring preterm delivery (170). More recent evidence suggests that all hypertensive conditions in pregnancy are associated with later cardiovascular disease with an approximately doubling of the rate of incident cardiovascular disease and a five times higher rate of hypertension (171).

The mechanisms that account for an increased risk of cardiovascular disease in women with a history of preeclampsia are not yet well understood, but endothelial dysfunction, which has been linked to atherosclerosis, persists in women with a history of preeclampsia many years after an affected pregnancy (172). A study of cardiovascular risk factors present before and after pregnancy suggested that nearly one half of the elevated risk of future hypertension after preeclampsia can be explained by prepregnancy risk factors (173). Yet, it may be possible that the stress incurred to the cardiovascular system during gestation triggers a biological response that would otherwise not have occurred despite any genetic predisposition or risk factors (171). It remains

unclear if cardiovascular changes associated with preeclampsia during pregnancy causally lead to cardiovascular remodeling increasing the risk of cardiovascular disease later in life or if preeclampsia is a manifestation of an underlying increased risk of cardiovascular disease (for example, a common genetic–environmental risk factor(s) interaction [such as hyperlipidemia, obesity, diabetes mellitus, or renal disease] that predisposes women to develop preeclampsia during pregnancy and cardiovascular diseases later in life) (174). Preventive strategies to be considered by patients and health care providers may warrant closer long-term follow-up and lifestyle modifications to better manage risk factors for cardiovascular disease (eg, achieving healthful weight, exercise, diet, smoking cessation), for which women and their primary care providers may maintain ongoing care and vigilance.

Clinical Considerations and Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Women with any of the high-risk factors for preeclampsia (previous pregnancy with preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, and chronic hypertension) and those with more than one of the moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index of more than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors) should receive low-dose (81 mg/day) aspirin for preeclampsia prophylaxis, initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continuing until delivery.
- In women with gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery rather than expectant management upon diagnosis is recommended.
- Magnesium sulfate should be used for the prevention and treatment of seizures in women with gestational hypertension and preeclampsia with severe features or eclampsia.
- Nonsteroidal anti-inflammatory medications should continue to be used preferentially over opioid analgesics. Postpartum patients on magnesium for seizure prophylaxis for preeclampsia did not show differences in blood pressure, antihypertensive requirements, or other adverse events for patients managed with NSAIDs in the postpartum period.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Delivery is recommended when gestational hypertension or preeclampsia with severe features is diagnosed at or beyond 34 0/7 weeks of gestation, after maternal stabilization or with labor or prelabor rupture of membranes. Delivery should not be delayed for the administration of steroids in the late preterm period.
- The expectant management of preeclampsia with severe features before 34 0/7 weeks of gestation is based on strict selection criteria of those appropriate candidates and is best accomplished in a setting with resources appropriate for maternal and neonatal care. Because expectant management is intended to provide neonatal benefit at the expense of maternal risk, expectant management is not advised when neonatal survival is not anticipated. During expectant management, delivery is recommended at any time in the case of deterioration of maternal or fetal condition.
- Antihypertensive treatment should be initiated expeditiously for acute-onset severe hypertension (systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more, or both) that is confirmed as persistent (15 minutes or more). The available literature suggests that antihypertensive agents should be administered within 30–60 minutes. However, it is recommended to administer antihypertensive therapy as soon as reasonably possible after the criteria for acute-onset severe hypertension are met.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- It is recommended that women with gestational hypertension in the absence of proteinuria are diagnosed with preeclampsia if they present with any of the following severe features: thrombocytopenia (platelet count less than 100,000 x 10^9/L); impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit of normal concentration); severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); pulmonary edema, or new-onset headache

unresponsive to acetaminophen and not accounted for by alternative diagnoses, or visual disturbances.

- ▶ Women with gestational hypertension who present with severe-range blood pressures should be managed with the same approach as for women with severe preeclampsia.
- ▶ Among women with gestational hypertension or preeclampsia without severe features, expectant management up to 37 0/7 weeks of gestation is recommended, during which frequent fetal and maternal evaluation is recommended. Fetal monitoring consists of ultrasonography to determine fetal growth every 3–4 weeks of gestation, and amniotic fluid volume assessment at least once weekly. In addition, an antenatal test one-to-two times per week for patients with gestational hypertension or preeclampsia without severe features is recommended.
- ▶ Epidural or spinal anesthesia is considered acceptable, and the risk of epidural hematoma is exceptionally low, in patients with platelet counts 70 x 10^9/L or more provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not on any antiplatelet or anticoagulant therapy.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985–June 2018. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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