HYPERTENSION IN PREGNANCY

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

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Hypertension in Pregnancy was developed by the Task Force on Hypertension in Pregnancy. The information in *Hypertension in Pregnancy* should not be viewed as a body of rigid rules. The guidelines are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or the type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

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Endorsements

The following professional organizations have reviewed, endorsed, and support this report:

American Academy of Physician Assistants
American Academy of Neurology*
American College of Occupational and Environmental Medicine
American Optometric Association
American Osteopathic Association
American Society of Hypertension
Preeclampsia Foundation
Society for Maternal-Fetal Medicine

*The American Academy of Neurology has affirmed the value of this report. Please see the American Academy of Neurology Guideline Endorsement Policy for further information.

Foreword

Hypertensive disorders of pregnancy, including preeclampsia, complicate up to 10% of pregnancies worldwide, constituting one of the greatest causes of maternal and perinatal morbidity and mortality worldwide. In early 2011, as the 62nd President Elect of the American College of Obstetricians and Gynecologists (the College) and the American Congress of Obstetricians and Gynecologists, I decided to make this issue a Presidential Initiative for the following reasons:

- The incidence of preeclampsia has increased by 25% in the United States during the past two decades (1).
- Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality, with an estimated 50,000–60,000 preeclampsia-related deaths per year worldwide (2, 3).
- For every preeclampsia-related death that occurs in the United States, there are probably 50–100 other women who experience “near miss” significant maternal morbidity that stops short of death but still results in significant health risk and health care cost (4, 5).
- What can be considered “less-than-optimal" care of patients with preeclampsia and other hypertensive disorders of pregnancy reportedly occurs with some frequency worldwide, contributing to maternal and perinatal injury that might have been avoidable (6).
- Hypertensive disorders of pregnancy are major contributors to prematurity.
- Preeclampsia is a risk factor for future cardiovascular disease and metabolic disease in women.
- Despite considerable research, the etiology of preeclampsia remains unclear.
- Within the past 10 years, substantial advances in the understanding of preeclampsia pathophysiology as well as increased efforts to obtain evidence to guide therapy have emerged. However, this information has not translated into improved clinical practice.
- New best practice recommendations are greatly needed to guide clinicians in the care of women with all forms of preeclampsia and hypertension that occur during pregnancy, particularly women with acute severe hypertension and superimposed preeclampsia. Also needed is a system for continually updating these guidelines and integrating them into daily obstetric practice.
- Identification of patients with severe forms of preeclampsia continues to challenge clinicians.
- Improved patient education and counseling strategies are needed to convey more effectively the dangers of preeclampsia and hypertension and the importance of early detection to women with varying degrees of health literacy.
- Research on preeclampsia and other hypertensive disorders of pregnancy in both the laboratory and clinical arenas requires continued emphasis and funding.

To address these important issues, the Task Force on Hypertension in Pregnancy, composed of 17 experts in the fields of obstetrics, maternal–fetal medicine, hypertension, internal medicine, nephrology, anesthesiology, physiology, and patient advocacy, was created and charged with three tasks: 1) summarize the current state of knowledge about preeclampsia and other hypertensive disorders in pregnancy by reviewing and grading the quality of the extant world literature; 2) translate this information into practice guidelines for health care providers who treat obstetric patients affected by these disorders; and 3) identify and prioritize the most compelling areas of laboratory and clinical research to bridge gaps in our current knowledge. Members of the task force met three times over 9 months during 2011 and 2012 at the College headquarters in Washington, DC. They spent countless additional hours writing and deliberating to achieve consensus on the practice recommendations that follow in the Executive Summary.

I am deeply grateful to each member of the Task Force on Hypertension in Pregnancy for their hard work and dedication to this important endeavor. In addition, I would like to give special thanks to Dr. James M. Roberts of the University of Pittsburgh's Magee-Womens Research Institute for his superb leadership of the task force and to Nancy O'Reilly, Senior Director of Practice Bulletins, and Dr. Gerald F. Joseph Jr, Vice President of Practice Activities, at the College for their support throughout the process.

Efforts are now underway to achieve global consensus on best practice guidelines for the diagnosis and management of preeclampsia and other hypertensive disorders of pregnancy. It is my fervent hope that the work of the Task Force on Hypertension in Pregnancy serves as a springboard to these efforts and ultimately translates into improved obstetric care for patients with preeclampsia and other hypertensive disorders of pregnancy in this country and throughout the world.

James N. Martin Jr, MD
Immediate Past President

The American College of Obstetricians and Gynecologists
2012–2013

The American Congress of Obstetricians and Gynecologists
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Executive Summary

The American College of Obstetricians and Gynecologists (the College) convened a task force of experts in the management of hypertension in pregnancy to review available data and publish evidence-based recommendations for clinical practice. The Task Force on Hypertension in Pregnancy comprised 17 clinician–scientists from the fields of obstetrics, maternal–fetal medicine, hypertension, internal medicine, nephrology, anesthesiology, physiology, and patient advocacy. This executive summary includes a synopsis of the content and task force recommendations of each chapter in the report and is intended to complement, not substitute, the report.

Hypertensive disorders of pregnancy remain a major health issue for women and their infants in the United States. Preeclampsia, either alone or superimposed on preexisting (chronic) hypertension, presents the major risk. Although appropriate prenatal care, with observation of women for signs of preeclampsia and then delivery to terminate the disorder, has reduced the number and extent of poor outcomes, serious maternal–fetal morbidity and mortality still occur. Some of these adverse outcomes are avoidable, whereas others can be ameliorated. Also, although some of the problems that face neonates are related directly to preeclampsia, a large proportion are secondary to prematurity that results from the appropriate induced delivery of the fetuses of women who are ill. Optimal management requires close observation for signs and premonitory findings and, after establishing the diagnosis, delivery at the optimal time for both maternal and fetal well-being. More recent clinical evidence to guide this timing is now available. Chronic hypertension is associated with fetal morbidity in the form of growth restriction and maternal morbidity manifested as severely increased blood pressure (BP). However, maternal and fetal morbidity increase dramatically with the superimposition of preeclampsia. One of the major challenges in the care of women with chronic hypertension is deciphering whether chronic hypertension has worsened or whether preeclampsia has developed. In this report, the task force provides suggestions for the recognition and management of this challenging condition.

In the past 10 years, there have been substantial advances in the understanding of preeclampsia as well as increased efforts to obtain evidence to guide therapy. Nonetheless, there remain areas on which evidence is scant. The evidence is now clear that preeclampsia is associated with later-life cardiovascular (CV) disease; however, further research is needed to determine how best to use this information to help patients. The task force also has identified issues in the management of preeclampsia that warrant special attention. First, is the failure by health care providers to appreciate the multisystemic nature of preeclampsia. This is in part

due to attempts at rigid diagnosis, which is addressed in the report. Second, preeclampsia is a dynamic process, and a diagnosis such as "mild preeclampsia" (which is discouraged) applies only at the moment the diagnosis is established because preeclampsia by nature is progressive, although at different rates. Appropriate management mandates frequent reevaluation for severe features that indicate the actions outlined in the recommendations (which are listed after the chapter summaries). It has been known for many years that preeclampsia can worsen or present for the first time after delivery, which can be a major scenario for adverse maternal events. In this report, the task force provides guidelines to attempt to reduce maternal morbidity and mortality in the postpartum period.

The Approach

The task force used the evidence assessment and recommendation strategy developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (available at www.gradeworkinggroup.org/index.htm). Because of its utility, this strategy has been adapted worldwide by a large number of organizations. With the GRADE Working Group approach, the function of expert task forces and working groups is to evaluate the available evidence regarding a clinical decision that, because of limited time and resources, would be difficult for the average health care provider to accomplish. The expert group then makes recommendations based on the evidence that are consistent with typical patient values and preferences. The task force evaluated the evidence for each recommendation, the implications, and the confidence in estimates of effect. With this combination, the available information was evaluated and recommendations were made. In this report, the confidence in estimates of effect (quality) of the available evidence is judged as very low, low, moderate, or high.

Recommendations are practices agreed to by the task force as the most appropriate course of action; they are graded as strong or qualified. A strong recommendation is one that is so well supported that it would be the approach appropriate for virtually all patients. It could be the basis for health care policy. A qualified recommendation is also one that would be judged as appropriate for most patients, but it might not be the optimal recommendation for some patients (whose values and preferences differ, or who have different attitudes toward uncertainty in estimates of effect). When the task force has made a qualified recommendation, the health care provider and patient are encouraged to work together to arrive at a decision based on the values and judgment and underlying health condition of a particular patient in a particular situation.

Classification of Hypertensive Disorders of Pregnancy

The task force chose to continue using the classification schema first introduced in 1972 by the College and modified in the 1990 and 2000 reports of the Working Group of the National High Blood Pressure Education Program. Similar classifications can be found in the American Society of Hypertension guidelines, as well as College Practice Bulletins. Although the task force has modified some of the components of the classification, this basic, precise, and practical classification was used, which considers hypertension during pregnancy in only four categories: 1) preeclampsia–eclampsia, 2) chronic hypertension (of any cause), 3) chronic hypertension with superimposed preeclampsia, and 4) gestational hypertension. Importantly, the following components were modified. In recognition of the syndromic nature of preeclampsia, the task force has eliminated the dependence of the diagnosis on proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances (see Box E-1). *Gestational hypertension* is BP elevation after 20 weeks of gestation in the absence of proteinuria or the aforementioned systemic findings, *chronic hypertension* is hypertension that predates pregnancy, and *superimposed preeclampsia* is chronic hypertension in association with preeclampsia.

Establishing the Diagnosis of Preeclampsia or Eclampsia

The BP criteria are maintained from prior recommendations. *Proteinuria* is defined as the excretion of 300 mg or more of protein in a 24-hour urine collection. Alternatively, a timed excretion that is extrapolated to this 24-hour urine value or a protein/creatinine ratio of at least 0.3 (each measured as mg/dL) is used. Because of the variability of qualitative determinations (dipstick test), this method is discouraged for diagnostic use unless other approaches are not readily available. If

BOX E-1. Severe Features of Preeclampsia (Any of these findings) ⇦

- Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,000/microliter)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive 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
- New-onset cerebral or visual disturbances

this approach must be used, a determination of 1+ is considered as the cutoff for the diagnosis of proteinuria. In view of recent studies that indicate a minimal relationship between the quantity of urinary protein and pregnancy outcome in preeclampsia, massive proteinuria (greater than 5 g) has been eliminated from the consideration of preeclampsia as severe. Also, because fetal growth restriction is managed similarly in pregnant women with and without preeclampsia, it has been removed as a finding indicative of severe preeclampsia (Table E-1).

Prediction of Preeclampsia

A great deal of effort has been directed at the identification of demographic factors, biochemical analytes, or biophysical findings, alone or in combination, to predict early in pregnancy the later development of preeclampsia. Although there are some encouraging findings, these tests are not yet ready for clinical use.

TASK FORCE RECOMMENDATION

- Screening to predict preeclampsia beyond obtaining an appropriate medical history to evaluate for risk factors is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Prevention of Preeclampsia

It is clear that the antioxidants vitamin C and vitamin E are not effective interventions to prevent preeclampsia or adverse outcomes from preeclampsia in unselected women at high risk or low risk of preeclampsia. Calcium may be useful to reduce the severity of preeclampsia in populations with low calcium intake, but this finding is not relevant to a population with adequate calcium intake, such as in the United States. The administration of low-dose aspirin (60–80 mg) to prevent preeclampsia has been examined in meta-analyses of more than 30,000 women, and it appears that there is a slight effect to reduce preeclampsia and adverse perinatal outcomes. These findings are not clinically relevant to low-risk women but may be relevant to populations at very high risk in whom the number to treat to achieve the desired outcome will be substantially less. There is no evidence that bed rest or salt restriction reduces preeclampsia risk.

TASK FORCE RECOMMENDATIONS

- For women with a medical history of early-onset preeclampsia and preterm delivery at less than 34 0/7 weeks of gestation or preeclampsia in more than one prior pregnancy, initiating the administration of daily low-dose (60–80 mg) aspirin beginning in the late first trimester is suggested.*

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

*Meta-analysis of more than 30,000 women in randomized trials of aspirin to prevent preeclampsia indicates a small reduction in the incidence and morbidity of preeclampsia and reveals no evidence of acute risk, although long-term fetal effects cannot be excluded. The number of women to treat to have a therapeutic effect is determined by prevalence. In view of maternal safety, a discussion of the use of aspirin in light of individual risk is justified.

TABLE E-1. Diagnostic Criteria for Preeclampsia ⇦

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	• Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio greater than or equal to 0.3* • Dipstick reading of 1+ (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/microliter
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	
Cerebral or visual symptoms	

* Each measured as mg/dL.

- The administration of vitamin C or vitamin E to prevent preeclampsia is not recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- It is suggested that dietary salt not be restricted during pregnancy for the prevention of preeclampsia.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- It is suggested that bed rest or the restriction of other physical activity not be used for the primary prevention of preeclampsia and its complications.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Management of Preeclampsia and HELLP Syndrome

Clinical trials have provided an evidence base to guide management of several aspects of preeclampsia. Nonetheless, several important questions remain unanswered. Reviews of maternal mortality data reveal that deaths could be avoided if health care providers remain alert to the likelihood that preeclampsia will progress. The same reviews indicate that intervention in acutely ill women with multiple organ dysfunction is sometimes delayed because of the absence of proteinuria. Furthermore, accumulating information indicates that the amount of proteinuria does not predict maternal or fetal outcome. It is for these reasons that the task force has recommended that alternative systemic findings with new-onset hypertension can fulfill the diagnosis of preeclampsia even in the absence of proteinuria.

Perhaps the biggest changes in preeclampsia management relate to the timing of delivery in women with preeclampsia without severe features, which based on evidence is suggested at 37 0/7 weeks of gestation, and an increasing awareness of the importance of preeclampsia in the postpartum period. Health care providers are reminded of the contribution of nonsteroidal antiinflammatory agents to increased BP. It is suggested that these commonly used postpartum pain relief agents be replaced by other analgesics in women with hypertension that persists for more than 1 day postpartum.

TASK FORCE RECOMMENDATIONS

- The close monitoring of women with gestational hypertension or preeclampsia without severe features, with serial assessment of maternal symptoms and fetal movement (daily by the woman), serial measurements of BP (twice weekly), and assessment of platelet counts and liver enzymes (weekly) is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For women with gestational hypertension, monitoring BP at least once weekly with proteinuria assessment in the office and with an additional weekly measurement of BP at home or in the office is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For women with mild gestational hypertension or preeclampsia with a persistent BP of less than 160 mm Hg systolic or 110 mm Hg diastolic, it is suggested that antihypertensive medications not be administered.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For women with gestational hypertension or preeclampsia without severe features, it is suggested that strict bed rest not be prescribed.*†

  Quality of evidence: Low
  Strength of recommendation: Qualified

  * The task force acknowledged that there may be situations in which different levels of rest, either at home or in the hospital, may be indicated for individual women. The previous recommendations do not cover advice regarding overall physical activity and manual or office work.

  † Women may need to be hospitalized for reasons other than bed rest, such as for maternal and fetal surveillance. The task force agreed that hospitalization for maternal and fetal surveillance is resource intensive and should be considered as a priority for research and future recommendations.

