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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 inci- dence 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 occasion- ally problematic in clinical practice. Right upper quad- rant 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 preeclamp- sia, but at gestational ages earlier than 20 weeks, alter- native diagnoses should to be considered, including but

Box Box 1. Risk Factors for Preeclampsia

2. Diagnostic Criteria for

Preeclampsia Nulliparity Multifetal gestations

Blood pressure

Preeclampsia in a previous pregnancy

c Systolic blood pressure of 140 mm Hg or more or Chronic hypertension

diastolic blood pressure of 90 mm Hg or more on Pregestational diabetes Gestational diabetes

two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure Thrombophilia

c Systolic blood pressure of 160 mm Hg or more or Systemic lupus erythematosus Prepregnancy body mass index greater than 30 Antiphospholipid antibody syndrome

diastolic blood pressure of 110 mm Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy). Maternal age 35 years or older and Kidney disease

Proteinuria Assisted reproductive technology Obstructive sleep apnea

c 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or not limited to thrombotic thrombocytopenic purpura, hemolytic–uremic syndrome, molar pregnancy, renal

c Protein/creatinine ratio of 0.3 mg/dL or more or c Dipstick reading of 2+ (used only if other quantitative methods not available) disease or autoimmune disease.

Although hypertension and proteinuria are consid-

Or in the absence of proteinuria, new-onset hyper- tension with the new onset of any of the ered to be the classical criteria to diagnose preeclampsia, following: other criteria are also important. In this context, it is

c Thrombocytopenia: Platelet count less than recommended that women with gestational hypertension 100,000 3 10^9/L in the absence of proteinuria are diagnosed with pre- eclampsia if they present with any of the following severe features: thrombocytopenia (platelet count less than 100,000 3 10^9/L); impaired liver function as indi-

c Renal insufficiency: Serum creatinine concen- trations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease c Impaired liver function: Elevated blood concen- cated by abnormally elevated blood concentrations of trations of liver transaminases to twice normal liver enzymes (to twice the upper limit of normal con- centration); severe persistent right upper quadrant or epi- gastric pain and not accounted for by alternative diagnoses; renal insufficiency (serum creatinine concen-

concentration c Pulmonary edema

B New-onset headache unresponsive to medi- cation and not accounted for by alternative diagnoses or visual symptoms tration 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 unre- sponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances (Box 2). *Ges-*

Proteinuria during pregnancy is defined as 300 mg/dL *tational hypertension* is defined as a systolic blood pres- of protein or more in a 24-hour urine collection (21, 23) sure of 140 mm Hg or more or a diastolic blood pressure or a protein-to-creatinine ratio of 0.30 or more (24). of 90 mm Hg or more, or both, on two occasions at least When quantitative methods are not available or rapid 4 hours apart after 20 weeks of gestation in a woman decisions are required, a urine protein dipstick reading with a previously normal blood pressure (21). Women can be substituted. However, dipstick urinalysis has high with gestational hypertension with severe range blood false-positive and false-negative test results. A test result pressures (a systolic blood pressure of 160 mm Hg or of 1+ proteinuria is false-positive in 71% of cases com- higher, or diastolic blood pressure of 110 mm Hg or pared with the 300 mg cutoff on 24-hour urine collection, higher) should be diagnosed with preeclampsia with

and even 3+ proteinuria test results may be false-positive severe features. These severe ranges of blood pressure
in 7% of cases. Using the same 24-hour urine collection or any of the severe features listed in Box 3 increase
standard, the false-negative rate for dipstick urinalysis is the risk of morbidity and mortality (22).
9% (25). If urinalysis is the only available means of

comes (17) and may not represent a separate entity from

Box 3. Severe Features

preeclampsia (28). Up to 50% of women with gestational hypertension will eventually develop proteinuria or other
- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more

end-organ dysfunction consistent with the diagnosis of preeclampsia, and this progression is more likely when on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than

100,000 3 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

the hypertension is diagnosed before 32 weeks of gesta- tion (29, 30). Although investigators have reported a higher perinatal mortality rate in women with nonpro- teinuric hypertension compared with proteinuric pre- eclampsia (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, epigastric pain unresponsive to medication and not accounted for by alternative diagnoses

women without proteinuria had a higher frequency of thrombocytopenia or liver dysfunction (17). Women with
- Renal insufficiency (serum creatinine concentra- tion 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

gestational hypertension who present with severe-range blood pressures should be managed with the same approach as for women with severe preeclampsia. Ges- tational hypertension and preeclampsia may also be un- distinguishable in terms of long-term cardiovascular risks, including chronic hypertension (32).
- Visual disturbances

Hemolysis, Elevated Liver Enzymes and Low Platelet Count Syndrome assessing proteinuria then overall accuracy is better using

The clinical presentation of hemolysis, elevated liver 2+ as the discriminant value (25, 26).
enzymes, and low platelet count (HELLP) syndrome is one of the more severe forms of preeclampsia because it has

Gestational Hypertension

been associated with increased rates of maternal morbidity

Gestational hypertension is defined as a systolic blood pressure 140 mm Hg or more or a diastolic blood pres- sure 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 (mi- nutes) than 4 hours to facilitate timely antihypertensive therapy (27). Gestational hypertension occurs when hypertension without proteinuria or severe features de- velops after 20 weeks of gestation and blood pressure levels return to normal in the postpartum period (21). It

and mortality (33). Although different diagnostic bench- marks have been proposed (34), many clinicians use the following criteria (35) to make the diagnosis: lactate dehy- drogenase (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).

appears that this diagnosis is more of an exercise of nomenclature than a pragmatic one because the manage-

Eclampsia

ment of gestational hypertension and that of preeclamp-

Eclampsia is the convulsive manifestation of the hyper- sia without severe features is similar in many aspects, and tensive disorders of pregnancy and is among the more both require enhanced surveillance. Outcomes in women severe manifestations of the disease. Eclampsia is with gestational hypertension usually are good, but the defined by new-onset tonic-clonic, focal, or multifocal notion that gestational hypertension is intrinsically less seizures in the absence of other causative conditions such concerning than preeclampsia is incorrect. Gestational as epilepsy, cerebral arterial ischemia and infarction, hypertension is associated with adverse pregnancy out- intracranial hemorrhage, or drug use. Some of these

a alternative diagnoses may be more likely in cases in

week) also may accompany preeclampsia with severe which new-onset seizures occur after 48–72 hours post- features and eclampsia (47). Posterior reversible enceph- partum (38) or when seizures occur during administration alopathy syndrome (PRES) is a constellation of a range of magnesium sulfate.

of clinical neurologic signs and symptoms such as vision Eclampsia is a significant cause of maternal death, loss or deficit, seizure, headache, and altered sensorium particularly in low-resource settings. Seizures may lead or confusion (48). Although suspicion for PRES is to severe maternal hypoxia, trauma, and aspiration increased in the setting of these clinical features, the pneumonia. Although residual neurologic damage is rare, diagnosis of PRES is made by the presence of vasogenic some women may have short-term and long-term con- edema and hyperintensities in the posterior aspects of the sequences such as impaired memory and cognitive brain on magnetic resonance imaging. Women are par- function, especially after recurrent seizures or uncor- ticularly at risk of PRES in the settings of eclampsia and rected severe hypertension leading to cytotoxic edema or preeclampsia with headache, altered consciousness, or infarction (39). Permanent white matter loss has been visual abnormalities (49). Another condition that may documented on magnetic resonance imaging after be confused with eclampsia or preeclampsia is reversible eclampsia in up to one fourth of women, however, this cerebral vasoconstriction syndrome (50). Reversible does not translate into significant neurologic deficits cerebral vasoconstriction syndrome is characterized by (39).reversible multifocal narrowing of the arteries of the

Eclampsia often (78–83% of cases) is preceded by

brain with signs and symptoms that typically include premonitory signs of cerebral irritation such as severe thunderclap headache and, less commonly, focal neuro- and persistent occipital or frontal headaches, blurred logic deficits related to brain edema, stroke, or seizure. vision, photophobia, and altered mental status. However, Treatment of women with PRES and reversible cerebral eclampsia can occur in the absence of warning signs or vasoconstriction syndrome may include medical control symptoms (40, 41). Eclampsia can occur before, during, of hypertension, antiepileptic medication, and long-term or after labor. Of note, a significant proportion of women neurologic follow-up. (20–38%) do not demonstrate the classic signs of pre- eclampsia (hypertension or proteinuria) before the sei- zure 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 symp- toms (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

Pathophysiology Several mechanisms of disease have been proposed in preeclampsia (1, 51, 52), including the following: chronic uteroplacental ischemia (53), immune maladap- tation (53), very low-density lipoprotein toxicity (53), genetic imprinting (53), increased trophoblast apoptosis or necrosis (54, 55), and an exaggerated maternal inflam- matory response to deported trophoblasts (56, 57). More recent observations suggest a possible role for imbalan- ces of angiogenic factors in the pathogenesis of pre- eclampsia (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 evi- dence (61, 62) suggesting that uteroplacental ischemia leads to increased circulating concentrations of antiangio- genic factors and angiogenic imbalances (63).

documentation of either hypertension or proteinuria in the hospital setting (46). Thus, the notion that preeclamp-