- For women with preeclampsia without severe features, use of ultrasonography to assess fetal growth and antenatal testing to assess fetal status is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- If evidence of fetal growth restriction is found in women with preeclampsia, fetoplacental assessment that includes umbilical artery Doppler velocimetry as an adjunct antenatal test is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with mild gestational hypertension or preeclampsia without severe features and no indication for delivery at less than 37 0/7 weeks of gestation, expectant management with maternal and fetal monitoring is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with mild gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery rather than continued observation is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For women with preeclampsia with systolic BP of less than 160 mm Hg and a diastolic BP less than 110 mm Hg and no maternal symptoms, it is suggested that magnesium sulfate not be administered universally for the prevention of eclampsia.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with severe preeclampsia at or beyond 34 0/7 weeks of gestation, and in those with unstable maternal or fetal conditions irrespective of gestational age, delivery soon after maternal stabilization is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with severe preeclampsia at less than 34 0/7 weeks of gestation with stable maternal and fetal conditions, it is recommended that continued pregnancy be undertaken only at facilities with adequate maternal and neonatal intensive care resources.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with severe preeclampsia receiving expectant management at 34 0/7 weeks or less of gestation, the administration of corticosteroids for fetal lung maturity benefit is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with preeclampsia with severe hypertension during pregnancy (sustained systolic BP of at least 160 mm Hg or diastolic BP of at least 110 mm Hg), the use of antihypertensive therapy is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with preeclampsia, it is suggested that a delivery decision should not be based on the amount of proteinuria or change in the amount of proteinuria.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with severe preeclampsia and before fetal viability, delivery after maternal stabilization is recommended. Expectant management is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- It is suggested that corticosteroids be administered and delivery deferred for 48 hours if maternal and fetal conditions remain stable for women with severe preeclampsia and a viable fetus at 33 6/7 weeks or less of gestation with any of the following:
  - preterm premature rupture of membranes
  - labor
  - low platelet count (less than 100,000/microliter)
  - persistently abnormal hepatic enzyme concentrations (twice or more the upper normal values)
  - fetal growth restriction (less than the fifth percentile)
  - severe oligohydramnios (amniotic fluid index less than 5 cm)
  - reversed end-diastolic flow on umbilical artery Doppler studies
  - new-onset renal dysfunction or increasing renal dysfunction

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- It is recommended that corticosteroids be given if the fetus is viable and at 33 6/7 weeks or less of gestation, but that delivery not be delayed after initial maternal stabilization regardless of gestational age for women with severe preeclampsia that is complicated further with any of the following:
  - uncontrollable severe hypertension
  - eclampsia
  - pulmonary edema
  - abruptio placentae
  - disseminated intravascular coagulation
  - evidence of nonreassuring fetal status
  - intrapartum fetal demise

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with preeclampsia, it is suggested that the mode of delivery need not be cesarean delivery. The mode of delivery should be determined by fetal gestational age, fetal presentation, cervical status, and maternal and fetal conditions.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For women with eclampsia, the administration of parenteral magnesium sulfate is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with severe preeclampsia, the administration of intrapartum–postpartum magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with preeclampsia undergoing cesarean delivery, the continued intraoperative administration of parenteral magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with HELLP syndrome and before the gestational age of fetal viability, it is recommended that delivery be undertaken shortly after initial maternal stabilization.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with HELLP syndrome at 34 0/7 weeks or more of gestation, it is recommended that delivery be undertaken soon after initial maternal stabilization.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with HELLP syndrome from the gestational age of fetal viability to 33 6/7 weeks of gestation, it is suggested that delivery be delayed for 24–48 hours if maternal and fetal condition remains stable to complete a course of corticosteroids for fetal benefit.*

  Quality of evidence: Low
  Strength of recommendation: Qualified

  *Corticosteroids have been used in randomized controlled trials to attempt to improve maternal and fetal condition. In these studies, there was no evidence of benefit to improve overall maternal and fetal outcome (although this has been suggested in observational studies). There is evidence in the randomized trials of improvement of platelet counts with corticosteroid treatment. In clinical settings in which an improvement in platelet count is considered useful, corticosteroids may be justified.

- For women with preeclampsia who require analgesia for labor or anesthesia for cesarean delivery and with a clinical situation that permits sufficient time for establishment of anesthesia, the administration of neuraxial anesthesia (either spinal or epidural anesthesia) is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with severe preeclampsia, it is suggested that invasive hemodynamic monitoring not be used routinely.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women in whom gestational hypertension, preeclampsia, or superimposed preeclampsia is diagnosed, it is suggested that BP be monitored in the hospital or that equivalent outpatient surveillance be performed for at least 72 hours postpartum and again 7–10 days after delivery or earlier in women with symptoms.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For all women in the postpartum period (not just women with preeclampsia), it is suggested that discharge instructions include information about the signs and symptoms of preeclampsia as well as the importance of prompt reporting of this information to their health care providers.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women in the postpartum period who present with new-onset hypertension associated with headaches or blurred vision or preeclampsia with severe hypertension, the parenteral administration of magnesium sulfate is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with persistent postpartum hypertension, BP of 150 mm Hg systolic or 100 mm Hg diastolic or higher, on at least two occasions that are at least 4–6 hours apart, antihypertensive therapy is suggested. Persistent BP of 160 mm Hg systolic or 110 mm Hg diastolic or higher should be treated within 1 hour.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Management of Women With Prior Preeclampsia

Women who have had preeclampsia in a prior pregnancy should receive counseling and assessments before their next pregnancy. This can be initiated at the postpartum visit but is ideally accomplished at a preconception visit before the next planned pregnancy. During the preconception visit, the previous pregnancy history should be reviewed and the prognosis for the upcoming pregnancy should be discussed. Potentially modifiable lifestyle activities, such as weight loss and increased physical activity, should be encouraged. The current status of medical problems should be assessed, including laboratory evaluation if appropriate. Medical problems such as hypertension and diabetes should be brought into the best control possible. The effect of medical problems on the pregnancy should be discussed. Medications should be reviewed and their administration modified for upcoming pregnancy. Folic acid supplementation should be recommended. If a woman has given birth to a preterm infant during a preeclamptic pregnancy or has had preeclampsia in more than one pregnancy, the use of low-dose aspirin in the upcoming pregnancy should be suggested.

Women with a medical history of preeclampsia should be instructed to return for care early in pregnancy. During the next pregnancy, early ultrasonography should be performed to determine gestational age, and assessment and visits should be tailored to the prior pregnancy outcome, with frequent visits beginning earlier in women with prior preterm preeclampsia. The woman should be educated about the signs and symptoms of preeclampsia and instructed when and how to contact her health care provider.

TASK FORCE RECOMMENDATION

- For women with preeclampsia in a prior pregnancy, preconception counseling and assessment is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Chronic Hypertension and Superimposed Preeclampsia

Chronic hypertension (hypertension predating pregnancy), presents special challenges to health care providers. Health care providers must first confirm that the BP elevation is not preeclampsia. Once this is established, if the BP elevation has not been previously evaluated, a workup should be performed to document that BP is truly elevated (ie, not white coat hypertension) and to check for secondary hypertension and end-organ damage. The choice of which women to treat and how to treat them requires special considerations during pregnancy, especially in light of emerging data that suggest lowering BP excessively might have adverse fetal effects.

Perhaps the greatest challenge is the recognition of preeclampsia superimposed on chronic hypertension, a condition that is commonly associated with adverse maternal and fetal outcomes. Recommendations are provided to guide health care providers in distinguishing women who may have superimposed preeclampsia without severe features (only hypertension and proteinuria) and require only observation from women who may have superimposed preeclampsia with severe features (evidence of systemic involvement beyond hypertension and proteinuria) and require intervention.

TASK FORCE RECOMMENDATIONS

- For women with features suggestive of secondary hypertension, referral to a physician with expertise in treating hypertension to direct the workup is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For pregnant women with chronic hypertension and poorly controlled BP, the use of home BP monitoring is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For women with suspected white coat hypertension, the use of ambulatory BP monitoring to confirm the diagnosis before the initiation of antihypertensive therapy is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- It is suggested that weight loss and extremely low-sodium diets (less than 100 mEq/d) not be used for managing chronic hypertension in pregnancy.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with chronic hypertension who are accustomed to exercising, and in whom BP is well controlled, it is recommended that moderate exercise be continued during pregnancy.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For pregnant women with persistent chronic hypertension with systolic BP of 160 mm Hg or higher or diastolic BP of 105 mm Hg or higher, antihypertensive therapy is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For pregnant women with chronic hypertension and BP less than 160 mm Hg systolic or 105 mm Hg diastolic and no evidence of end-organ damage, it is suggested that they not be treated with pharmacologic antihypertensive therapy.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For pregnant women with chronic hypertension treated with antihypertensive medication, it is suggested that BP levels be maintained between 120 mm Hg systolic and 80 mm Hg diastolic and 160 mm Hg systolic and 105 mm Hg diastolic.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For the initial treatment of pregnant women with chronic hypertension who require pharmacologic therapy, labetalol, nifedipine, or methyldopa are recommended above all other antihypertensive drugs.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with uncomplicated chronic hypertension in pregnancy, the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women of reproductive age with chronic hypertension, the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists is not recommended unless there is a compelling reason, such as the presence of proteinuric renal disease.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with chronic hypertension who are at a greatly increased risk of adverse pregnancy outcomes (history of early-onset preeclampsia and preterm delivery at less than 34 0/7 weeks of gestation or preeclampsia in more than one prior pregnancy), initiating the administration of daily low-dose aspirin (60–80 mg) beginning in the late first trimester is suggested.*

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

  *Meta-analysis of more than 30,000 women in randomized trials of aspirin to prevent preeclampsia indicates a small reduction in the incidence and morbidity of preeclampsia and reveals no evidence of acute risk, although long-term fetal effects cannot be excluded. The number of women to treat to have a therapeutic effect is determined by prevalence. In view of maternal safety, a discussion of the use of aspirin in light of individual risk is justified.

- For women with chronic hypertension, the use of ultrasonography to screen for fetal growth restriction is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- If evidence of fetal growth restriction is found in women with chronic hypertension, fetoplacental assessment to include umbilical artery Doppler velocimetry as an adjunct antenatal test is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with chronic hypertension complicated by issues such as the need for medication, other underlying medical conditions that affect fetal outcome, or any evidence of fetal growth restriction, and superimposed preeclampsia, antenatal fetal testing is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with chronic hypertension and no additional maternal or fetal complications, delivery before 38 0/7 weeks of gestation is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with superimposed preeclampsia who receive expectant management at less than 34 0/7 weeks of gestation, the administration of corticosteroids for fetal lung maturity benefit is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with chronic hypertension and superimposed preeclampsia with severe features, the administration of intrapartum–postpartum parenteral magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with superimposed preeclampsia without severe features and stable maternal and fetal conditions, expectant management until 37 0/7 weeks of gestation is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- Delivery soon after maternal stabilization is recommended irrespective of gestational age or full corticosteroid benefit for women with superimposed preeclampsia that is complicated further by any of the following:
  - uncontrollable severe hypertension
  - eclampsia
  - pulmonary edema
  - abruptio placentae
  - disseminated intravascular coagulation
  - nonreassuring fetal status

  Quality of evidence: Moderate
  Strength of the recommendation: Strong

- For women with superimposed preeclampsia with severe features at less than 34 0/7 weeks of gestation with stable maternal and fetal conditions, it is recommended that continued pregnancy should be undertaken only at facilities with adequate maternal and neonatal intensive care resources.

  Quality of evidence: Moderate
  Strength of evidence: Strong

- For women with superimposed preeclampsia with severe features, expectant management beyond 34 0/7 weeks of gestation is not recommended.

  Quality of evidence: Moderate
  Strength of the recommendation: Strong

Later-Life Cardiovascular Disease in Women With Prior Preeclampsia

Over the past 10 years, information has accumulated indicating that a woman who has had a preeclamptic pregnancy is at an increased risk of later-life CV disease. This increase ranges from a doubling of risk in all cases to an eightfold to ninefold increase in women with preeclampsia who gave birth before 34 0/7 weeks of gestation. This has been recognized by the American Heart Association, which now recommends that a pregnancy history be part of the evaluation of CV risk in women. It is the general belief that preeclampsia does not cause CV disease, but rather preeclampsia and CV disease share common risk factors. Awareness that a woman has had a preeclamptic pregnancy might allow for the identification of women not previously recognized as at-risk for earlier assessment and potential intervention. However, it is unknown if this will be a valuable adjunct to previous information. If this is the case, would the current recommendation of assessing risk factors for women by medical history, lifestyle evaluation, testing for metabolic abnormalities, and possibly inflammatory activation at age 40 years provide all of the information that would be gained by knowing a woman had a past preeclamptic pregnancy? Would it be valuable to perform this assessment at a younger age in women who had a past preeclamptic pregnancy? If the risk was identified earlier, what intervention (other than lifestyle modification) would potentially be useful and would it make a difference? Are there risk factors that could be unmasked by pregnancy other than conventional risk factors? Further research is needed to determine how to take advantage of this information relating preeclampsia to later-life CV disease. At this time, the task force cautiously recommends lifestyle modification (maintenance of a healthy weight, increased physical activity, and not smoking) and suggests early evaluation for the most high-risk women.

TASK FORCE RECOMMENDATION

- For women with a medical history of preeclampsia who gave birth preterm (less than 37 0/7 weeks of gestation) or who have a medical history of recurrent preeclampsia, yearly assessment of BP, lipids, fasting blood glucose, and body mass index is suggested.*

  Quality of evidence: Low
  Strength of recommendation: Qualified

*Although there is clear evidence of an association between preeclampsia and later-life CV disease, the value and appropriate timing of assessment is not yet established. Health care providers and patients should make this decision based on their judgment of the relative value of extra information versus expense and inconvenience.

Patient Education

Patient and health care provider education is key to the successful recognition and management of preeclampsia. Health care providers need to inform women during the prenatal and postpartum periods of the signs and symptoms of preeclampsia and stress the importance of contacting health care providers if these are evident. The recognition of the importance of patient education must be complemented by the recognition and use of strategies that facilitate the successful transfer of this information to women with varying degrees of health literacy. Recommended strategies to facilitate this process include using plain nonmedical language, taking time to speak slowly, reinforcing key issues in print using pictorially based information, and requesting feedback to indicate that the patient understands, and, where applicable, her partner.

TASK FORCE RECOMMENDATION

- It is suggested that health care providers convey information about preeclampsia in the context of prenatal care and postpartum care using proven health communication practices.

  Quality of evidence: Low
  Strength of recommendation: Qualified

The State of the Science and Research Recommendations

In the past 10 years, striking increases in the understanding of the pathophysiology of preeclampsia have occurred. Clinical research advances also have emerged that have provided evidence to guide therapy. It is now understood that preeclampsia is a multisystemic disease that affects all organ systems and is far more than high BP and renal dysfunction. The placenta is evident as the root cause of preeclampsia. It is with the delivery of the placenta that preeclampsia begins to resolve. The insult to the placenta is proposed as an immunologically initiated alteration in trophoblast function, and the reduction in trophoblast invasion leads to failed vascular remodeling of the maternal spiral arteries that perfuse the placenta. The resulting reduced perfusion and increased velocity of blood perfusing the intervillous space alter placental function. The altered placental function leads to maternal disease through putative primary mediators, including oxidative and endoplasmic reticulum stress and inflammation, and secondary mediators that include modifiers of endothelial function and angiogenesis. This understanding of preeclampsia pathophysiology has not translated into predictors or preventers of preeclampsia or to improved clinical care. This has led to a reassessment of this conceptual framework, with attention to the possibility that preeclampsia is not one disease but that the syndrome may include subsets of pathophysiology.

Clinical research advances have shown approaches to therapy that work (eg, delivery for women with gestational hypertension and preeclampsia without severe features at 37 0/7 weeks of gestation) or do not work (vitamin C and vitamin E to prevent preeclampsia). However, there are few clinical recommendations that can be classified as "strong" because there are huge gaps in the evidence base that guides therapy. These knowledge gaps form the basis for research recommendations to guide future therapy.

Conclusion

The task force provides evidence-based recommendations for the management of patients with hypertension during and after pregnancy. Recommendations are graded as strong or qualified based on evidence of effectiveness weighed against evidence of potential harm. In all instances, the final decision is made by the health care provider and patient after consideration of the strength of the recommendations in relation to the values and judgments of the individual patient.

CHAPTER 1

Classification of Hypertensive Disorders

The major goals of a hypertension classification schema, which describes hypertension that complicates pregnancy, are to differentiate diseases preceding conception from those specific to pregnancy, identify the most ominous causes, and create categories ideal for record keeping and eventual epidemiologic research. Nevertheless, health care professionals continue to be confused by the differences in terminology that abound in the literature, especially the differences in publications from national and international societies. These latter reports continue to introduce schema that differ in various documents and may contrast with those recommended here. This confusion has obviously affected both management and outcome research and recommendations.

The American College of Obstetricians and Gynecologists (the College) Task Force on Hypertension in Pregnancy chose to continue using the classification schema first introduced in 1972 by the College and modified in the 1990 and 2000 reports of the National High Blood Pressure Education Program Working Group (1). Similar classifications can be found in the American Society of Hypertension guidelines, as well as College Practice Bulletins (2, 3). Although the task force has modified some of the components of the classification, it continues with this basic, precise, and practical classification, which considers hypertension during pregnancy in only four categories: 1) preeclampsia–eclampsia, 2) chronic hypertension (of any cause), 3) chronic hypertension with superimposed preeclampsia; and 4) gestational hypertension.

It has been suggested that an older category, "unclassified," be reintroduced or replaced by "suspected" or "presumptive" preeclampsia. This may be useful in management because one should always be prepared for the disorder with the greatest risk. However, although these latter terms may help guide clinical practice, they may hinder record keeping for precise epidemiological research.

Preeclampsia–Eclampsia

Preeclampsia is a pregnancy-specific hypertensive disease with multisystem involvement. It usually occurs after 20 weeks of gestation, most often near term, and can be superimposed on another hypertensive disorder. *Preeclampsia*, the most common form of high blood pressure (BP) that complicates pregnancy, is primarily defined by the occurrence of new-onset hypertension plus new-onset proteinuria. However, although these two criteria are considered the classic definition of preeclampsia, some women present with hypertension and multisystemic signs usually indicative of disease severity in the absence of proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired

liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances.

Hypertension is defined as either a systolic BP of 140 mm Hg or greater, a diastolic BP of 90 mm Hg or greater, or both. Hypertension is considered mild until diastolic or systolic levels reach or exceed 110 mm Hg and 160 mm Hg, respectively. It is recommended that a diagnosis of hypertension require at least two determinations at least 4 hours apart, although on occasion, especially when faced with severe hypertension, the diagnosis can be confirmed within a shorter interval (even minutes) to facilitate timely antihypertensive therapy.

Proteinuria is diagnosed when 24-hour excretion equals or exceeds 300 mg in 24 hours or the ratio of measured protein to creatinine in a single voided urine measures or exceeds 3.0 (each measured as mg/dL), termed the protein/creatinine ratio. As discussed in Chapter 2 "Establishing the Diagnosis of Preeclampsia and Eclampsia," qualitative dipstick readings of 1+ suggest proteinuria but have many false-positive and false-negative results and should be reserved for use when quantitative methods are not available or rapid decisions are required.

Eclampsia is the convulsive phase of the disorder and is among the more severe manifestations of the disease. It is often preceded by premonitory events, such as severe headaches and hyperreflexia, but it can occur in the absence of warning signs or symptoms.

Specific biochemical markers have been linked to increased morbidity in hypertensive complications of pregnancy (eg, hyperuricemia), but these should not be used for diagnosis. Although some label preeclampsia as "less severe" or "more severe", or "mild" and "severe," these are not specific classifications, and the consideration of preeclampsia as "mild" should be avoided. The task force recommends that the term "mild preeclampsia" be replaced by "preeclampsia without severe features." These points are more extensively discussed in Chapter 2 "Establishing the Diagnosis of Preeclampsia and Eclampsia."

Chronic Hypertension

During pregnancy, *chronic hypertension* is defined as high BP known to predate conception or detected before 20 weeks of gestation. Previously, some suggested that when high BP is first diagnosed in the first half of pregnancy and normalizes postpartum, the diagnosis should be changed to "transient hypertension of pregnancy." However, because discharge records are rarely modified, the task force recommends against instituting this latter terminology.

Chronic Hypertension With Superimposed Preeclampsia

Preeclampsia may complicate all other hypertensive disorders, and in fact the incidence is four to five times that in nonhypertensive pregnant women (4). In such cases, prognosis for the woman and her fetus is worse than either condition alone. Although evidence from renal biopsy studies suggests that the diagnosis of superimposed preeclampsia may be often erroneous (5), the diagnosis is more likely in the following seven scenarios: women with hypertension only in early gestation who develop proteinuria after 20 weeks of gestation and women with proteinuria before 20 weeks of gestation who 1) experience a sudden exacerbation of hypertension, or a need to escalate the antihypertensive drug dose especially when previously well controlled with these medications; 2) suddenly manifest other signs and symptoms, such as an increase in liver enzymes to abnormal levels; 3) present with a decrement in their platelet levels to below 100,000/microliter; 4) manifest symptoms such as right upper quadrant pain and severe headaches; 5) develop pulmonary congestion or edema; 6) develop renal insufficiency (creatinine level doubling or increasing to or above 1.1 mg/dL in women without other renal disease); and 7) have sudden, substantial, and sustained increases in protein excretion.

If the only manifestation is elevation in BP to levels less than 160 mm Hg systolic and 110 mm Hg diastolic and proteinuria, this is considered to be superimposed preeclampsia without severe features. The presence of organ dysfunction is considered to be superimposed preeclampsia with severe features. For classification purposes, both variants are termed "superimposed preeclampsia," but management is guided by the subcategory (analogous to "preeclampsia with severe features" and "preeclampsia without severe features").

Gestational Hypertension

Gestational hypertension is characterized most often by new-onset elevations of BP after 20 weeks of gestation, often near term, in the absence of accompanying proteinuria. The failure of BP to normalize postpartum requires changing the diagnosis to chronic hypertension.

Outcomes in women with gestational hypertension usually are quite successful, although some of these women experience BP elevations to the severe level with outcomes similar to women with preeclampsia (6). The cause of this entity is unclear, but many of these women have preeclampsia before proteinuria and other organ manifestations have occurred. Thus, gestational hypertension, even when BP elevations are mild, requires enhanced surveillance.

Gestational hypertension, although transient in nature, may also be a sign of future chronic hypertension. Thus, even when benign, it is an important marker regarding follow-up and preventive medicine decisions (7).

Postpartum Hypertension

It is important to remember that preeclampsia—including preeclampsia with severe systemic organ involvement and seizures—can first develop in the postpartum period. Because early hospital discharge is the current practice in the United States, this mandates instruction of women at discharge from the hospital to be aware of symptoms (eg, severe headache, visual disturbances, or epigastric pain) that should be reported to a health care provider.

Although not recommended in this classification schema, the task force calls attention to a phenomenon once labeled "late postpartum hypertension," a disorder that was more frequently diagnosed when women in the postpartum period routinely remained hospitalized for as long as 2 weeks. It was defined as women with normotensive gestations who develop hypertension (usually mild) in a period that ranges from 2 weeks to 6 months postpartum. Blood pressure remains labile for months postpartum, usually normalizing by the end of the first year. Little is known of this entity, and, like gestational hypertension, it may be a predictor of future chronic hypertension.

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CHAPTER 2

Establishing the Diagnosis of Preeclampsia and Eclampsia

Specific criteria must be met to establish the diagnosis of preeclampsia, preeclampsia with severe features, and eclampsia. More recent criteria for the definition of preeclampsia have been established based on their association with adverse clinical outcomes. Several preexisting criteria for preeclampsia with severe features have been eliminated based largely on whether evidence suggests that their presence should outline clinical management in the preterm setting.

Preeclampsia

Definition

Preeclampsia is a syndrome that chiefly includes the development of new-onset hypertension in the second half of pregnancy. Although often accompanied by new-onset proteinuria, preeclampsia can be associated with many other signs and symptoms, including visual disturbances, headaches, epigastric pain, and the rapid development of edema.

Diagnostic criteria include the development of *hypertension,* defined as a persistent systolic blood pressure (BP) of 140 mm Hg or higher, or a diastolic BP of 90 mm Hg or higher after 20 weeks of gestation in a women with previously normal blood pressure (1, 2) (Table 2-1). The optimal measurement of BP is made with the patient comfortably seated, legs uncrossed, and the back and arm supported, so that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum). The patient should be instructed to relax and not talk during the measurement procedure; ideally, 5 minutes should elapse before the first reading is taken. If elevated on initial assessment, the BP measurement should be repeated after several minutes to attempt to eliminate spuriously elevated BP determinations (3). It is worth noting that measurement of BP taken in the upper arm with the woman in the left lateral position will falsely lower BP readings because the blood pressure cuff will be above the heart when these readings are made. This approach is discouraged.

Hypertension does not mean that a patient has preeclampsia; other criteria are required. In most cases, this will be new-onset proteinuria, but in the absence of proteinuria that meets or exceeds the diagnostic threshold, any of the following can establish the diagnosis: new-onset thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or visual or cerebral disturbances. *Proteinuria* is defined by the excretion of 300 mg or more of protein in a 24-hour urine collection (or this amount extrapolated from a timed collection) (4). Alternatively, a protein/creatinine ratio of at least 0.3 (each measured as mg/dL) is an equivalent acceptable threshold for the diagnosis to be established because this ratio has been demonstrated to match or exceed a 24-hour urine protein collection of 300 mg (5). A dipstick reading of 1+ also suggests

TABLE 2-1. Diagnostic Criteria for Preeclampsia ⇦

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	• Greater than or equal to 300 mg per 24 hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio greater than or equal to 0.3* • Dipstick reading of 1+ (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/microliter
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	
Cerebral or visual symptoms	

* Each measured as mg/dL.

proteinuria, but because this qualitative method has many false-positive and false-negative results, it should be used for diagnosis only when quantitative methods are not available. Alternatively, the diagnosis may be established by the presence of hypertension as defined previously in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood concentrations of liver transaminases to twice the normal concentration), the new development of 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 cerebral or visual disturbances. Proteinuria is not absolutely required for the diagnosis of preeclampsia (6).

Preeclampsia with the absence of severe manifestations often has been characterized as "mild." It should be noted that this characterization can be misleading; even in the absence of severe disease (defined in this chapter), morbidity and mortality are significantly increased. Therefore, the task force recommends that the term "preeclampsia without severe features" be used instead. Some pregnant women present with a specific constellation of laboratory findings—hemolysis, elevated liver enzymes, and low platelet count—that has been labeled "HELLP syndrome." This constellation of laboratory findings is often considered a preeclamptic subtype. The segregation of HELLP syndrome from thrombotic thrombocytopenic purpura may be helped by the measurement of serum lactate dehydrogenase when additional criteria for preeclampsia are absent (7).

Prediagnostic Findings Warranting Increased Surveillance

Some maternal symptoms, even in the absence of a confirmed diagnosis of preeclampsia, should prompt the obstetric care provider to closely evaluate maternal status for specific signs of preeclampsia. These include the new onset of headache or visual disturbances, as well as abdominal pain, particularly in the right upper quadrant, or epigastric pain.

Additional findings that warrant close observation for the subsequent development of preeclampsia include fetal growth restriction or new-onset proteinuria in the second half of pregnancy (8, 9). Elevations in BP during pregnancy (comparing late pregnancy with early pregnancy) that exceed 15 mm Hg diastolic or 30 mm Hg systolic are common in uncomplicated pregnancies (10). Nevertheless, women who demonstrate this degree of elevation in BP "warrant close observation," as suggested by the National High Blood

Pressure Education Program Working Group (2). Additionally, biochemical markers can be associated with poorer outcomes in women in whom preeclampsia has been diagnosed. These markers may have value in the management of specific patients, but they do not contribute to establishing the diagnosis. Among these markers is uric acid concentration (11). It is important to note that these findings warn that preeclampsia may be impending, which may influence patterns of clinical observation, but the findings do not support the initiation of specific interventions in and of themselves.

Although clinically evident edema or rapid weight gain, or both, may raise the clinical suspicion for preeclampsia, it is not a diagnostic criterion. Nondependent edema occurs in 10–15% of women who remain normotensive throughout pregnancy, and it is neither a sensitive nor specific sign of preeclampsia (12).

Assessing the Severity of Preeclampsia

Some clinical findings increase the risk of morbidity and mortality in the setting of preeclampsia and, when present, segregate preeclampsia into a more severe category (13). The more severe forms of preeclampsia are characterized by the certain findings in women meeting the basic criteria for diagnosing the disorder (Box 2-1). Additionally, women who have met the basic criteria for preeclampsia with systolic BP levels of 140–160 mm Hg or diastolic BP levels of 90–110 mm Hg, along with new evidence of thrombocytopenia, impaired liver dysfunction, renal insufficiency, pulmonary edema, or visual loss or cerebral disturbance, also should be considered as having severe disease.

In view of recent studies that indicate a minimal relationship between the quantity of urinary protein and pregnancy outcome in preeclampsia, massive proteinuria (greater than 5 g) has been eliminated from the consideration of preeclampsia as severe. Also, because fetal growth restriction is managed similarly in pregnant women with and without preeclampsia, it has been removed as a finding indicating severe preeclampsia.

Eclampsia

Eclampsia is defined as the presence of new-onset grand mal seizures in a woman with preeclampsia. Eclampsia can occur before, during, or after labor. Other causes of seizures in addition to eclampsia include a bleeding arteriovenous malformation, ruptured aneurysm, or idiopathic seizure disorder. These alternative diagnoses may be more likely in cases in which new-onset seizures occur after 48–72 hours postpartum or when seizures occur during use of antiepileptic therapy with magnesium sulfate.

BOX 2-1. Severe Features of Preeclampsia (Any of these findings) ⇦

- Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,000/microliter)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive 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
- New-onset cerebral or visual disturbances

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CHAPTER 3

Prediction of Preeclampsia

A great deal of effort has been directed at the identification of demographic factors, biochemical analytes, or biophysical findings, alone or in combination, to predict early in pregnancy the later development of preeclampsia. Evidence relating to the reliability of prediction tests for preeclampsia is reviewed as follows.

Definition of an Ideal Predictive Test

The utility of a predictive test will depend on the overall prevalence of the disease (1). Although sensitivity and specificity have been used to assess how well a test is able to identify patients with a disease, they do not focus on the meaning of a single test result. In this respect, the best way to assess the value of a specific test result is by use of likelihood ratios (2). The likelihood ratio (LR) of a particular test result is the proportion of participants with the target condition who have a positive test result relative to the proportion without the target condition who have the same test result. Because the incidence of preeclampsia is relatively low, screening tests with positive test results require high LRs to adequately predict the disease's probability, and tests with negative results require low LRs to confidently exclude the disorder. Thus, useful prediction for preeclampsia would require a high LR (greater than 10) for a positive test as well as a low LR for a negative result (less than 0.2). Even the most reliable prediction test will only have clinical utility if effective preventive approaches and therapeutic interventions are available or if close follow-up after prediction demonstrates improved maternal or fetal outcomes.

Epidemiology of and Risk Factors for Preeclampsia

A number of clinical circumstances, summarized in Box 3-1, increase the risk of preeclampsia (3). The risk of preeclampsia is increased twofold to fourfold if a patient has a first-degree relative with a medical history of the disorder and is increased sevenfold if preeclampsia complicated a previous pregnancy (3, 4). Multiple gestation is an additional risk factor; triplet gestation is a greater risk than twin gestation. Classic cardiovascular risk factors also are associated with increased probability of preeclampsia, as are maternal age older than 40 years, diabetes, obesity, and preexisting hypertension. The increased prevalence of chronic hypertension and other comorbid medical illnesses in women older than 35 years may explain the increased frequency of preeclampsia among older women. Racial differences in the incidence and severity of preeclampsia have been difficult to assess because of confounding by socioeconomic and cultural factors. Nonetheless, it is important to remember that most cases of preeclampsia occur in healthy nulliparous women with no other obvious risks.

Attempts to predict preeclampsia during early pregnancy using clinical risk factors have revealed modest

BOX 3-1. Risk Factors for Preeclampsia ⇦

- Primiparity
- Previous preeclamptic pregnancy
- Chronic hypertension or chronic renal disease or both
- History of thrombophilia
- Multifetal pregnancy
- In vitro fertilization
- Family history of preeclampsia
- Type I diabetes mellitus or type II diabetes mellitus
- Obesity
- Systemic lupus erythematosus
- Advanced maternal age (older than 40 years)

predictive values, with detection of 37% of those who developed early-onset preeclampsia and 29% who developed late-onset preeclampsia, with false-positive rates of 5% (5). A study, which used an algorithm that included known risk factors for preeclampsia in nulliparous women, detected 37% of women who developed preeclampsia with a false-positive rate of 10% (positive LR = 3.6) (6).

Prediction of Preeclampsia Using Uterine Artery Doppler Velocimetry

The utility of uterine artery Doppler studies to predict preeclampsia has been extensively studied (7). Increased resistance to flow within the uterine arteries results in an abnormal waveform pattern, represented by either an increased resistance or pulsatility indices or by the persistence of a unilateral or bilateral diastolic notch (1). In general, uterine artery Doppler studies are better at predicting early preeclampsia than term preeclampsia (7). Several studies have assessed the predictive value for early-onset preeclampsia and have noted positive LRs that ranged from 5.0 to 20 and negative LRs that ranged from 0.1 to 0.8 (7). It appears that irrespective 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. Major pitfalls with this technique are the wide variability (likely related to operator expertise) and poor predictive accuracy. A review of the literature found no randomized clinical trials that demonstrated improved maternal outcomes or fetal outcomes or both in patients who have undergone uterine artery Doppler screening.

Prediction of Preeclampsia Using Biomarkers

Biomarkers for the prediction of preeclampsia are integral to disease stratification and targeted therapy (1). Results from mechanistic studies not only have provided insights into the pathogenesis of the disease, but also have created opportunities to study circulating and urinary biomarkers to predict the disease (8).

Angiogenesis-Related Biomarkers

Alterations in a number of circulating antiangiogenic proteins (soluble fms-like tyrosine kinase 1 [sFlt-1] and soluble endoglin) and proangiogenic proteins (placenta growth factor [PlGF] and vascular endothelial growth factor [VEGF]) have been evaluated as potential biomarkers for use in preeclampsia (8). Because alterations in concentrations of sFlt-1, PlGF, and soluble endoglin in the maternal circulation precede the clinical onset of preeclampsia by several weeks to months, their predictive potential has been evaluated. Many of the studies focused on sFlt-1, an antiangiogenic protein, as a potential predictor of early-onset preeclampsia (9). Examining odds ratios, sensitivity, and specificity for various sFlt-1 cutoff values in different trimesters led to the conclusion that the higher the sFlt-1 concentration, the more predictive it is of early-onset preeclampsia (1). However, because sFlt-1 is altered only 4–5 weeks before the onset of clinical symptoms, it is not useful when used alone as a screening test earlier in gestation. In contrast, PlGF concentrations begin to decrease 9–11 weeks before the appearance of hypertension and proteinuria, which accelerates during the 5 weeks before the onset of disease (10). There are several studies evaluating first-trimester use of PlGF that reveal, at most, modest predictive values for early-onset preeclampsia. However, combining PlGF concentrations with other biochemical markers, uterine artery Doppler studies, or both, substantially improves the predictive value. One study evaluated 7,797 women with singleton pregnancies during 11–13 weeks of gestation (11).

An algorithm developed by logistic regression that combined the logs of uterine pulsatility index, mean arterial pressure, pregnancy-associated plasma protein A (PAPP-A), serum-free PlGF, body mass index, and presence of nulliparity or previous preeclampsia revealed the following: at a 5% false-positive rate, the detection rate for early preeclampsia was 93.1%; more impressively, the positive LR was 16.5 and the negative LR was 0.06 (11). Although the results of these studies are promising, the task force does not recommend using this for clinical practice because

evidence that maternal–fetal outcomes are improved by early screening is still lacking.