Vascular Changes sia has a natural linear progression from preeclampsia

In addition to hypertension, women with preeclampsia or without severe features to preeclampsia with severe fea-
eclampsia typically lack the hypervolemia associated tures and eventually to eclamptic convulsions is
with normal pregnancy; thus, hemoconcentration is inaccurate.
a frequent finding (64). In addition, the interaction of Nervous system manifestations frequently encoun-
various vasoactive agents, such as prostacyclin (vasodi- tered in preeclampsia are headache, blurred vision,

lator), thromboxane A_2 (potent vasoconstrictor), nitric scotomata, and hyperreflexia. Although uncommon,
oxide (potent vasodilator), and endothelins (potent vaso- temporary blindness (lasting a few hours to as long as
constrictors) results in another significant change

necrotic described in preeclampsia: intense vasospasm. Attempts
tissues, or both) and hemolysis (LDH from red to correct the contraction of the intravascular space in
blood cell destruction). Increase in bilirubin secondary to preeclampsia with vigorous fluid therapy are likely to
significant hemolysis may develop only in the late stages be ineffective and could be dangerous because of the
of the disease. Similarly, alterations in hepatic synthetic frequent capillary leak and decreased colloid oncotic
function, as reflected by abnormalities of prothrombin pressure often associated with preeclampsia. Aggressive
time, partial prothrombin time, and fibrinogen, usually fluid therapy may result in elevation of the pulmonary
develop in advanced preeclampsia. Evaluation of these capillary wedge pressure and increased risk of pulmonary
coagulation parameters is probably only useful when the edema. A study using invasive hemodynamic monitoring
platelet count is below 150,000 x 10^9/L, there is signif- in women with preeclampsia found that before intrave-
icant liver dysfunction, or there is suspected placental nous fluid therapy, women with preeclampsia had hyper-
abruption (70). dynamic ventricular function with low pulmonary capillary wedge pressure (65). However, after
aggressive

Renal Changes fluid therapy, the pulmonary capillary wedge pressure increased significantly above normal levels (65) with increased risk of pulmonary edema.

The histopathologic renal changes classically described in preeclampsia as glomerular endotheliosis consist of

swollen, vacuolated endothelial cells with fibrils, swollen

Hematologic Changes

mesangial cells, subendothelial deposits of protein re- absorbed from the glomerular filtrate, and tubular casts

Various hematologic changes also may occur in women (71, 72). Proteinuria in preeclampsia is nonselective, as with preeclampsia, especially in preeclampsia with a result of increased tubular permeability to most large- severe features. Thrombocytopenia and hemolysis may molecular-weight proteins (albumin, globulin, transfer- occur and may reach severe levels as part of HELLP rin, and hemoglobin). Urinary calcium decreases because syndrome. Thrombocytopenia results from increased of an increased tubular reabsorption of calcium. platelet activation, aggregation, and consumption (66) In women with preeclampsia, contraction of the and is a marker of disease severity. A platelet count less intravascular space secondary to vasospasm leads to than 150,000 x 10^9/L is found in approximately 20% of worsening renal sodium and water retention (73). The patients with preeclampsia, varying from 7% in cases normal increase in renal blood flow and glomerular fil- without severe manifestations to 50% in cases with tration rate and the expected decrease in serum creatinine severe manifestations (67). However, reduced platelet may not occur in women with preeclampsia, especially if counts are not found in all cases of preeclampsia or the disease is severe. Preeclampsia with severe features eclampsia (68). Interpretation of hematocrit levels in pre- may include acute renal deterioration as part of the clin- eclampsia should take into consideration that hemolysis ical spectrum. Oliguria in severe preeclampsia is a conse- and hemoconcentration may occur (69). In some cases, quence of intrarenal vasospasm with an approximate the hematocrit may not appear decreased despite hemo- 25% reduction in glomerular filtration rate. In these pa- lysis because of baseline hemoconcentration. Lactate tients, transient oliguria (less than 100 mL over 4 hours) dehydrogenase is present in erythrocytes in high concen- is a common observation in labor or the first 24 hours of tration. High serum concentrations of LDH (more than the postpartum period. Plasma concentrations of uric acid 600 IU/L) may be a sign of hemolysis (34, 35).

normally increase in late pregnancy, and this is thought to be due to increased rates of fetal or placental produc-

Hepatic Changes

tion, or both, decreased binding to albumin, and

Hepatic function may be significantly altered in women with preeclampsia with severe features. Alanine amino- transferase and AST may be elevated. Aspartate amino- transferase is the dominant transaminase released into the peripheral circulation in liver dysfunction due to pre- eclampsia and is related to periportal necrosis. The fact a decrease in uric acid clearance. The serum uric acid concentration increases to a greater extent in preeclamp- sia (74). The most commonly accepted explanation for hyperuricemia in preeclampsia, besides increased pro- duction, is the increased reabsorption and decreased excretion of uric acid in the proximal renal tubules.

that AST is increased to a greater extent than ALT, at least initially, may help in distinguishing preeclampsia

Fetal Consequences

from other potential causes of parenchymal liver disease

As a result of impaired uteroplacental blood flow in which ALT usually is higher than AST. Increased secondary to failure of physiologic transformation of serum levels of LDH in preeclampsia are caused by the spiral arteries or placental vascular insults, or both, hepatic dysfunction (LDH derived from ischemic, or manifestations of preeclampsia also may be seen in the

no fetal–placental unit (63). Abnormalities in the placental

single test reliably predicts preeclampsia and further bed and subsequent failure of physiologic transformation prospective investigation is required to demonstrate of the spiral arteries in the first or early second trimester clinical utility. In the first trimester of pregnancy, it (75, 76) limit the blood flow to the uteroplacental unit.