Because PlGF is a small protein, it is easily filtered by the normally functioning kidney; therefore, measuring urinary PlGF combined with confirmation by measuring the circulating sFlt-1/PlGF ratio has been proposed as another strategy for the prediction of preterm preeclampsia (12). In one study, researchers measured sFlt-1, PlGF, and soluble endoglin in 1,622 consecutive pregnant women with singleton gestations during early pregnancy and in midtrimester and found superior performances for the PlGF/soluble endoglin ratio during midtrimester with sensitivity of 100% and specificity of 98% for early-onset preeclampsia (positive LR, 57.6; 95% confidence interval, 37.6–57.6, and negative LR, 0.0; 95% confidence interval, 0.0–0.3) (13). Other studies that used angiogenic markers in high-risk populations have found more modest results (14, 15). None of these findings have been validated in an independent cohort. Future studies to evaluate the clinical utility of early prediction using biomarkers as it relates to preeclampsia-related adverse maternal–fetal outcomes are needed.

Placental Protein-13 and Other Markers

A few studies have suggested first-trimester circulating levels of placental protein-13 are significantly lower in women who go on to develop early-onset preeclampsia and preterm birth (16, 17). Combining first-trimester placental protein-13 with other predictive markers may further improve predictive performance. One study suggested that 14 different plasma metabolites have robust discriminatory power in identifying preeclampsia at 15 weeks of gestation (18). Larger prospective studies are needed to determine whether these novel biomarkers will be valuable for the prediction of early preeclampsia.

Prediction of Adverse Outcomes in Patients With Gestational Hypertension and Preeclampsia

Biomarkers also may be useful to evaluate adverse outcomes in patients who present with gestational hypertension or preeclampsia. Uric acid has been extensively studied in this setting, and elevated concentrations have been suggested as useful in identifying women with gestational hypertension who may progress to preeclampsia, develop adverse maternal–fetal outcomes, or both (19–21). A recent prospective study suggested that uric acid might be an accurate predictor in this population, with a positive predictive value of 91.4% for a cutoff of 5.2 mg/dL (22). Circulating angiogenic factors also have been evaluated in the triage setting in women with suspicion of preeclampsia and have been found to be of potential use in identifying subsequent adverse maternal–fetal outcomes (23–25). Among participants who presented preterm (less than 34 weeks of gestation), an sFlt-1/PlGF ratio of 85 or greater had a positive predictive value of 86.0% and a positive LR of 12.2 for predicting adverse maternal–fetal outcomes occurring within 2 weeks of presentation (24).

The greatest utility of these tests would be to rule out progression of gestational hypertension to preeclampsia or adverse outcomes. Angiogenic factors also have been evaluated for this purpose. In one study, among participants who were evaluated in the triage unit before 34 weeks of gestation (n=176), a plasma sFlt-1/PlGF ratio of less than 85 had a negative predictive value of 87.3% and a negative LR of 0.29 (24). A total of 16 women had false-negative test results; 10 of them had adverse outcomes that could not be attributed to preeclampsia. Another study found that a PlGF/sFlt-1 ratio of 0.033 multiples of the median had a 93% sensitivity with a negative LR of 0.09 for the identification of patients who presented at less than 34 weeks of gestation and who gave birth within 14 days because of preeclampsia (25). The availability of biomarkers to quickly and accurately assess at initial presentation the risk of progression to preeclampsia or to adverse outcomes could greatly aid in the management of patients with gestational hypertension. Similarly, being able to differentiate preeclampsia that would or would not be associated with adverse outcomes would be useful to guide management. However, both of these demand high certainty (negative predictive value and low negative LRs) that the patient will not progress to adverse outcomes. Large prospective trials evaluating the clinical utility of biomarkers in this context are needed before recommendations can be made.

Clinical Considerations

As of 2012, no single test reliably predicts preeclampsia. Extensive work clearly identifies angiogenic factors—especially sFlt-1, PlGF, and soluble endoglin early in the second trimester—as likely tools for the prediction of early-onset preeclampsia; however, this requires further investigation (1). Current evidence suggests that a combination of these biomarkers along with uterine artery Doppler studies may provide the best predictive accuracy for the identification of early-onset preeclampsia (26). It also is important for practicing obstetricians to realize that these biomarkers are

not approved by the U.S. Food and Drug Administration and, therefore, are not available for clinical use. Standardization of these assays across the various automated platforms and prospective studies that demonstrate clinical utility are needed. No evidence was located to support the hypothesis that accurate prediction of early-onset preeclampsia can be followed by interventions or close follow-up that improve maternal outcome or fetal outcome or both. The use of predictors to differentiate women with gestational hypertension who are at risk of progression to preeclampsia or adverse outcomes would be useful. Tests for this purpose demand high certainty that outcomes will not be bad and demand rigorous testing for clinical utility, which has not yet taken place.

TASK FORCE RECOMMENDATION

- Screening to predict preeclampsia beyond obtaining an appropriate medical history to evaluate for risk factors is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

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CHAPTER 4

Prevention of Preeclampsia

Strategies to prevent preeclampsia have been studied extensively over the past 20 years. No intervention to date has been proved unequivocally effective.

Antiplatelet Agents

It has been hypothesized that alterations in systemic prostacyclin–thromboxane balance contribute to preeclampsia. Furthermore, inflammation is increased in preeclampsia (1). Low-dose aspirin (81 mg or less), an antiinflammatory agent that blocks the production of thromboxanes, has been studied in dozens of trials for the prevention of preeclampsia, both in high-risk groups and in healthy nulliparous women. For women at high risk of preeclampsia, several small, early trials suggested daily aspirin had a significant protective effect (2, 3). These initially promising findings were not confirmed in three large randomized controlled trials (4–6). All three studies found a nonsignificant trend toward a lower incidence of preeclampsia in the aspirin-treated groups with no major adverse effects. A subsequent comprehensive meta-analysis of antiplatelet agents to prevent preeclampsia that included more than 30,000 women from 31 trials at varying risk statuses suggested that antiplatelet agents have a modest benefit, with a relative risk (RR) of preeclampsia of 0.90 (95% confidence interval [CI], 0.84–0.97) for aspirin-treated participants (7).

A follow-up Cochrane meta-analysis of 59 trials with more than 37,000 women found a 17% reduction in risk of preeclampsia associated with use of antiplatelet agents, with a significant increase in absolute risk reduction in women who are at high risk of the disease (7). Concern remains that this finding may reflect publication bias (ie, a small, early, positive trial is more likely to be published than a small, negative trial) or chance findings because the largest trials in the analysis did not show a significant protective effect. Nevertheless, low-dose aspirin appears to be safe with no major adverse effects or evidence of increased bleeding or abruptio placentae. The number of patients needed to treat is determined by the disease prevalence and the effect size of the treatment. For low-risk women with a prevalence of 2%, it would be necessary to treat 500 women to prevent one case of preeclampsia. In contrast, among high-risk women with a prevalence of 20%, it would be necessary to treat 50 women to prevent one case of preeclampsia (see Table 4-1 for numbers needed to treat based on prevalence.) Several high-risk conditions (chronic hypertension, previous preterm preeclampsia, and diabetes) exhibit this degree of risk. Given the modest but significant protective effect, low-dose aspirin prophylaxis may be considered as primary prevention for preeclampsia in women at high baseline risk and, if used, should be initiated in the late first trimester (8).

TABLE 4-1. PARIS number needed-to-treat with sample baseline event rates ⇦

	Sample baseline event rate	PARIS relative risk (95%CI)	Number needed-to-treat (95% CI)
Pre-eclampsia	18%	0·90 (0·84–0·97)	56 (35–185)
	6%		167 (104–556)
	2%		500 (313–1667)
Preterm <34 weeks	20%	0·90 (0·83–0·98)	50 (29–250)
	10%		100 (59–500)
	2%		500 (294–2500)
Perinatal death	7%	0·91 (0·81–1·03)	159 (75–476)
	4%		278 (132–833)
	1%		1111 (526–3333)
Small for gestational age baby	15%	0·90 (0·81–1·01)	67 (35–667)
	10%		100 (53–1000)
	1%		1000 (526–10 000)
Pregnancy with serious adverse outcome	25%	0·90 (0·85–0·96)	40 (27–100)
	15%		67 (44–167)
	7%		143 (95–357)

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TASK FORCE RECOMMENDATION

- For women with a medical history of early-onset preeclampsia and preterm delivery at less than 34 0/7 weeks of gestation or preeclampsia in more than one prior pregnancy, initiating the administration of daily low-dose (60–80 mg) aspirin beginning in the late first trimester is suggested.*

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

*Meta-analysis of more than 30,000 women in randomized trials of aspirin to prevent preeclampsia indicates a small reduction in the incidence and morbidity of preeclampsia and reveals no evidence of acute risk, although long-term fetal effects cannot be excluded. The number of women to treat to have a therapeutic effect is determined by prevalence. In view of maternal safety, a discussion of the use of aspirin in light of individual risk is justified.

Antioxidant Supplementation With Vitamin C and Vitamin E

Because oxidative stress appears to contribute to the pathogenesis of preeclampsia, it has been suggested that antioxidants may prevent preeclampsia. Despite initial enthusiasm for using a combination of the antioxidants vitamin C and vitamin E for this purpose, large randomized, placebo-controlled trials conducted during pregnancy found that supplementation with vitamin C and vitamin E did not reduce the risk of preeclampsia or improve maternal and fetal outcomes in various populations (9–12). A recent Cochrane systematic review of 15 randomized controlled trials (20,748 women) that used vitamin C and vitamin E for the prevention of preeclampsia found no benefit (RR, 0.94; 95% CI, 0.82–1.07) (13).

TASK FORCE RECOMMENDATION

- The administration of vitamin C or vitamin E to prevent preeclampsia is not recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

Other Nutritional Interventions

Several studies have examined the effectiveness of calcium supplementation to prevent preeclampsia. In a large U.S. cohort of healthy primiparous women, calcium supplementation did not reduce incidence of preeclampsia (14). However, calcium supplementation might be expected to be of greater benefit in women who have a nutritional deficiency of calcium. A meta-analysis of 13 trials that involved 15,730 women reported a significant reduction in preeclampsia risk with calcium supplementation (RR, 0.45; 95% CI, 0.31–0.65), with the greatest effect among women with low baseline calcium intake (RR, 0.36; 95% CI, 0.20–0.65) (15). Thus, calcium supplementation (1.5–2 g) may be considered in pregnant women from populations with low baseline calcium intake (less than

600 mg/d). This is not the case in the United States or other developed countries.

Vitamin D deficiency has been suggested as a factor contributing to preeclampsia (16); however, whether supplementation with vitamin D is helpful is unknown. Evidence is insufficient for reliable conclusions with regard to other nutritional interventions, such as fish oil or garlic, which have been used to prevent preeclampsia. Protein and calorie restriction for obese pregnant women shows no reduction in the risk of preeclampsia or gestational hypertension and may increase the risk of intrauterine growth restriction and should be avoided.

Dietary Salt Intake

One systematic review of all the trials that studied sodium restriction (603 women) found no significant benefits (RR, 1.11) (17). However, the trials may not have had adequate power to detect a benefit. Similarly, meta-analysis of approximately 7,000 randomized patients from clinical trials suggested that diuretics did not reduce the incidence of preeclampsia (18).

TASK FORCE RECOMMENDATION

- It is suggested that dietary salt not be restricted during pregnancy for the prevention of preeclampsia.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Lifestyle Modifications

Although bed rest has been suggested as a preventive strategy, the evidence for this is scarce (19). The only two studies located that evaluated bed rest as a preventive strategy were both small (32 participants and 72 participants) and did not evaluate perinatal and maternal morbidity and mortality and adverse effects of bed rest. However, regular exercise has been hypothesized to prevent preeclampsia by improving vascular function (20, 21). In women who are not pregnant, moderate exercise has been shown to reduce hypertension and cardiovascular disease. Thirty minutes of moderate exercise on most days is currently recommended during normal pregnancy (22). Moderate exercise also has been hypothesized to stimulate placental angiogenesis and improve maternal endothelial dysfunction. Several small clinical trials have evaluated the utility of modest exercise for the prevention of preeclampsia, but the CIs were too wide to make any reliable conclusions about the efficacy (23). Large randomized controlled clinical trials are needed that can evaluate whether moderate exercise can reverse markers of endothelial dysfunction and prevent adverse pregnancy outcomes.

TASK FORCE RECOMMENDATION

- It is suggested that bed rest or the restriction of other physical activity not be used for the primary prevention of preeclampsia and its complications.

  Quality of evidence: Low
  Strength of recommendation: Qualified

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CHAPTER 5

Management of Preeclampsia and HELLP Syndrome

⇦49 ⇦83

The first consideration in the management of women with mild gestational hypertension or preeclampsia without severe features is always safety of the woman and her fetus. The second is delivery of a mature newborn that will not require intensive or prolonged neonatal care (1). Once the diagnosis of mild gestational hypertension or preeclampsia without severe features is established, subsequent management will depend on the results of maternal and fetal evaluation, gestational age, presence of labor or rupture of membranes, vaginal bleeding, and wishes of the woman (Fig. 5-1).

Antepartum Management

Initial Evaluation

At time of diagnosis, all women should have a complete blood count (CBC) with platelet count and assessment of serum creatinine and liver enzyme levels, be evaluated for urine protein (24-hour collection or protein/creatinine ratio), and be asked about symptoms of severe preeclampsia. Fetal evaluation should include ultrasonographic evaluation for estimated fetal weight and amniotic fluid index (calculated in centimeters), nonstress test (NST), and biophysical profile (BPP) if NST is nonreactive. Best practice indicates hospitalization and delivery for one or more of the following:

- 37 0/7 weeks or more of gestation
- Suspected abruptio placentae
- 34 0/7 weeks or more of gestation, plus any of the following:
  - Progressive labor or rupture of membranes
  - Ultrasonographic estimate of fetal weight less than fifth percentile
  - Oligohydramnios (persistent amniotic fluid index less than 5 cm)
  - Persistent BPP 6/10 or less (normal 8/10–10/10)

For women who have not given birth, management can occur in the hospital or at home with restricted activity and serial maternal and fetal evaluation.

Continued Evaluation

Continued evaluation of women who have not given birth who have mild gestational hypertension or preeclampsia without severe features consists of the following:

- Fetal evaluation includes daily kick count, ultrasonography to determine fetal growth every 3 weeks, and amniotic fluid volume assessment at least once weekly. In addition, an NST once weekly for patients with gestational hypertension and an NST twice weekly for patients with preeclampsia without severe features is suggested. The presence of a nonreactive NST requires BPP testing. The frequency of these tests may be modified based on subsequent clinical findings.

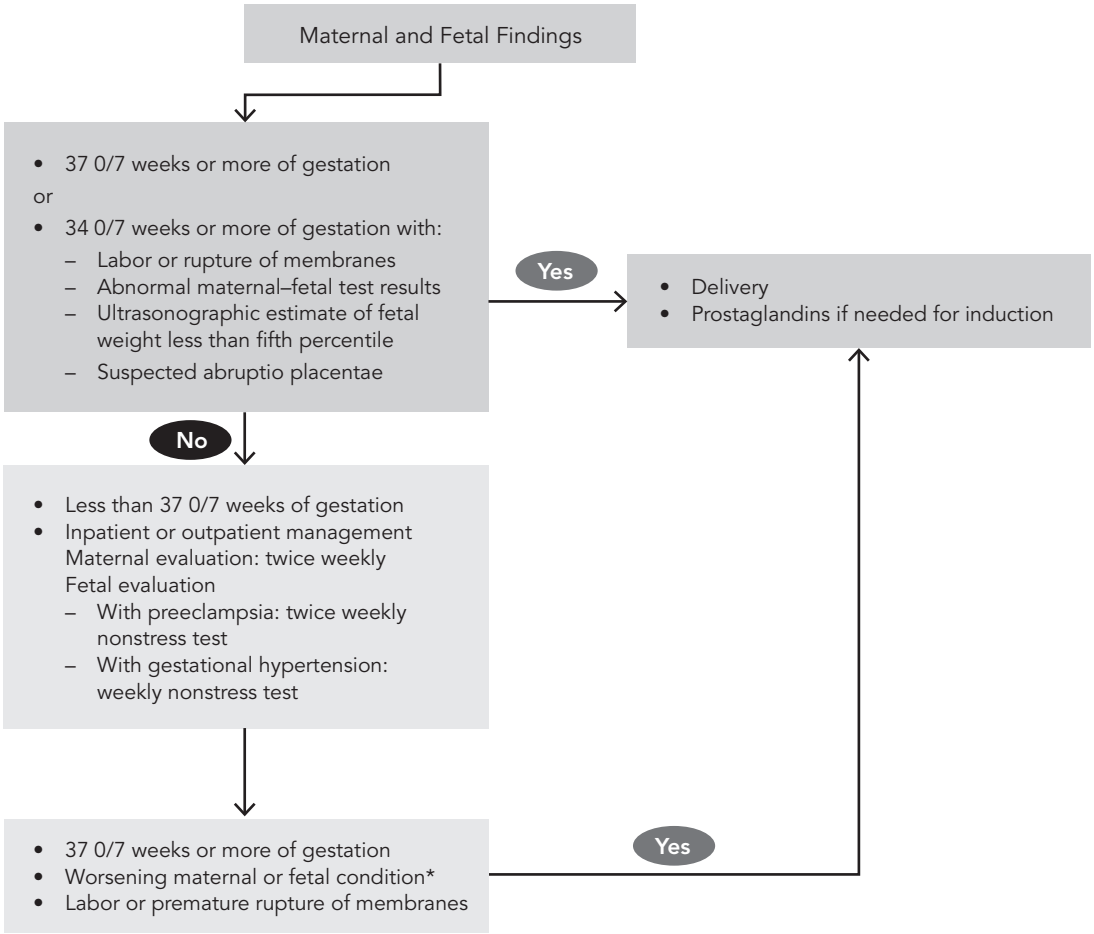

FIGURE 5-1. Management of mild gestational hypertension or preeclampsia without severe features. ⇦

- At the time of office or clinic visit for antenatal testing, blood pressure (BP) is to be assessed. In patients with gestational hypertension, an additional BP determination should be performed in addition to that obtained at the weekly NST. This additional BP determination may be performed in the office or at home. Further, women with gestational hypertension are to be evaluated for proteinuria at each antenatal visit, but following the diagnosis of preeclampsia, additional evaluation of proteinuria is no longer necessary.
- Maternal laboratory evaluation includes a CBC and liver enzyme and serum creatinine level assessment at least once a week. The frequency of these tests may be modified based on subsequent clinical findings.
- Patients are instructed to have a regular diet with no salt restriction.
- At the time of diagnosis and at each subsequent visit, women are instructed to report symptoms of severe preeclampsia (severe headaches, visual changes, epigastric pain, and shortness of breath). They also are advised to immediately come to the hospital or office if they develop persistent symptoms, abdominal pain, contractions, vaginal spotting, rupture of membranes, or decreased fetal movements.
- During management outside of the hospital, the onset of decreased fetal movement or abnormal fundal height growth (less than 3 cm of what is expected for gestational age) requires prompt fetal testing with NST and estimation of amniotic

fluid volume. The development of new signs or symptoms of severe preeclampsia or severe hypertension (systolic BP of 160 mm Hg or higher or diastolic BP of 110 mm Hg or higher on repeat measurements) or evidence of fetal growth restriction require immediate hospitalization. In addition, an increased concentration of liver enzymes or thrombocytopenia requires hospitalization.