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 case2control study applied to a large cohort of almost 7,800 patients in which PlGF was measured only in the case2control 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.

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

< 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 preeclampsia and an even lower value for late-onset reduction in preeclampsia was noted when low-dose preeclampsia (88). Extensive work has identified some aspirin was started after 16 weeks of gestation (relative angiogenic factors (soluble fms-like tyrosine kinase- risk [RR], 0.81; 95% CI, 0.66–0.99) but a more signifi- [sFlt-1], placental growth factor [PlGF], and soluble cant reduction in severe preeclampsia (RR, 0.47; 95% CI, endoglin) in the second trimester as likely tools for 0.26–0.83) and fetal growth restriction (RR, 0.56; 95% the prediction of early-onset preeclampsia. However, CI, 0.44–0.70) was demonstrated when low-dose aspirin

In was started before 16 weeks of gestation (100). In con- a recent multicenter, double blind, placebo- trast, in pooled individual data from 31 high-quality ran- controlled trial, pregnant women at increased risk of domized trials, the beneficial effects of low-dose aspirin preterm preeclampsia (less than 37 weeks of gestation) were consistent, whether treatment was started before or were randomly assigned to receive aspirin, at a higher after 16 weeks of gestation (101). Women with any of the dose (150 mg/day), or placebo from 11 weeks to 14 high-risk factors for preeclampsia (previous pregnancy weeks of gestation until 36 weeks of gestation (89). with preeclampsia, multifetal gestation, renal disease, Preterm preeclampsia occurred in 1.6% of the partic- autoimmune disease, type 1 or type 2 diabetes mellitus, ipants in the aspirin group, as compared with 4.3% in and chronic hypertension) and those with more than one the placebo group (odds ratio, 0.38; 95% CI, of the moderate-risk factors (first pregnancy, maternal 0.2020.74; *P*5.004). The authors also reported that age of 35 years or older, a body mass index [BMI; cal- there were no significant differences in the incidence culated as weight in kilograms divided by height in me- of neonatal adverse outcomes between groups. The ters squared] of more than 30, family history of authors concluded that low-dose aspirin in women at preeclampsia, sociodemographic characteristics, and per- high risk of preeclampsia was associated with a lower sonal history factors) should receive low-dose (81 mg/ incidence for preterm preeclampsia. However, there day) aspirin for preeclampsia prophylaxis initiated were no differences in the rates of term preeclampsia between 12 weeks and 28 weeks of gestation (optimally between study groups. Of note, as a possible study before 16 weeks of gestation) and continuing until deliv- limitation, the prevalence of preterm preeclampsia in ery (Table 1). 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. [z]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.

delivery a high-risk population based on first-trimester param-
before 37 0/7 weeks of gestation (39). In the eters (89).
HYPITAT trial, women with gestational hypertension The use of metformin for the prevention of pre-
and preeclampsia without severe features after 36 weeks eclampsia has been suggested. In a meta-analysis of five
of gestation were allocated to expectant management or randomized controlled trials comparing metformin treat-
induction of labor. The latter option was associated with ment (n5611) with placebo and control (n5609), no
a significant reduction in a composite of adverse maternal difference in the risk of preeclampsia was found
outcome including new-onset severe preeclampsia, (combined/pooled risk ratio, 0.86; 95% CI, 0.33–2.26;
HELLP syndrome, eclampsia, pulmonary edema, or pla- *P*5.76; $I^2$566%) (102). Because preeclampsia was a sec-
cental abruption (RR, 0.71; 95% CI, 0.59–0.86) (107). In ondary outcome in most studies in this meta-analysis, the
addition, no differences in rates of neonatal complica- effect of metformin needs to be assessed by a study de-
tions or cesarean delivery were reported by the authors signed to evaluate the reduction in the prevalence of pre-
(107).eclampsia as a primary endpoint. In the meantime, the

Continued monitoring of women with gestational use of metformin for the prevention of preeclampsia re-
hypertension or preeclampsia without severe features mains investigational, as is the use of sildenafil and sta-
consists of serial ultrasonography to determine fetal tins (103–105). These drugs are not recommended for
growth, weekly antepartum testing, close monitoring of this indication outside of the context of clinical trials.
blood pressure, and weekly laboratory tests for pre- < What is the optimal treatment for women with ges-
tational hypertension or preeclampsia?
eclampsia. The frequency of these tests may be modified based on clinical findings and patient symptoms. Fol-
lowing the initial documentation of proteinuria and the 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 evalu- ation 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 retro-
spective 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 prel-
abor rupture of membranes (also referred to as premature rupture of membranes) or vaginal bleeding, for neonatal
establishment of the diagnosis of preeclampsia, addi- tional quantifications of proteinuria are no longer neces- sary.
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 fea- tures, 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 pre- eclampsia could happen within days (72). Gestational hypertension and preeclampsia are known risk factors for fetal death and antenatal testing is indicated. How- ever, 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 benefit (106). The risks associated with expectant man- edema, myocardial infarction, stroke, acute respiratory agement in the late preterm period include the develop- distress syndrome, coagulopathy, renal failure, and ment of severe hypertension, eclampsia, HELLP retinal injury. These complications are more likely to syndrome, placental abruption, fetal growth restriction occur in the presence of preexistent medical disorders. and fetal death; however, these risks are small and coun- The clinical course of preeclampsia with severe features terbalanced by the increased rates of admission to the is characterized by progressive deterioration of maternal neonatal intensive care unit, neonatal respiratory compli- and fetal condition. Therefore, delivery is recommended cations and neonatal death that would be associated with when gestational hypertension or preeclampsia with