In women with mild gestational hypertension, the progression to severe gestational hypertension or preeclampsia often develops within 1–3 weeks after diagnosis, whereas in women with preeclampsia without severe features, the progression to severe preeclampsia could happen within days (2).

TASK FORCE RECOMMENDATIONS

- The close monitoring of women with gestational hypertension or preeclampsia without severe features with serial assessment of maternal symptoms and fetal movement (daily by the woman) and serial measurements of BP (twice weekly), and assessment of platelet counts and liver enzymes (weekly) is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- For women with gestational hypertension, monitoring at least once weekly with proteinuria assessment in the office and with an additional weekly measurement of BP at home or in the office is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

Antihypertensive Therapy

Antihypertensive therapy is used to prevent severe gestational hypertension and maternal hemorrhagic strokes. Overall, there is no consensus regarding the management of nonsevere hypertension; prior trials have not been designed to define the maternal and perinatal benefits and risks. Therapy may decrease progression to severe hypertension but also may be associated with impairment of fetal growth (3–6). A recent systematic review of 46 trials (4,282 women) evaluated BP control in women with mild to moderate hypertension (4, 6). The authors concluded that it is unclear whether antihypertensive therapy is worthwhile. In trials that compared therapy with placebo, the risk of developing severe hypertension was cut in half (risk ratio [RR], 0.50; 95% confidence interval [CI], 0.41–0.61) but no effect on the development of or progression to preeclampsia (RR, 0.97; 95% CI, 0.83–1.13), eclampsia, pulmonary edema, fetal or neonatal death (RR, 0.73; 95% CI, 0.50–10.8), preterm birth (RR, 1.02; 95% CI, 0.89–1.16), or small-for-gestational-age infants (RR, 1.04; 95% CI, 0.84–1.27) (7). Of 29 trials that evaluated oral β-blockers, these agents were found to be associated with a decrease in risk of severe hypertension (RR, 0.37; 95% CI, 0.26–0.53) but with an increase in the rate of small-for-gestational-age infants (RR, 1.36; 95% CI, 1.02–1.82) (7). These reviews concluded that there was insufficient evidence that treatment of nonsevere hypertension improves maternal and neonatal outcomes (4, 7). The National Institute for Health and Clinical Excellence guidelines recommended treatment at BP levels at 150 mm Hg systolic or 100 mm Hg diastolic, or both (8). Given the rarity of cerebral hemorrhage and congestive heart failure and their lack of association with gestational hypertension, antihypertensive therapy for this outcome is not beneficial in patients with mild to moderate gestational hypertension, and treatment exposes the woman and her fetus to potentially harmful medications without clear evidence of benefit (9, 10). In addition, concern exists that reducing maternal BP may compromise blood flow to the fetoplacental unit (11).

TASK FORCE RECOMMENDATION

- For women with mild gestational hypertension or preeclampsia with a persistent BP of less than 160 mm Hg systolic or 110 mm Hg diastolic, it is suggested that antihypertensive medications not be administered.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

Bed Rest

Complete or partial bed rest has been recommended to improve pregnancy outcome in women with gestational hypertension or preeclampsia without severe features. However, a Cochrane review of four randomized trials that compared bed rest with no rest in pregnant women with mild hypertension found insufficient evidence to provide guidance for clinical practice, suggesting that bed rest should not routinely be recommended for management of hypertension in pregnancy (12). In addition, prolonged bed rest for the duration of pregnancy increases the risk of thromboembolism.

TASK FORCE RECOMMENDATION

- For women with gestational hypertension or preeclampsia without severe features, it is suggested that strict bed rest not be prescribed.*†

  Quality of evidence: Low
  Strength of recommendation: Qualified

*The task force acknowledged that there may be situations in which different levels of rest, either at home or in the hospital, may be indicated for individual women. The previous recommendations do not cover advice regarding overall physical activity and manual or office work.

†Women may need to be hospitalized for reasons other than bed rest, such as for maternal and fetal surveillance. The task force agreed that hospitalization for maternal and fetal surveillance is resource intensive and should be considered as a priority for research and future recommendations.

Fetal Testing

Maternal hypertension or preeclampsia is a known risk factor for perinatal death and is a common indication for antenatal testing. Limited to no data exist regarding when to start fetal testing, the frequency of testing, and which test to use in the absence of fetal growth restriction (13). In the absence of randomized trials comparing testing versus no testing, it remains unclear whether antenatal fetal testing improves outcome in these pregnancies (14).

TASK FORCE RECOMMENDATIONS

- For women with preeclampsia without severe features, use of ultrasonography to assess fetal growth and antenatal testing to assess fetal status is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- If evidence of fetal growth restriction is found in women with preeclampsia, fetoplacental assessment that includes umbilical artery Doppler velocimetry as an adjunct antenatal test is recommended.

  Quality of evidence: Moderate
  Strength of the recommendation: Strong

Intrapartum Management

Timing of Delivery

In women with mild gestational hypertension or preeclampsia without severe features between 34 0/7 weeks of gestation and 37 0/7 weeks of gestation, there are no randomized controlled trials that indicate that expectant management will either improve perinatal outcomes or increase maternal or fetal risks. The risks associated with expectant management include the development of severe hypertension (10–15%), eclampsia (0.2–0.5%), HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome (1–2%), abruptio placentae (0.5–2%), fetal growth restriction (10–12%), and fetal death (0.2–0.5%) (15). However, immediate delivery is associated with increased rates of admission to the neonatal intensive care unit, neonatal respiratory complications, and a slight increase in neonatal death compared with infants born at or beyond 37 0/7 weeks of gestation. Therefore, considering the risk–benefit ratio between the two management plans, available retrospective data suggest that the balance should be in favor of continued monitoring and delivery to 37 0/7 weeks of gestation in the absence of abnormal fetal testing or other severe conditions (eg, premature rupture of membranes, preterm labor, or vaginal bleeding) (15).

TASK FORCE RECOMMENDATION

- For women with mild gestational hypertension or preeclampsia without severe features and no indication for delivery at less than 37 0/7 weeks of gestation, expectant management with maternal and fetal monitoring is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

In women with mild gestational hypertension or preeclampsia without severe features, a large multicenter trial from the Netherlands was conducted, which included 756 women with singleton gestations at 36–41 6/7 weeks of gestation who were allocated to induction of labor or expectant monitoring (16). The primary outcome was a composite of adverse maternal outcome (new-onset severe preeclampsia, HELLP syndrome, eclampsia, pulmonary edema, or abruptio placentae). Secondary outcomes were neonatal morbidities and rate of cesarean delivery. Induction of labor was associated with a significant reduction in composite adverse maternal outcome (RR, 0.71; 95% CI, 0.59–0.86) but no differences in rates of neonatal complications or cesarean delivery.

TASK FORCE RECOMMENDATION

- For women with mild gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery rather than continued observation is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

Magnesium Sulfate Prophylaxis

There are only two double-blind, placebo controlled trials that have evaluated the use of magnesium sulfate in women with preeclampsia without severe features (17, 18). No instances of eclampsia occurred among 181 women assigned to placebo, and no differences occurred in the percentage of women who progressed to severe preeclampsia (12.5% in magnesium group versus 13.8% in the placebo group; RR, 0.90; 95% CI, 0.52–1.54). However, the number of women enrolled in these trials is too limited to draw any valid conclusions (17, 18). Based on a rate of eclampsia of 0.5%, and assuming a 50% reduction by magnesium sulfate (0.25% rate) ($\alpha = .05$ and $\beta = 0.2$) approximately 10,000 women would need to be enrolled in each group to find a significant reduction in eclampsia in women with preeclampsia without severe features treated with magnesium sulfate (17). The number of women necessary to be studied to address serious maternal morbidity other than eclampsia is even higher (18).

Although the universal use of magnesium sulfate therapy in preeclampsia without severe features is not recommended, certain signs and symptoms (headache, altered mental state, blurred vision, scotomata, clonus, and right upper quadrant abdominal pain) have traditionally been considered as premonitory to seizures and should be considered in the choice for initiation of magnesium sulfate therapy. Because the clinical course of women with preeclampsia without severe features can suddenly change during labor, all women with preeclampsia without severe features who are in labor must be monitored closely for early detection of progression to severe disease. This should include monitoring of BP and maternal symptoms during labor and delivery as well as immediately postpartum. Magnesium sulfate therapy should then be initiated if there is progression to severe disease.

TASK FORCE RECOMMENDATION

- For women with preeclampsia with systolic BP of less than 160 mm Hg and a diastolic BP of less than 110 mm Hg and no maternal symptoms, it is suggested that magnesium sulfate not be administered universally for the prevention of eclampsia.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Antihypertensive Drugs to Treat Severe Hypertension in Pregnancy

The objectives of treating severe hypertension are to prevent potential cardiovascular (congestive heart failure and myocardial ischemia), renal (renal injury or failure), or cerebrovascular (ischemic or hemorrhagic stroke) complications related to uncontrolled severe hypertension. No randomized trials in pregnancy could be identified to determine the level of hypertension to treat to prevent these complications. Data from case series—as well as from developing countries where antihypertensive medications were not used in women with severe gestational hypertension or severe preeclampsia—reveal increased rates of heart failure, pulmonary edema, and death. These life-threatening maternal complications justify recommending the use of medications to lower BP to a safe range even though the magnitude of this risk is unknown.

Several randomized trials compared different antihypertensive drugs in pregnancy. In these trials, parenteral hydralazine was compared with labetalol or oral nifedipine. An updated Cochrane systematic review of 35 trials that involved 3,573 women found no significant differences regarding either efficacy or safety between hydralazine and labetalol, or between hydralazine and any calcium channel blocker (19). The results of these trials suggest that hydralazine, labetalol, or oral nifedipine can be used to treat acute severe hypertension in pregnancy as long as the medical provider is familiar with the drug to be used, including dosage, expected time of onset of action, and potential adverse effects and contraindications (19).

Theoretical concern exists that the combined use of nifedipine and magnesium sulfate can result in excessive hypotension and neuromuscular blockade. A review on the subject concluded that the combined use of these drugs does not increase such risks; however, this recommendation was based on limited data (20).

In women requiring antihypertensive medications for severe hypertension, the choice and route of administration of drugs should be based primarily on the physician's familiarity and experience, adverse effects and contraindications to the prescribed drug, local availability, and cost.

TASK FORCE RECOMMENDATION

- For women with preeclampsia with severe hypertension during pregnancy (sustained systolic BP of at least 160 mm Hg or diastolic BP of at least 110 mm Hg), the use of antihypertensive therapy is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Severe Preeclampsia

Severe preeclampsia can result in both acute and long-term complications for both the woman and her newborn (1, 4, 21–23). Maternal complications of severe preeclampsia include pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome, coagulopathy, severe renal failure, and retinal injury. These complications are more likely to occur in the presence of preexistent medical disorders and with acute maternal organ dysfunction related to preeclampsia (1, 21–23). Fetal and newborn complications of severe preeclampsia result from exposure to uteroplacental insufficiency or from preterm birth, or both (1, 21–23).

The clinical course of severe preeclampsia is often characterized by progressive deterioration of maternal and fetal conditions if delivery is not pursued (21–23). Therefore, in the interest of the woman and her fetus, delivery is recommended when gestational age is at or beyond 34 0/7 weeks. In addition, prompt delivery is the safest option for the woman and her fetus when there is evidence of pulmonary edema, renal failure, abruptio placentae, severe thrombocytopenia, disseminated intravascular coagulation, persistent cerebral symptoms, nonreassuring fetal testing, or fetal demise irrespective of gestational age in women with severe preeclampsia at less than 34 0/7 weeks of gestation (21–23) (Fig. 5-2).

TASK FORCE RECOMMENDATION

- For women with severe preeclampsia at or beyond 34 0/7 weeks of gestation, and in those with unstable maternal–fetal conditions irrespective of gestational age, delivery soon after maternal stabilization is recommended.

  Quality of data: Moderate
  Strength of recommendation: Strong

Expectant Management

Randomized Trials

The task force found only two published randomized trials of delivery versus expectant management of preterm severe preeclampsia (24, 25). One group of researchers studied 38 women with severe preeclampsia between 28 weeks of gestation and 34 weeks of gestation (24). Eighteen women received antenatal corticosteroids for fetal maturation and were then treated expectantly, with delivery only for specific maternal or fetal indications. Another 20 patients were assigned to receive antenatal corticosteroids with planned delivery after 48 hours. Latency to delivery (7.1 days versus 1.3 days; $P<.05$) and gestational age at delivery (223 days versus 221 days; $P<.05$) were both greater with expectant management, whereas total neonatal complications were reduced (33% versus 75%; $P<.05$) compared with planned delivery. Another group of researchers studied 95 women with severe preeclampsia and no concurrent medical (renal disease, type 1 diabetes mellitus, or connective tissue disease) or obstetric (vaginal bleeding, premature rupture of membranes, multifetal gestation, or preterm labor) complications at 28–32 weeks of gestation (25). Those randomized to receive expectant management gave birth at a more advanced gestational age (32.9 weeks of gestation versus 30.8 weeks of gestation; $P=.01$) and had newborns who required less frequent neonatal intensive care unit admission (76% versus 100%; $P<.01$), had less frequent respiratory distress syndrome (22.4% versus 50%; $P=.002$), and had less frequent necrotizing enterocolitis (0% versus 10.9%; $P=.02$), but more frequent small-for-gestational-age birth weight (30.1 versus 10.9; $P=.04$). No cases of maternal eclampsia or pulmonary edema were reported in either trial. Cases of abruptio placentae were similar in frequency between the randomized groups in both studies; HELLP syndrome complicated only two expectantly managed cases and one aggressively managed case in the latter study (4.1% versus 2.1%).

Observational Studies

Observational studies of expectant management of severe preeclampsia have varied in their inclusion criteria and indications for delivery (21–23, 26). Some included only women who remained stable after 24–48 hours of observation, whereas others included women expectantly managed from the time of diagnosis. In one review, maternal outcomes for expectant management of severe preeclampsia at less than 34 weeks of gestation (presented as median percentile; interquartile range) included intensive care unit admission, 27.6 (1.5, 52.6); HELLP syndrome, 11.0 (5.3, 17.6); recurrent severe hypertension, 8.5 (3.3, 27.5); abruptio placentae, 5.1 (2.2, 8.5); pulmonary edema, 2.9 (1.4, 4.3); eclampsia, 1.1 (0, 2.0); subcapsular liver hematoma, 0.5 (0.2, 0.7); and stroke, 0.4 (0, 3.1) (26). Perinatal outcomes in this study included stillbirth, 2.5 (0, 11.3); neonatal death, 7.3 (5.0, 10.7); perinatal asphyxia, 7.4 (5.0, 10.0); and any neonatal complication, 65.9 (39.7, 75.7) (26). Small-for-gestational-age infants were common (30–50%) after expectant management. Indications for delivery with expectant management of severe preeclampsia at less than 34 weeks of gesta-

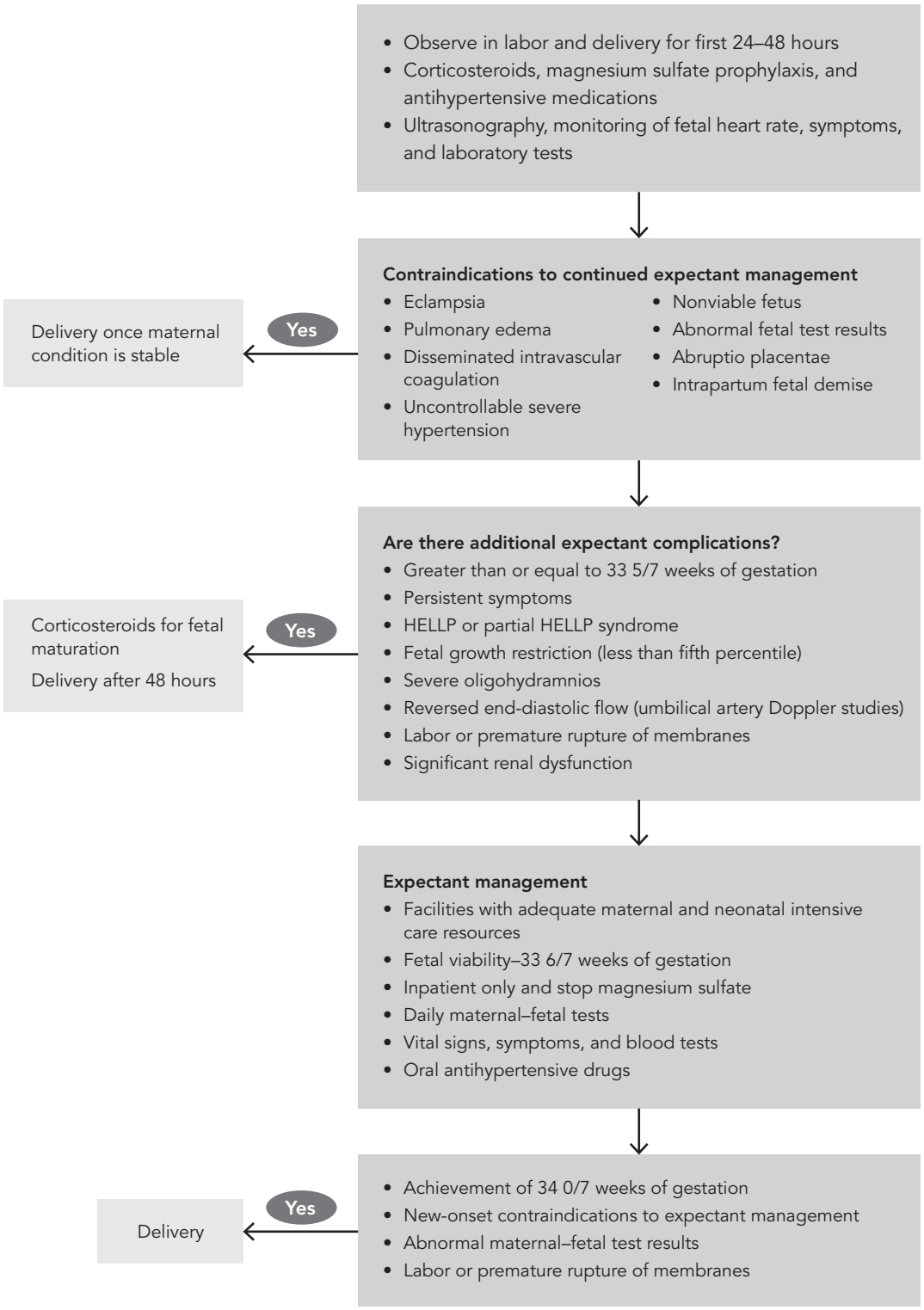

FIGURE 5-2. Management of severe preeclampsia at less than 34 weeks of gestation. ⇦

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

tion were fetal (36%), maternal (40%), or maternal and fetal (8.8%) (26). The frequency of these complications, however, is unknown in the absence of expectant management.

TASK FORCE RECOMMENDATION

- For women with severe preeclampsia at less than 34 0/7 weeks of gestation with stable maternal and fetal conditions, it is recommended that continued pregnancy be undertaken only at facilities with adequate maternal and neonatal intensive care resources.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Corticosteroids for Fetal Lung Maturity

Although data specific to expectantly managed severe preeclampsia are limited, randomized controlled trials that involved pregnancies complicated by hypertension syndromes have found antenatal corticosteroid treatment to result in less frequent respiratory distress syndrome (RR, 0.50; 95% CI, 0.35–0.72), neonatal death (RR, 0.50; 95% CI, 0.29–0.87), and intraventricular hemorrhage (RR, 0.38; 95% CI, 0.17–0.87) (27). In a single placebo-controlled study of weekly betamethasone for women with severe preeclampsia between 26 weeks of gestation and 34 weeks of gestation, treatment (mean exposure 1.7 doses) reduced the frequency of respiratory distress syndrome (RR, 0.53; 95% CI, 0.35–0.82) and intraventricular hemorrhage (RR, 0.35; 95% CI, 0.15–0.86), among other complications (28). If not previously given, and if it is anticipated that there will be time for fetal benefit from this intervention, antenatal corticosteroid administration should be considered regardless of a plan for expectant management.

TASK FORCE RECOMMENDATION

- For women with severe preeclampsia receiving expectant management at 34 0/7 weeks or less of gestation, the administration of corticosteroids for fetal lung maturity benefit is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

Severe Proteinuria

The presence of severe proteinuria in women with severe preeclampsia undergoing expectant management is not associated with worse outcomes. In one study of 42 expectantly managed women with severe proteinuria (defined as 5 g/24 h or greater), significant pregnancy prolongation occurred, maternal complications were not increased, and resolution of renal dysfunction occurred in all women by 3 months after delivery (29). A second study categorized women with severe preeclampsia according to the severity of proteinuria as mild (less than 5 g/24 h), severe (5–9.9 g/24 h), or massive (more than 10 g/24 h) (30). No differences in the rates of eclampsia, abruptio placentae, pulmonary edema, HELLP syndrome, neonatal death, or neonatal morbidity were identified between these groups. Although the amount of proteinuria increases over time with expectant management, this change is not predictive of pregnancy prolongation or perinatal outcomes (29). On the basis of these data, severe proteinuria alone and the degree of change in proteinuria should not be considered criteria to avoid or terminate expectant management.

TASK FORCE RECOMMENDATION

- For women with preeclampsia, it is suggested that a delivery decision should not be based on the amount of proteinuria or change in the amount of proteinuria.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Management Before the Limit of Fetal Viability

Severe preeclampsia that develops near the limit of fetal viability is associated with a high likelihood of perinatal morbidities and mortality, regardless of expectant management (21–23, 26, 31, 32). However, data regarding outcomes with expectant management categorized by gestational week at diagnosis are limited. Survival rates of 0/34 (0%), 4/22 (18.2%), and 15/26 (57.7%) have been reported after expectant management of severe preeclampsia initiated before 23 0/7 weeks of gestation, at 23 0/7 weeks of gestation, and at 24 0/7 weeks of gestation, respectively (21, 23, 31). Other reports also have suggested rare survival with expectant management of severe preeclampsia at less than 23–24 weeks of gestation (32). Explicit counseling regarding the likelihood of poor perinatal outcomes—including severe respiratory distress syndrome, chronic lung disease, and severe intraventricular hemorrhage—with expectant management should be provided. This is especially important in the presence of severe fetal growth restriction at less than 23 0/7 weeks of gestation, when the perinatal mortality rate approaches 100% (31, 32). Further, maternal complications such as

HELLP syndrome, pulmonary edema, and renal failure must be balanced with poor perinatal outcome.

TASK FORCE RECOMMENDATION

- For women with severe preeclampsia and before fetal viability, delivery after maternal stabilization is recommended. Expectant management is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Maternal and Fetal Monitoring

During expectant management, maternal and fetal conditions should be frequently monitored as follows:

Maternal assessment

- Vital signs, fluid intake, and urine output should be monitored at least every 8 hours
- Symptoms of severe preeclampsia (headaches, visual changes, retrosternal pain or pressure, shortness of breath, nausea and vomiting, and epigastric pain) should be monitored at least every 8 hours
- Presence of contractions, rupture of membranes, abdominal pain, or bleeding should be monitored at least every 8 hours
- Laboratory testing (CBC and assessment of platelet count, liver enzyme, and serum creatinine levels) should be performed daily. (These tests can then be spaced to every other day if they remain stable and the patient remains asymptomatic.)

Fetal assessment

- Kick count and NST with uterine contraction monitored daily
- Biophysical profile twice weekly
- Serial fetal growth should be performed every 2 weeks and umbilical artery Doppler studies should be performed every 2 weeks if fetal growth restriction is suspected

Indications for Delivery During Expectant Management

In the published studies of preterm severe preeclampsia managed expectantly, delivery has typically been pursued at approximately 34 weeks of gestation. However, deterioration of maternal or fetal conditions before this gestational age is the most common reason for delivery (21, 23, 27). Maternal indications for delivery are delineated in Figure 5-2. Delivery should also be considered for women whose health is declining or who are nonadherent with ongoing inpatient observation; those developing persistent epigastric or right upper quadrant pain, nausea, or vomiting; and those who develop preterm labor or premature rupture of membranes (21, 23).

Maternal indications for delivery

- Recurrent severe hypertension
- Recurrent symptoms of severe preeclampsia
- Progressive 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)
- Persistent thrombocytopenia or HELLP syndrome
- Pulmonary edema
- Eclampsia
- Suspected abruptio placentae
- Progressive labor or rupture of membranes

Fetal indications for delivery

- Gestational age of 34 0/7 weeks
- Severe fetal growth restriction (ultrasonographic estimate of fetal weight less than the fifth percentile)
- Persistent oligohydramnios (maximum vertical pocket less than 2 cm)
- BPP of 4/10 or less on at least two occasions 6 hours apart
- Reversed end-diastolic flow on umbilical artery Doppler studies
- Recurrent variable or late decelerations during NST
- Fetal death

TASK FORCE RECOMMENDATIONS

- It is suggested that corticosteroids be administered and delivery deferred for 48 hours if maternal and fetal conditions remain stable for women with severe preeclampsia and a viable fetus at 33 6/7 weeks or less of gestation with any of the following:
  - preterm premature rupture of membranes
  - labor
  - low platelet count (less than 100,000/microliter)
  - persistently abnormal hepatic enzyme concentrations (twice or more the upper normal values)
  - fetal growth restriction (less than the fifth percentile)
  - severe oligohydramnios (amniotic fluid index less than 5 cm)
  - reversed end-diastolic flow on umbilical artery Doppler studies
  - new-onset renal dysfunction or increasing renal dysfunction

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

- It is recommended that corticosteroids be given if the fetus is viable and at 33 6/7 weeks or less of gestation, but delivery not be delayed after initial maternal stabilization regardless of gestational age for women with severe preeclampsia that is complicated further with any of the following:
  - uncontrollable severe hypertension
  - eclampsia
  - pulmonary edema
  - abruptio placentae
  - disseminated intravascular coagulation
  - evidence of nonreassurring fetal status
  - intrapartum fetal demise

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Route of Delivery in Preeclampsia

When delivery is indicated, vaginal delivery can often be accomplished, but this is less likely with decreasing gestational age. With labor induction, the likelihood of cesarean delivery increases with decreasing gestational age (range, 93–97% at less than 28 weeks of gestation, 53–65% at 28–32 weeks of gestation, and 31–38% at 32–34 weeks of gestation) (23, 33, 34).

TASK FORCE RECOMMENDATION

- For women with preeclampsia, it is suggested that the mode of delivery does not need to be cesarean delivery. The mode of delivery should be determined by fetal gestational age, fetal presentation, cervical status, and maternal–fetal condition.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

Eclampsia

Eclampsia is defined as the presence of new-onset grand mal seizures in a woman with preeclampsia. Eclampsia is preceded by a wide range of signs and symptoms, ranging from severe to absent or minimal hypertension, massive to no proteinuria, and prominent to no edema (35). Several clinical symptoms are potentially helpful in predicting impending eclampsia. These include persistent occipital or frontal headaches, blurred vision, photophobia, epigastric or right upper quadrant pain or both, and altered mental status (35, 36). Eclamptic seizures contribute substantially to maternal morbidity and mortality, especially in developing countries (36). For many years, these were treated with several different anticonvulsants, and attempts to prevent eclamptic seizures were exercised sporadically (37).

Systematic reviews of magnesium sulfate for the treatment of eclampsia have demonstrated its superiority to phenytoin and diazepam (38). For women with eclampsia, magnesium sulfate should be continued for at least 24 hours after the last convulsion. Furthermore, a systematic review of six randomized trials that included more than 11,000 women demonstrated that in women with preeclampsia, magnesium decreases the rate of eclampsia by 50% (RR, 0.41; 95% CI, 0.29–0.58) (39). In this review, the regimens of magnesium sulfate used included an intravenous loading dose of 4–6 g followed by a maintenance dose of 1–2 g/h for at least 24 hours. In addition, some studies used an intramuscular maintenance regimen that is not used in the United States. Women treated with magnesium sulfate to prevent or treat eclamptic seizures should receive an intravenous loading dose of 4–6 g followed by a maintenance dose of 1–2 g/h continued for at least 24 hours.

Several observational and retrospective studies found that expectant management of eclampsia to prolong gestation for fetal benefit is associated with a substantial increase of maternal and perinatal morbidity and mortality (40). One retrospective study, however, found that expectant management of eclampsia (antepartum onset before 34 weeks of gestation) for 24–48 hours to administer corticosteroids for fetal benefit can be undertaken if meticulous maternal and fetal monitoring remains reassuring while continuously infused magnesium sulfate and antihypertensive agents to prevent severe hypertension are administered for maternal stabilization; however, the safety of such an approach has not been proved (41). In all other circumstances, there is general agreement that women with eclampsia should undergo delivery following stabilization. Patients with severe preeclampsia undergoing cesarean delivery remain at risk of developing eclampsia. The induction of anesthesia and the stress of delivery may reduce their seizure threshold and increase the likelihood of eclampsia. Discontinuing magnesium sulfate infusions in the operative suite will not abate the potential interactions of magnesium sulfate with anesthetic agents and furthermore increases the likelihood of a subtherapeutic serum magnesium level in the recovery room or postpartum suite, placing the patient at risk of postpartum eclampsia.

TASK FORCE RECOMMENDATIONS

- For women with eclampsia, the administration of parenteral magnesium sulfate is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with severe preeclampsia, the administration of intrapartum–postpartum magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with preeclampsia undergoing cesarean delivery, the continued intraoperative administration of parenteral magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

HELLP Syndrome

Hemolysis, abnormal liver function tests, and thrombocytopenia have been recognized as complications of preeclampsia and eclampsia for many years. The term "HELLP syndrome" is an acronym for the following presentation: hemolysis, elevated liver enzymes, and low platelet count (42).

The development of HELLP syndrome may occur antepartum or postpartum (43). The clinical course of women with HELLP syndrome is often characterized by progressive and sometimes sudden deterioration in maternal and fetal condition. Because the presence of this syndrome has been associated with increased rates of maternal morbidity and mortality, many authors consider its presence to be an indication for immediate delivery. A consensus of opinion is that prompt delivery is indicated if the syndrome develops beyond 34 weeks of gestation or earlier if there is disseminated intravascular coagulation, liver infarction or hemorrhage, renal failure, pulmonary edema, suspected abruptio placentae, or nonreassuring fetal status (43). 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 (43).

The task force found no randomized trials that evaluated the benefits versus risks of a short course of corticosteroids for fetal lung maturation in women with HELLP syndrome. Because a significant fetal benefit of corticosteroid administration exists for women with severe preeclampsia, similar fetal benefit should exist for women with antepartum HELLP syndrome.

Several observational and retrospective studies have found that in combination with magnesium sulfate therapy and control of severe hypertension, different regimens of steroids have been associated with a major maternal morbidity–related decrease in HELLP syndrome (44, 45). However, data on maternal benefits of dexamethasone in women with HELLP syndrome are conflicting (46, 47). A 2010 Cochrane meta-analysis of 11 randomized controlled trials evaluated the effect of antenatal maternal corticosteroid treatment on perinatal outcomes during expectant management of HELLP syndrome (48). Among these trials, only four trials (362 women) reported maternal death; three trials (278 women) reported maternal death or severe maternal morbidity; two trials (91 women) reported maternal liver hematoma, rupture, or failure; and three trials (297 women) reported maternal pulmonary edema. This systematic review found significantly improved maternal platelet counts when corticosteroids are given, but no evidence of improvements in maternal mortality or severe maternal morbidities was reported. More robust and properly performed randomized trials are needed to clarify what value this intervention may bring to HELLP syndrome management.