of delivery versus expectant management of preterm

Box 4. Conditions Precluding Expectant Management*

preeclampsia with severe features demonstrated that expectant management is associated with higher ges- tational age at delivery and improved neonatal out- **Maternal**
comes (110, 111). These observations were reiterated by a Cochrane systematic review (112). The limited
- Uncontrolled severe-range blood pressures (per- sistent systolic blood pressure 160 mm Hg or

available randomized data are consistent with observa- tional evidence suggesting that expectant management more or diastolic blood pressure 110 mm Hg or
of early preeclampsia with severe features prolongs more not responsive to antihypertensive medication
- Persistent headaches, refractory to treatment
- Epigastric pain or right upper pain unresponsive to repeat analgesics

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
- Visual disturbances, motor deficit or altered

expectant management of preeclampsia with severe sensorium
- Stroke
- Myocardial infarction
- HELLP syndrome
- New or worsening renal dysfunction (serum cre-

features from 28 weeks to 34 weeks of gestation (114). These different results may reflect the limita- tions in neonatal intensive care in low-resource settings. atinine 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

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 **Fetal**
clinical monitoring is necessary, and laboratory testing (complete blood count including platelets, liver enzymes,
-

Abnormal fetal testing

and serum creatinine) should be performed serially (115). ◦ Fetal death

The expectant management of preeclampsia with ◦ 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

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

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

neonatal benefit at the expense of maternal risk, expec- tant 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).

*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, manage- ment, and outcome in women with severe preeclampsia at 23 to 28 weeksL gestation. Clin Obstet Gynecol 2017;60:183X9.

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 treat- ment. 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 man- agement may be reasonable in the absence of other, aforementioned maternal and fetal criteria.

If home management is selected, frequent fetal and maternal evaluation are required. No randomized trials have

In women with preeclampsia with 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 severe features before 34 0/7 weeks of gestation, with stable maternal and fetal condition, expectant management may be considered. Two randomized controlled trials

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).

determined the best tests for fetal or maternal evaluation. Among women with gestational hypertension or preeclampsia without severe features, expectant man- agement up to 37 0/7 weeks of gestation is recommen- ded, during which frequent fetal and maternal evaluation is recommended. Fetal monitoring consists of ultraso- nography 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 random- ized 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 mor- bidity or perinatal mortality. A quarter of women re- ported 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 n5357) allocated women with preeclampsia with- out severe features to either placebo or magnesium sul- fate and reported no cases of eclampsia among women allocated to placebo and no significant differences in the proportion of women that progressed to severe pre- eclampsia (120, 121). However, given the small sample size, the results of these studies cannot be used for clin- ical guidance (122, 123).

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

infusion times higher than in those without severe features (4 in
initiation when an intravenous loading dose of 200 versus 1 in 200). It has been calculated that 129
4.5 g followed by 1.8 g/hour is used (131). However, women need to be treated to prevent one case of
infusion rates in excess of 2 g/hour have been associated eclampsia in asymptomatic cases, whereas in symptom-
with increased perinatal mortality in a systematic review atic cases (severe headache, blurred vision, photophobia,