TASK FORCE RECOMMENDATIONS

- For women with HELLP syndrome and before the gestational age of fetal viability, it is recommended that delivery be undertaken shortly after initial maternal stabilization.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with HELLP syndrome at 34 0/7 weeks or more of gestation, it is recommended that delivery be undertaken soon after initial maternal stabilization.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with HELLP syndrome from the gestational age of fetal viability to 33 6/7 weeks of gestation, it is suggested that delivery be delayed for 24–48 hours if maternal and fetal condition remain

stable to complete a course of corticosteroids for fetal benefit.*

Quality of evidence: Low
Strength of recommendation: Qualified

*Corticosteroids have been used in randomized controlled trials to attempt to improve maternal and fetal condition. In these studies, there was no evidence of benefit to improve overall maternal and fetal outcome (although this has been suggested in observational studies). There is evidence in the randomized trials of improvement of platelet counts with corticosteroid treatment. In clinical settings in which an improvement in platelet count is considered useful, corticosteroids may be justified.

Anesthetic Considerations

Hypotension

Spinal anesthesia results in hypotension secondary to sympathetic blockade, which decreases uteroplacental blood flow. The incidence and severity of hypotension following spinal anesthesia was compared in parturient women with severe preeclampsia (65 patients) and women without the disease process (71 patients) (49). *Hypotension,* defined as a 30% decrease in mean arterial pressure, was less common in the parturient women with severe preeclampsia (24.6% versus 40.8%), with no difference in the severity of the hypotension.

The task force found no meta-analyses that compared spinal anesthesia with general anesthesia for cesarean delivery in women with severe preeclampsia. However, there is one randomized trial that compared spinal anesthesia with epidural anesthesia for women with severe preeclampsia who underwent cesarean delivery (50). The spinal group consisted of 53 patients, and 47 patients were in the epidural group. Hypotension was defined as a systolic BP less than 100 mm Hg. 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). There were no adverse effects on the woman or the neonate.

Thrombocytopenia

Thrombocytopenia is the most common hematologic abnormality in women with preeclampsia. Its incidence depends on the severity of the disease and the presence or absence of abruptio placentae. In one survey, a platelet count of less than 150,000/microliter was found in 50% of parturient women with preeclampsia and a platelet count of less than 100,000/microliter in 36% of the women (51). The major concern with neuraxial anesthesia and analgesia in parturient women with thrombocytopenia is the development of an epidural hematoma. The enlarged epidural veins accompanying pregnancy increase the risk of puncture of these vessels during needle or catheter placement. Risk factors for hematoma include difficult placement, coagulopathy, and catheter removal (52). The task force found no studies that examined the safe limit for platelet count and neuraxial anesthesia. There are numerous case reports of epidural placement in patients with low platelet counts (as low as 20,000/microliter). These case reports do not establish a safe limit. The American Society of Anesthesiologists has not recommended a safe limit for the platelet count in parturient women with preeclampsia, relying on the health care provider's judgment following review of the laboratory values (53). A review article of case series and case reports on epidural and spinal anesthesia in patients with thrombocytopenia concluded that 80,000/microliter is a safe platelet count for the placement of epidural or spinal anesthesia and for the removal of an epidural catheter. This conclusion by these authors is dependent on a stable platelet count and the absence of coagulopathy (54).

Magnesium Sulfate

Magnesium sulfate has significant anesthetic implications. It prolongs the duration of nondepolarizing muscle relaxants and has led to practitioners stopping magnesium sulfate administration during surgical procedures. However, because magnesium has a half-life of 5 hours, discontinuing the intravenous infusion of magnesium sulfate before cesarean delivery minimally reduces magnesium concentration at the time of delivery and possibly increases the risk of seizure (55). Women with preeclampsia who require cesarean delivery should continue magnesium sulfate infusion during the delivery.

Invasive Hemodynamic Monitoring

Invasive monitoring allows for the direct measurement of BP as well as cardiac filling pressure. The use of an arterial catheter for direct measurement of BP is used in parturient women who may require frequent arterial specimens for pH and blood gas analysis. It also may be indicated in patients who receive continuous infusions of potent vasoactive drugs. With proper use, the risk of arterial catheterization is low, primarily including infection (dependent on location of arterial catheter, with femoral placement having a greater risk) and thrombosis (56). There are, however, no specific data concerning the risk of arterial catheterization in the parturient woman.

Placement of a catheter in a central vein for determination of a central venous pressure (CVP) or of a pulmonary artery catheter allows for the administration of medication, improved venous access, and hemodynamic monitoring. These monitors may allow for the measurement of filling pressure of the heart and assessment of vascular resistance, cardiac function, and oxygen uptake and delivery. The correlation between CVP and pulmonary artery occlusion pressure in preeclampsia is moderate, which limits the usefulness of CVP determinations (57). In 30 parturient women with severe preeclampsia, the correlation coefficient between CVP and pulmonary artery occlusion pressure was 0.64, if the patient did not receive treatment. Treatment of the disease process reduced the correlation coefficient to 0.53. This lack of correlation is further confounded by the lack of data from randomized controlled trials that demonstrate the usefulness of pulmonary artery catheters (58), but pulmonary artery catheterization is not without risk (59). Four of the 100 patients who were reviewed retrospectively had either a venous thrombosis or cellulitis. A retrospective case series of patients who received central venous catheters was performed. Of 85 patients, 20 had preeclampsia. A high incidence of infection (14%) was reported in those parturient women who received central venous catheters (60). Other complications included superficial and deep vein thrombosis, hematoma, ventricular tachycardia, and discomfort.

TASK FORCE RECOMMENDATIONS

- For women with preeclampsia who require analgesia for labor or anesthesia for cesarean delivery and with a clinical situation that permits sufficient time for establishment of anesthesia, the administration of neuraxial anesthesia (either spinal or epidural anesthesia) is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with severe preeclampsia, it is suggested that invasive hemodynamic monitoring not be used routinely.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Postpartum Hypertension and Preeclampsia

The exact incidence of postpartum hypertension and preeclampsia is difficult to ascertain because most women in the postpartum period will not have their BP checked until the 6-week postpartum visit (61). In addition, most women with hypertension usually are asymptomatic, and those with symptoms frequently are seen and managed in emergency departments. Several studies have reported that many women will be hospitalized postpartum because of severe hypertension and preeclampsia, and a 2010 large population-based study reported that 0.3% of all postpartum visits to emergency departments were due to hypertension and preeclampsia (62). Postpartum hypertension and preeclampsia are either secondary to persistent hypertension or exacerbation of hypertension in women with previous gestational hypetension, preeclampsia, chronic hypertension or because of a new-onset condition (61). In women with preeclampsia or superimposed preeclampsia, BP usually decreases within 48 hours following delivery, but the BP increases again 3–6 days postpartum (61). Several studies have emphasized the potential value of educating patients and health care providers to report signs and symptoms of preeclampsia that commonly precede eclampsia, hypertensive encephalopathy, pulmonary edema, or stroke (63–66). However, it remains unclear whether such reporting will lead to the prevention of eclampsia and adverse maternal outcomes.

Several retrospective studies have found that most women who presented with eclampsia and stroke in the postpartum period had these symptoms for hours and days before presentation (63–66). In addition, many of these symptoms were not considered important by patients or medical providers. The group also believed that many medical providers (nurses, obstetricians, nurse–midwives, emergency department physicians, and internists) may not be aware that preeclampsia and eclampsia can develop up to 4 weeks postpartum. Health care providers are reminded of the contribution of nonsteroidal antiinflammatory agents to increase BP. It is suggested that these commonly used postpartum pain relief agents be replaced by other analgesics in women with hypertension that persists for more than 1 day postpartum.

TASK FORCE RECOMMENDATIONS

- For women in whom gestational hypertension, preeclampsia, or superimposed preeclampsia is diagnosed, it is suggested that BP be monitored in the hospital or that equivalent outpatient surveillance

be performed for at least 72 hours postpartum and again 7–10 days after delivery or earlier in women with symptoms.

Quality of evidence: Moderate
Strength of recommendation: Qualified

- For all women in the postpartum period (not just women with preeclampsia), it is suggested that discharge instructions include information about the signs and symptoms of preeclampsia as well as the importance of prompt reporting of this information to their health care providers.

  Quality of evidence: Low
  Strength of recommendation: Qualified

The task force is not aware of any randomized trials that evaluated therapy to prevent postpartum hypertension and preeclampsia (67, 68). The task force found no placebo-controlled trials that evaluated the treatment of postpartum hypertension or evaluated magnesium sulfate versus placebo in women with late postpartum preeclampsia (61). A few trials that had limited sample sizes compared oral antihypertensive drugs with each other or with no treatment. However, the outcome studied in these trials is not clinically important (68). In addition, uncertainty exists regarding the level of BP to treat, as well as the target BP to achieve during treatment, and when to stop these medications (61, 67, 68). Health care providers should be reminded of the contribution of nonsteroidal antiinflammatory agents to increased BP. It is suggested that these commonly used postpartum pain relief agents be replaced by other analgesics in women with hypertension that persists for more than 1 day postpartum. Experts recommend antihypertensive therapy in the postpartum period when BP is persistently higher than 150 mm Hg systolic or 100 mm Hg diastolic (on at least two occasions that are at least 4–6 hours apart) (67–69). In addition, magnesium sulfate is recommended for women who present during the postpartum period with hypertension or preeclampsia in association with severe headaches, visual changes, altered mental status, epigastric pain, or shortness of breath. Magnesium sulfate is to be given for at least 24 hours from diagnosis (61).

TASK FORCE RECOMMENDATIONS

- For women in the postpartum period who present with new-onset hypertension associated with headaches or blurred vision or preeclampsia with severe hypertension, the parenteral administration of magnesium sulfate is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with persistent postpartum hypertension, BP of 150 mm Hg systolic or higher or 100 mm Hg diastolic or higher, on at least two occasions that are at least 4–6 hours apart, antihypertensive therapy is suggested. Persistent BP of 160 mm Hg systolic or 100 mm Hg diastolic or higher should be treated within 1 hour.

  Quality of evidence: Low
  Strength of recommendation: Qualified

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CHAPTER 6

Management of Women With Prior Preeclampsia

The primary objectives in the management of patients with a history of preeclampsia are to reduce risk factors for recurrence by optimizing maternal health before conception, to detect obstetric complications, and to achieve optimal perinatal outcome during subsequent pregnancy. These objectives can be achieved by formulating a rational approach that includes preconception evaluation and counseling, early antenatal care, frequent antepartum visits to monitor both maternal and fetal well-being, and timely delivery (see Box 6-1) (1).

Preconception Management

Treatment of a patient with a previous pregnancy complicated by preeclampsia ideally should begin before conception. If the patient is unlikely to have a preconception visit, this assessment should be conducted at the 6-week postpartum visit, including patient counseling on risk of preeclampsia recurrence and risk-modification strategies. Results should be forwarded to her primary health care provider.

For women who present before conception, management should include a thorough medical history of preexisting risk factors and medical conditions reportedly associated with preeclampsia to allow appropriate counseling as to the magnitude of the risk of preeclampsia in subsequent pregnancy. Also, attention should be given to the outcome of the previous pregnancy as well as assessment of maternal risk factors, including the presence of infertility and preexisting comorbidities such as obesity, chronic hypertension, renal disease, diabetes mellitus, connective tissue disorders, and acquired thrombophilias. A baseline laboratory evaluation could include a complete blood count, metabolic profile, and urinalysis. A detailed obstetric history should include maternal as well as perinatal outcomes in the previous pregnancy (2, 3). Therefore, information should be obtained from medical records concerning the gestational age at onset of preeclampsia, maternal complications (HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome, eclampsia, pulmonary edema, renal failure, and abruptio placentae), perinatal complications (fetal growth restriction, perinatal morbidity, and perinatal death), and laboratory test values, including those for acquired thrombophilia and connective tissue disorders as well as placental pathology, if available.

The status of maternal comorbidities ideally should be optimized before conception. High body mass index is a risk factor for preeclampsia. Overweight or obese patients should be counseled on the potential benefit of weight loss as a modifiable risk factor. They should be referred for nutritional counseling in an attempt to achieve a healthy body mass index. Weight loss and lifestyle modification also may reduce the likelihood of chronic hypertension and type 2 diabetes mellitus. Because the risk of preeclampsia correlates with the severity of maternal hypertension and glycemic control,

BOX 6-1. Evaluation and Management of Women at Risk of Preeclampsia Recurrence ⇦

Preconception

- Identify risk factors (ie, type 2 diabetes mellitus, obesity, hypertension, and family history).
- Review outcome of previous pregnancy (abruptio placentae, fetal death, fetal growth restriction, and gestational age at delivery).
- Perform baseline metabolic profile and urinalysis.
- Optimize maternal health.
- Supplement with folic acid.

First Trimester

- Perform the following:
  - Ultrasonography for assessment of gestational age and fetal number
  - Baseline metabolic profile and complete blood count
  - Baseline urinalysis
- Continue folic acid supplementation.
- Offer first-trimester combined screening.
- For women with prior preeclampsia that led to delivery before 34 weeks of gestation or occurring in more than one pregnancy, offer low-dose aspirin late in the first trimester and discuss the risks and benefits of low-dose aspirin with other women.

Second Trimester

- Counsel patient about signs and symptoms of preeclampsia beginning at 20 weeks of gestation; reinforce this information with printed handouts.
- Monitor for signs and symptoms of preeclampsia.
- Monitor blood pressure at prenatal visits, with nursing contacts, or at home.
- Perform ultrasonography at 18–22 weeks of gestation for fetal anomaly evaluation and to rule out molar gestation.
- Hospitalize for severe gestational hypertension, severe fetal growth, or recurrent preeclampsia.

Third Trimester

- Monitor for signs and symptoms of preeclampsia.
- Monitor blood pressure at prenatal visits, with nursing contacts, or at home.
- Perform the following as indicated by clinical situation:
  - Laboratory testing
  - Serial ultrasonography for fetal growth and amniotic fluid assessment
  - Umbilical artery Doppler with nonstress test, biophysical profile, or both
- Hospitalize for severe gestational hypertension or recurrent preeclampsia.

Modified from Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. Obstet Gynecol 2008;112:359–72.

women with chronic hypertension, diabetes mellitus, or both, should have their blood pressure, blood glucose, or both, optimized before conception. It is unknown, however, whether amelioration of altered hemodynamics or optimization of glucose control will definitively reduce the recurrence risk of preeclampsia. During the preconception visit, discussion should include the effects of these diseases on pregnancy outcome as well as the effect of pregnancy on these conditions. In addition, if the patient is taking medications for a chronic medical disorder, there should be a review of these medications with special emphasis on those to be avoided, such as angiotensin receptor blockers and some immunosuppressive agents. As for any woman contemplating conception, folic acid supplementation should be prescribed.

Antepartum Management

Early and frequent prenatal visits are the key for a successful pregnancy outcome in women with preeclampsia in a previous pregnancy, particularly those with early-onset disease. First-trimester ultrasound examination is essential to determine accurate gestational age and establish fetal number. For women with prior preeclampsia leading to delivery before 34 weeks of gestation or occurring in more than one pregnancy, low-dose aspirin should be offered late in the first trimester, and the risks and benefits of low-dose aspirin should be discussed with other women with prior preeclampsia.

During each antepartum visit, the woman should be monitored closely for signs and symptoms of preeclampsia (Box 6-2). She also should be educated about symptoms of organ dysfunction and instructed to report any symptoms, such as severe headache, visual change, right upper quadrant or epigastric pain, nausea and vomiting, and changes in fetal movement. The frequency of antepartum visits may be modified according to the gestational age at the onset of preeclampsia in the previous pregnancy as well as the results of maternal and fetal surveillance. Health care providers must be cautioned that these recommendations concerning antepartum management and assessment are not evidence-based because there are no randomized studies addressing this subject. Fetal growth should be monitored serially, given the known relationship between fetal growth restriction and preeclampsia. During antepartum surveillance of women with previous preeclampsia, the development of severe gestational hypertension, fetal growth restriction, or recurrent preeclampsia requires maternal hospitalization for more frequent maternal and fetal evaluation (see Chapter 5 "Management of Preeclampsia and HELLP Syndrome").

BOX 6-2. Symptoms of Preeclampsia

- Swelling of the face or hands
- Headache that will not go away
- Seeing spots or changes in eyesight
- Pain in upper right quadrant or stomach
- Nausea or vomiting (in second half of pregnancy)
- Sudden weight gain
- Difficulty breathing

TASK FORCE RECOMMENDATION

- For women with preeclampsia in a prior pregnancy, preconception counseling and assessment is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

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CHAPTER 7

Chronic Hypertension in Pregnancy and Superimposed Preeclampsia

Chronic hypertension presents special challenges to health care providers. Health care providers must first confirm that blood pressure (BP) elevation is not preeclampsia. Perhaps the greatest challenge is the recognition of preeclampsia superimposed on chronic hypertension, a condition that is commonly associated with adverse maternal and fetal outcomes.