of randomized studies of magnesium sulfate used for hyperreflexia, epigastric pain), the number needed to
tocolysis (132). These data may be considered supportive treat is 36 (124). The evidence regarding the benefit-to-
for the regimen generally preferred in the United States risk ratio of magnesium sulfate prophylaxis is less sup-
(intravenous [IV] administration of a 4–6 g loading dose portive of routine use in preeclampsia without severe
over 20–30 minutes, followed by a maintenance dose of features (122). The clinical decision of whether to use
1–2 g/hour). For women requiring cesarean delivery magnesium sulfate for seizure prophylaxis in patients
(before onset of labor), the infusion should ideally begin with preeclampsia without severe features should be
before surgery and continue during surgery, as well as for determined by the physician or institution, considering
24 hours afterwards. For women who deliver vaginally, patient values or preferences, and the unique risk-
the infusion should continue for 24 hours after delivery. benefit trade-off of each strategy. Although the benefit-
In case of difficulties with establishing venous access, to-risk ratio for routine prophylaxis is less compelling for
magnesium sulfate can be administered by intramuscular patients in high resource settings, it is recommended that
(IM) injection, 10 g initially as a loading dose (5 g IM in magnesium sulfate should be used for the prevention and
each buttock), followed by 5 g every 4 hours. The treatment of seizures in women with gestational hyper-
medication can be mixed with 1 mL of xylocaine 2% tension and preeclampsia with severe features or eclamp-
solution because the intramuscular administration is sia (124, 125).
painful. The rate of adverse effects is also higher with the Magnesium sulfate is more effective than phenytoin,
intramuscular administration (44). The adverse effects of diazepam, or nimodipine (a calcium-channel blocker
magnesium sulfate (respiratory depression and cardiac used in clinical neurology to reduce cerebral vasospasm)
arrest) come largely from its action as a smooth muscle in reducing eclampsia and should be considered the drug
relaxant. Deep tendon reflexes are lost at a serum mag- of choice in the prevention of eclampsia in the intra-
nesium level of 9 mg/dL (7 mEq/L), respiratory depres- partum and postpartum periods (119, 126, 127). Benzo-
sion occurs at 12 mg/dL (10 mEq/L), and cardiac arrest at diazepines and phenytoin are justified only in the context
30 mg/dL (25 mEq/L). Accordingly, provided deep ten- of antiepileptic treatment or when magnesium sulfate is
don reflexes are present, more serious toxicity is avoided. contraindicated or unavailable (myasthenia gravis, hypo-
(Table 2) Because magnesium sulfate is excreted almost calcemia, moderate-to-severe renal failure, cardiac ische-
exclusively in the urine, measuring urine output should mia, heart block, or myocarditis).
be part of the clinical monitoring, in addition to moni- There are still sparse data regarding the ideal dosage
toring of respiration status and tendon reflexes. If renal of magnesium sulfate. Even the therapeutic range of 4.8–
function is impaired, serum magnesium levels will 9.6 mg/dL (4–8 mEq/L) quoted in the literature is ques-
increase quickly, which places the patient at risk of sig- tionable (128, 129). Although there is a relationship
nificant adverse effects. In patients with mild renal failure between toxicity and plasma concentration of magne-
(serum creatinine 1.0–1.5 mg/dL) or oliguria (less than sium, with higher infusion rates increasing the potential
30 mL urine output per hour for more than 4 hours), the for toxicity, the accurate magnesium concentration clin-
loading dose of 4–6 g should be followed by a mainte- ically effective in prevention of eclampsia has not been
nance dose of only 1 gm/hour. Using a lower loading established. Seizures occur even with magnesium at
dose, such as 4 g, may be associated with subtherapeutic a therapeutic level, whereas several trials using infusion
levels for at least 4 hours after loading (133). In cases rates of 1 g/hour, frequently associated with subtherapeu-
with renal dysfunction, laboratory determination of tic magnesium levels, were able to significantly reduce
serum magnesium levels every 4 hours becomes neces- the rate of eclampsia or recurrent convulsions (44, 130).
sary. If the serum level exceeds 9.6 mg/dL (8 mEq/L), Further complicating aspects are that steady magnesium
the infusion should be stopped and serum magnesium levels are reached more slowly during the antepartum
levels should be determined at 2-hour intervals. The infu- period than postpartum period. Larger volume of distri-
sion can be restarted at a lower rate when the serum level bution and higher BMI also affect the dosage and dura-
decreases to less than 8.4 mg/dL (7 mEq/L) (133). The tion needed to reach adequate circulating levels. It has
serum concentration of magnesium is related to the been reported in patients with a high BMI (especially
occurrence of adverse effects and toxicities (see Table 2) greater than 35) that the antepartum level of magnesium
(128, 134). Patients at risk of impending respiratory may remain subtherapeutic for as long as 18 hours after

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% solu-
oral nifedipine are the three agents most commonly tion, 10 mL IV over 3 minutes, along with furosemide
used for this purpose (see Table 3). A recent Cochrane intravenously to accelerate the rate of urinary excretion.
systematic review that involved 3,573 women found

Antihypertensive Approach: Drugs and Thresholds for Treatment

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

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

Drug	Dose	Onset of Action	Comments
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	1–2 minutes	Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.
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	10–20 minutes	Tachycardia is less common and fewer adverse effects.
Nifedipine (immediate release)	10–20 mg orally, repeat in 20 minutes if		May observe reflex tachycardia and

Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings; may be more common than other agents.

5–10 minutes needed; then 10–20 mg every 2–6 hours;
headaches maximum daily dose is 180 mg 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 pre- eclampsia without severe features who are in labor must be monitored for early detection of progression to severe disease. This should include monitoring of blood pres- sure 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 accom- plished, 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 pre- eclampsia 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 con- cluded 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 individ- ualized, based on anticipated probability of vaginal deliv- ery 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 5 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 intu- bation and extubation (145, 146). However, neuraxial anesthesia and analgesia are contraindicated in the pres- ence of a coagulopathy because of the potential for hem- orrhagic 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 3 10^9/L is exceptionally low (less than 0.2%) (148). Extrapolating this expanded data to previous recommen- dations (149) would suggest that epidural or spinal anes- thesia is considered acceptable, and the risk of

epidural hematoma is exceptionally low, in patients with platelet counts of 70 3 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 impli- cations because it prolongs the duration of nondepolariz- ing 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 discon- tinuation of the infusion of magnesium sulfate before cesarean delivery would only minimally reduce magne- sium concentration at the time of delivery while possibly increasing the risk of seizure (150). Women with pre- eclampsia 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

sulfate period if the infusion of magnesium sulfate is stopped
is not necessary to arrest the seizure but to during delivery.
prevent recurrent convulsions.

During eclamptic seizures, there are usually pro- longed fetal heart rate decelerations, even fetal brady- cardia, and sometimes an increase in uterine contractility

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 con- tinue to be used preferentially over opioid analgesics; however, women with chronic hypertension may theoret- ically require intensification of blood pressure monitor- ing and regimen adjustments when on these medications. Overall, data support the safe use of NSAIDs in post- partum patients with blood pressure issues. In a random- ized 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 prophy- laxis for preeclampsia did not show differences in blood pressure, antihypertensive requirements, or other adverse events for patients managed with NSAIDs in the post- partum period (157). < What is the optimal treatment for eclampsia?

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. Further- more, 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 mor- tality with the use of magnesium sulfate. Magnesium sulfate administered intramuscularly or intravenously is superior to phenytoin, diazepam, or lytic cocktail (usu- ally 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 abso- lutely 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 augmenta- tion 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, The initial steps in the management of a woman with a further 2–4 grams of magnesium sulfate could be eclampsia are basic supportive measures such as calling administered IV over 5 minutes (130). In cases refractory for help, prevention of maternal injury, placement in to magnesium sulfate (still seizing at 20 minutes after the lateral decubitus position, prevention of aspiration, bolus or more than two recurrences), a health care pro- administration of oxygen, and monitoring vital signs vider can use sodium amobarbital (250 mg IV in 3 mi- including oxygen saturation. Only subsequently is atten- nutes), thiopental, or phenytoin (1,250 mg IV at a rate of tion directed to the administration of magnesium sulfate. 50 mg/minute). Endotracheal intubation and assisted ven- Most eclamptic seizures are self-limited. Magnesium tilation in the intensive care unit are appropriate in these

and circumstances. Head imaging should also be considered
liver enzymes to increase after 4 days postpartum, because most of cases refractory to magnesium sulfate
the validity of the initial diagnosis of HELLP syndrome therapy may prove to have abnormal findings on brain
should be reassessed. With supportive care alone, 90% of imaging (160).
patients with HELLP syndrome will have platelet count < 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

more than 100,000 3 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 3 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? units and personnel with special

expertise, patients with

Women with a history of preeclampsia continue to HELLP syndrome who are remote from term should have an elevated risk of cardiovascular disease in sub- receive care at a tertiary care center (116, 161). sequent years. Several systematic reviews and meta- It has been hypothesized that the antiinflammatory analyses have linked preeclampsia with an increased risk and immunosuppressive effects of corticosteroids may of cardiovascular disease (hypertension, myocardial modify some of the proinflammatory features of pre- infarction, congestive heart failure), cerebrovascular eclampsia with severe features and favorably affect the events (stroke), peripheral arterial disease, and cardio- clinical course. Several randomized controlled trials of vascular mortality later in life, with an estimated high-dose corticosteroid treatment for antepartum or doubling of odds compared with women unaffected by postpartum stabilization of HELLP syndrome have been preeclampsia (165–167). Meta-regression analysis re- conducted. The use of corticoids in the management of veals a graded relationship between the severity of pre- HELLP syndrome compared with placebo or no treat- eclampsia or eclampsia and the risk of cardiac disease ment was reviewed in a Cochrane Database Systematic (mild RR, 2.00; 95% CI, 1.83–2.19; moderate RR, 2.99; Review, which included 11 randomized trials (550 95% CI, 2.51–3.58; severe RR, 5.36; 95% CI, 3.96–7.27, women) (162). There was no difference in the risk of *P*,.0001) (168). The risk is even higher (428 times the maternal death, severe maternal morbidity, or perinatal risk for women with normal pregnancies) in women with or infant death. The only effect of treatment on individual recurrent preeclampsia (169) and women with early- outcomes was improved platelet count (standardized onset preeclampsia or preeclampsia requiring preterm mean difference [SMD] 0.67; 95% CI, 0.2421.10). delivery (170). More recent evidence suggests that all The authors concluded that the evidence is insufficient hypertensive conditions in pregnancy are associated with to support the use of corticosteroids for attenuation of the later cardiovascular disease with an approximately dou- disease process in HELLP syndrome (162). bling of the rate of incident cardiovascular disease and Very close monitoring is required in HELLP syn- a five times higher rate of hypertension (171). drome until delivery and in the postpartum period, with The mechanisms that account for an increased risk of laboratory testing at least at 12-hour intervals. Aspartate cardiovascular disease in women with a history of aminotransferase levels more than 2,000 IU/L or LDH preeclampsia are not yet well understood, but endothelial more than 3,000 IU/L suggest an increased mortality risk. dysfunction, which has been linked to atherosclerosis, In the natural history of HELLP syndrome there is an persists in women with a history of preeclampsia many inverse relationship between the trends in platelet values years after an affected pregnancy (172). A study of car- and liver enzymes level. During the aggravation slope in diovascular risk factors present before and after preg- the disease evolution, platelet count usually decreases at nancy suggested that nearly one half of the elevated an average rate of approximately 40% per day, whereas risk of future hypertension after preeclampsia can be ex- the liver enzymes values tend to increase. The lowest plained by prepregnancy risk factors (173). Yet, it may observed platelet count occurs at a mean of 23 hours after be possible that the stress incurred to the cardiovascular delivery. The disease may achieve peak intensity during system during gestation triggers a biological response the first 2 days after delivery, including a downward that would otherwise not have occurred despite any trend in hematocrit. If the platelet count continues to drop genetic predisposition or risk factors (171). It remains

quirements, unclear if cardiovascular changes associated with pre-
or other adverse events for patients eclampsia during pregnancy causally lead to cardiovas-
managed with NSAIDs in the postpartum period. cular remodeling increasing the risk of cardiovascular disease later in life or if preeclampsia is a manifestation of an underlying increased risk of cardiovascular disease

The following recommendations are based on limited or inconsistent scientific evidence (Level B): (for example, a common genetic–environmental risk factor(s) interaction [such as hyperlipidemia, obesity,

< Delivery is recommended when gestational hyper- tension or preeclampsia with severe features is diabetes mellitus, or renal disease] that predisposes

diagnosed at or beyond 34 0/7 weeks of gestation, women to develop preeclampsia during pregnancy and after maternal stabilization or with labor or prelabor 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.

rupture of membranes. Delivery should not be de- layed 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 pro-

vide neonatal benefit at the expense of maternal risk, expectant management is not advised when neonatal survival is not anticipated. During expectant man-

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

agement, delivery is recommended at any time in the case of deterioration of maternal or fetal condition. <

Antihypertensive treatment should be initiated expe- < Women with any of the high-risk factors for pre-

ditiously for acute-onset severe hypertension (systolic eclampsia (previous pregnancy with preeclampsia,

blood pressure of 160 mm Hg or more or diastolic multifetal gestation, renal disease, autoimmune

blood pressure of 110 mm Hg or more, or both) that disease, type 1 or type 2 diabetes mellitus, and

is confirmed as persistent (15 minutes or more). The chronic hypertension) and those with more than one

available literature suggests that antihypertensive of the moderate-risk factors (first pregnancy,

agents should be administered within 30–60 minutes. maternal age of 35 years or older, a body mass

However, it is recommended to administer antihy- index of more than 30, family history of pre-

pertensive therapy as soon as reasonably possible eclampsia, sociodemographic characteristics, and

after the criteria for acute-onset severe hypertension personal history factors) should receive low-dose

are met. (81 mg/day) aspirin for preeclampsia prophylaxis, initiated between 12 weeks and 28 weeks of ges- tation

(optimally before 16 weeks of gestation) and

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

delivery. < In women with gestational hypertension or pre-

< It is recommended that women with gestational hypertension in the absence of proteinuria are diag- eclampsia without severe features at or beyond 37 0/7

nosed with preeclampsia if they present with any of weeks of gestation, delivery rather than expectant

the following severe features: thrombocytopenia management upon diagnosis is recommended.

(platelet count less than 100,000 x 10^9/L); impaired < Magnesium sulfate should be used for the prevention

liver function as indicated by abnormally elevated and treatment of seizures in women with gestational

blood concentrations of liver enzymes (to twice the hypertension and preeclampsia with severe features

upper limit of normal concentration); severe persis- or eclampsia.

tent right upper quadrant or epigastric pain and not < Nonsteroidal anti-inflammatory medications should

accounted for by alternative diagnoses; renal insuf- continue to be used preferentially over opioid an-

ficiency (serum creatinine concentration more than algesics. Postpartum patients on magnesium for sei-

1.1 mg/dL or a doubling of the serum creatinine zure prophylaxis for preeclampsia did not show concentration in the absence of other renal disease); differences in blood pressure, antihypertensive re- 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 pre- eclampsia without severe features, expectant man- agement up to 37 0/7 weeks of gestation is recommended, during which frequent fetal and maternal evaluation is recommended. Fetal monitor- ing 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 pre- eclampsia 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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Published online on December 20, 2018. 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
American College of Obstetricians and Gynecologists 409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920
Gestational hypertension and preeclampsia. ACOG Practice Bulletin No. 202. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;133:e1–25. 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 de-
signed 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 uncon- trolled 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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