Chronic Hypertension in Pregnancy

Definition and Diagnosis

Chronic hypertension in pregnancy is defined as hypertension present before pregnancy or before 20 weeks of gestation (1). Chronic hypertension is present in up to 5% of pregnant women; rates vary according to the population studied and the criteria used to establish the diagnosis (1–3). Chronic hypertension complicating pregnancy is diagnosed when high BP is known to predate pregnancy. When prepregnancy BP is not known, elevated BP detected before 20 weeks of gestation is often due to chronic hypertension. However, if BP was normal in the first trimester and then increases before 20 weeks of gestation, gestational hypertension or early preeclampsia also should be considered (4). *Hypertension* is defined as either a systolic BP of 140 mm Hg or greater, or a diastolic BP of 90 mm Hg or greater, or both. In pregnancy, BP is categorized as mild to moderate (systolic, 140–159 mm Hg or diastolic, 90–109 mm Hg) or severe (systolic, 160 mm Hg or higher, diastolic 110 mm Hg or higher), although a distinction is not made between chronic, gestational, or preeclamptic hypertension. Most women with chronic hypertension will have essential (also called primary) hypertension, but as many as 10% may have underlying renal or endocrine disorders (ie, secondary hypertension).

The diagnosis of chronic hypertension is easily established when prepregnancy hypertension is well documented and in women already receiving antihypertensive medications. Chronic hypertension also is the most likely diagnosis when hypertension is present in the first trimester. Difficulties may arise when pregnant women with prepregnancy, undiagnosed hypertension initially present in the second trimester with normal BP after having experienced the pregnancy-associated physiologic decrease in BP. These women will have been presumed to be normotensive, and if BP increases in the third trimester, they may be erroneously diagnosed with either gestational hypertension or, if proteinuria is present, with preeclampsia rather than superimposed preeclampsia. Thus, chronic hypertension may not be diagnosed until well after delivery. In other instances, women with well-documented hypertension before pregnancy will demonstrate normal BP throughout the entire pregnancy only to return to prepregnancy hypertensive levels postpartum.

Maternal and Fetal Outcomes

Reports of outcomes of pregnancies complicated by chronic hypertension have not uniformly distinguished

between women with superimposed preeclampsia and those with uncomplicated chronic hypertension. Preexisting hypertension is a recognized risk factor for preeclampsia. Superimposed preeclampsia develops in 13–40% of women with chronic hypertension, depending on diagnostic criteria, etiology (essential versus secondary), duration, and the severity of hypertension (5, 6). A major reason for this wide range in incidence is that the definition of superimposed preeclampsia is used liberally in some studies.

Women with chronic hypertension who develop superimposed preeclampsia have higher rates of adverse maternal–fetal outcomes, but the independent risks associated with uncomplicated chronic hypertension are less clear. An analysis of 1,807 deliveries in women with chronic hypertension found that uncomplicated chronic hypertension was still associated with a greater risk of cesarean delivery (odds ratio [OR], 2.7; 95% confidence interval [CI], 2.4–3.0) and postpartum hemorrhage (OR, 2.2; 95% CI, 1.4–3.7) compared with women without hypertension (2). Other adverse maternal outcomes in women with chronic hypertension include accelerated hypertension with resultant target organ damage (eg, to the heart, brain, and kidneys), although in the absence of preeclampsia, this is extremely uncommon. Women with higher prepregnancy BP or those with secondary hypertension are at greater risk of developing severe hypertension during pregnancy. Chronic hypertension is associated with an increased risk of gestational diabetes (OR, 1.8; 95% CI, 1.4–2) (2, 7, 8). This may reflect similar risk factors for both conditions (eg, obesity) as well as similar pathogenetic mechanisms (eg, insulin resistance). The risk of abruptio placentae is increased threefold in women with chronic hypertension, although most of the increased risk is associated with superimposed preeclampsia (5, 9, 10). Women with chronic hypertension in pregnancy are more likely to be hospitalized for hypertension (8).

Perinatal mortality is higher in pregnancies associated with chronic hypertension, most of this increased attributable risk is the result of superimposed preeclampsia (5, 10). The relative risk of perinatal death is reported to be approximately 3.6 in women with superimposed preeclampsia compared with those with uncomplicated chronic hypertension (8). Perinatal death also is higher in women with uncomplicated hypertension compared with normotensive controls (relative risk, 2.3) (8).

Fetal growth restriction is more frequent with chronic hypertension and is usually associated with superimposed preeclampsia (6). Another risk associated with chronic hypertension in pregnancy is the exposure to antihypertensive medications in utero that may cause growth restriction and fetal malformations; this has been extensively evaluated. Although most antihypertensive agents considered safe in pregnancy have not been shown to be associated with fetal malformations, the question of whether they have an effect on growth is still controversial. Clinical trials that evaluated long-term outcomes of exposed offspring have been conducted with a limited number of agents, primarily, methyldopa.

Chronic Hypertension With Superimposed Preeclampsia

Preexisting hypertension is a recognized risk factor for preeclampsia, and superimposed preeclampsia is associated with considerable maternal–fetal morbidity and mortality. Superimposed preeclampsia develops in 13–40% of women with chronic hypertension, depending on diagnostic criteria, etiology (essential versus secondary), duration, and the severity of hypertension (5, 6). A major reason for this wide range in incidence is that the definition of superimposed preeclampsia is liberally used in some studies.

Preconception Counseling

Preconception counseling should include explanation of the risks associated with chronic hypertension and education about the signs and symptoms of preeclampsia. Maternal characteristics that increase the risk of superimposed preeclampsia include the presence of diabetes, obesity, or renal disease; history of preeclampsia, particularly early preeclampsia; severity and duration of hypertension before pregnancy; and presence of secondary hypertension, such as pheochromocytoma and renovascular hypertension (5, 11). Medications with known fetal adverse effects often prescribed to women with chronic hypertension should be discontinued before conception. In particular, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and mineralocorticoid antagonists are contraindicated. Statins, which are widely used in individuals with hypertension who also have elevated cholesterol, should be avoided because there is conflicting evidence about the safety of their use in pregnancy (12).

Antepartum Management

Initial Evaluation of Women With Known or Suspected Chronic Hypertension

All women with preexisting hypertension should be assessed either before pregnancy or early in pregnancy

as outlined by the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* and the National High Blood Pressure Education Program guidelines to rule out secondary (and potentially curable) hypertension if appropriate and to seek out evidence of target organ damage, unless such evaluations were previously performed. Baseline concentrations of serum creatinine, electrolytes, uric acid, liver enzymes, platelet count, and urine protein (either dipstick test or quantification of urine protein) should be documented to use as comparators if superimposed preeclampsia is suspected later in pregnancy. Glucose tolerance testing should be performed early in pregnancy for women at risk of gestational diabetes (obese, history of gestational diabetes, or strong family history of type 2 diabetes mellitus). Good clinical practice suggests performing assessment of left ventricular function with either echocardiography or electrocardiography in women with severe hypertension of long duration (eg, more than 4 years).

Screening for Secondary Hypertension

The most common cause of secondary hypertension is chronic kidney disease, and screening is easily accomplished with routine blood chemistries and urinalysis. If proteinuria is detected on urinalysis (1+ or greater), either a 24-hour urine should be collected or a protein/creatinine ratio measured in a spot urine to quantify the level of proteinuria. If evidence of chronic kidney disease is detected (abnormal urinalysis or elevated serum creatinine), or if there is a strong family history of kidney disease, then renal ultrasonography should be performed to rule out polycystic kidney disease, the most common genetic type of kidney disease. Other causes of secondary hypertension that may be present in women of childbearing age include primary aldosteronism, renovascular hypertension, pheochromocytoma, and Cushing disease. Suggestive clinical features of secondary hypertension (resistant hypertension, hypokalemia, palpitations, lack of family history of hypertension, and age younger than 35 years) warrant consideration of further diagnostic workup. Case series and case reports suggest that particular diagnoses such as pheochromocytoma and renovascular hypertension are associated with adverse maternal and fetal outcomes, and that if the underlying disorder is treated, outcomes are improved. There is variability in the recommended strategies for diagnosing secondary hypertension; therefore, the task force suggests referral to a hypertension specialist if secondary hypertension is a consideration (Box 7-1).

BOX 7-1. Findings Suggestive of Secondary Hypertension ⇦

Any of the following findings are suggestive of secondary hypertension:

- Resistant hypertension
- Hypokalemia (potassium level less than 3.0 mEq/L)
- Elevated serum creatinine level (greater than 1.1 mg/dL)
- Strong family history of kidney disease

TASK FORCE RECOMMENDATION

- For women with features suggestive of secondary hypertension, referral to a physician with expertise in treating hypertension to direct the workup is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Monitoring Blood Pressure

Blood pressure is checked monthly in all pregnant women as part of standard obstetric practice. Although increased frequency of BP monitoring has not been evaluated as a strategy for improving pregnancy outcomes, good clinical practice dictates increased monitoring for women with BP above desired targets. Although most superimposed preeclampsia occurs near term, it can occur before 24 weeks of gestation, and there are even anecdotal reports of its occurrence before 20 weeks of gestation. Therefore, increased monitoring may be particularly useful in the second half of pregnancy. Because of a considerable body of literature of hypertension in patients who are not pregnant, which documents the use of home BP monitoring as an aid to achieving BP targets and monitoring responses to treatment, the task force suggests this approach for pregnant women.

TASK FORCE RECOMMENDATION

- For pregnant women with chronic hypertension and poorly controlled BP, the use of home BP monitoring is suggested.

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

White coat hypertension, defined as elevated BP primarily in the presence of health care providers, may account for up to 10–15% of individuals with office hypertension. The prevalence in pregnancy is not known. Ambulatory BP monitoring is the preferred test to diagnose white coat hypertension in an individual who is not pregnant. White coat hypertension should be suspected if BP is higher in the doctor's office compared with other settings. Failure to recognize white coat hypertension may result in overtreatment of BP and unnecessary adverse effects of treatment.

TASK FORCE RECOMMENDATION

- For women with suspected white coat hypertension, the use of ambulatory BP monitoring to confirm the diagnosis before the initiation of antihypertensive therapy is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Treatment

Hypertension is a strong risk factor for stroke, coronary heart disease, congestive heart failure, kidney disease, and death; lowering BP has been conclusively shown to prevent these complications in hypertensive individuals who are not pregnant. The course of vascular damage and cardiovascular (CV) complications associated with hypertension is years; stage 1 hypertension (BP, 140–159 mm Hg, systolic/90–99 mm Hg, diastolic) is associated with a 40% increased risk of stroke (compared with age-matched individuals without hypertension), which is usually apparent after 10 years of untreated hypertension. In populations of individuals who are not pregnant, demonstration of such benefits requires years of treatment, whereas in pregnancy, the goals of treatment are more focused on preventing acute complications of hypertension in the woman and maintaining a healthy pregnancy for as long as possible. The goals of therapy also include minimizing risks to the fetus that are attributable to hypertension, vascular disease, and the possible effects of antihypertensive medications that may alter maternal hemodynamics and reduce uteroplacental perfusion, or that may cross the placenta and be harmful to the fetus. Preventing long-term maternal CV morbidity and mortality is not the primary concern during pregnancy.

Nonpharmacologic treatment. Treatment of hypertensive individuals who are not pregnant is focused on two basic strategies: 1) lowering BP and 2) minimizing additional CV risk factors. Nonpharmacologic approaches that have successfully lowered BP in individuals who are not pregnant include regular aerobic exercise, maintaining ideal body weight, moderation of alcohol intake, adopting specific diets (such as the DASH [Dietary Approaches to Stop Hypertension] diet, a diet with abundant fruits and vegetables, low-fat dairy products, and high fiber), and reducing sodium intake. Some of these approaches are either not appropriate for pregnancy or have not been evaluated in the context of pregnancy. Weight loss and regular aerobic exercise have been shown to be beneficial in hypertensive individuals who are not pregnant because it lowers BP and favorably affects weight and insulin sensitivity (13, 14). Exercise regimens have been tested in pregnancy, primarily as a strategy for preventing excessive weight gain (15), and moderate-level physical activity in pregnant women without medical and obstetric complications is recommended (16). This approach has not been assessed as a strategy for lowering BP in pregnant women with chronic hypertension. Observational research and small clinical trials suggest that exercise may be beneficial in preventing preeclampsia (16, 17); however, these studies have not specified the effect in women with chronic hypertension. Whether any exercise or vigorous aerobic exercise is harmful in women with chronic hypertension has not been adequately studied.

TASK FORCE RECOMMENDATIONS

- It is suggested that weight loss and extremely low-sodium diets (less than 100 mEq/d) not be used for managing chronic hypertension in pregnancy.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with chronic hypertension who are accustomed to exercising, and in whom BP is well controlled, it is suggested that moderate exercise be continued during pregnancy.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Antihypertensive pharmacologic treatment. Treatment of severe hypertension—The task force found limited evidence regarding the precise BP level at which antihypertensive therapy is indicated during pregnancy in women with chronic hypertension. Severe elevations in BP are associated with acute maternal cerebrovascular and coronary events, although the BP level at which risk of these adverse events increases is not precisely known and is likely to vary and depend on comorbidities and other factors such as baseline BP, and rate of increase. In an adult who is not pregnant, antihypertensive therapy is recommended when the

systolic BP is 140 mm Hg or higher or the diastolic BP is 90 mm Hg or higher, and this approach is supported by large clinical trials that have clearly demonstrated benefits of treatment (18).

Few clinical trials have been performed that specifically address the optimum level of BP during pregnancy in women with preexisting (chronic) hypertension. Most studies that address this have not been limited to women with chronic hypertension and also have included women with gestational hypertension or preeclampsia. Antihypertensive therapy has been compared with placebo or no therapy, and outcomes assessed in these studies have been variable (eg, development of superimposed preeclampsia, progression of hypertension, and fetal weight and survival.) A Cochrane systematic review of drug treatment for severe hypertension during pregnancy, which included 35 trials involving 3,573 women, included few women with chronic hypertension (19). Drug therapy was instituted when diastolic BP levels reached or exceeded 100–110 mm Hg, and in the majority of the studies, not until the third trimester. Women with chronic hypertension were generally excluded, and if included, no subgroup analysis was reported. Thus, there is a paucity of evidence addressing thresholds for initiating antihypertensive drugs in pregnant women with chronic hypertension. Future placebo-controlled trials addressing the treatment of severe hypertension are unlikely to be initiated and are not recommended given ethical considerations. Therefore, recommendations for treating women with chronic hypertension with severely elevated BP are based on indirect evidence from treating pregnant women with new acute onset of severe gestational hypertension or preeclampsia (19). Given the limitations of the data as well as the higher likelihood of outpatient therapy with less frequent BP monitoring among pregnant women with chronic hypertension, treatment is suggested at a lower diastolic BP threshold of 105 mm Hg. Most of these trials focused on diastolic BP, and specific cutoff values for the treatment of elevated systolic BP are not as well defined; however, if indirect evidence from these trials and the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* recommendations for adults who are not pregnant are applied to pregnant women with chronic hypertension, pharmacologic treatment should be used to maintain systolic BP below 160 mm Hg (18, 19). Overly aggressive BP lowering is discouraged because of concerns that uteroplacental blood flow may be compromised at pharmacologically induced low BP.

TASK FORCE RECOMMENDATION

- For pregnant women with persistent chronic hypertension with systolic BP of 160 mm Hg or higher or diastolic BP of 105 mm Hg or higher, antihypertensive therapy is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Treatment of mild to moderate hypertension—When and how to use antihypertensive drugs in women with chronic hypertension in pregnancy who do not have severely elevated levels of BP is less clear. To justify the use of antihypertensive therapy during pregnancy in women with chronic hypertension with mild to moderately elevated BP (systolic BP of 140 mm Hg or higher and less than 160 mm Hg or diastolic BP of 90 mm Hg or higher and less than 110 mm Hg), the maternal benefit and improvement in perinatal outcomes that are due to treatment must outweigh the potential risk of adverse effects on fetal and neonatal safety, including the possibility that pharmacologic reductions in maternal systemic BP result in compromised uteroplacental blood flow.

Results from seven placebo-controlled randomized trials that involved 650 women with mild to moderate chronic hypertension did not demonstrate an improvement in either maternal or perinatal outcomes with antihypertensive therapy (6, 20–26). Published in 2007, a Cochrane systematic review of antihypertensive drug therapy for mild to moderate hypertension in pregnancy (including all diagnoses) that included 46 trials (4,282 women) concluded that treatment reduced the risk of developing severe hypertension but had no effect on the incidence of preeclampsia (27). There were no effects, either positive or negative, on perinatal outcomes such as preterm birth, small-for-gestational-age (SGA) infants, or fetal death. Of the studies included, only five trials focused exclusively on women with chronic hypertension. Similar to the overall findings, there was a risk reduction in progression to severe hypertension with treatment in this subgroup (RR, 0.57; 95% CI, 0.34–0.98) but no effect on perinatal outcomes (27). No harm was associated with treatment. Thus, the currently available evidence suggests potential maternal benefit of antihypertensive treatment by reducing the progression to severe hypertension, but no direct fetal benefit or significant improvement in perinatal outcomes among women with chronic hypertension.

Although the 2007 Cochrane review did not find evidence of fetal harm associated with lowering BP, two meta-regression analyses evaluated the effect of

lowering BP specifically on fetal birth weight; there were seven trials of women with chronic hypertension and 38 trials of women with late-onset hypertension in pregnancy (27–29). A decrease of 10 mm Hg (mean arterial pressure) was associated with an average decrease in infant birth weight of 145 g; however, the relationship between a decrease in BP and SGA was less convincing in women with chronic hypertension, possibly because of the limited power of the overall study. A 2010 case–control analysis of the Quebec Pregnancy Registry data reported that after adjusting for potential confounders, antihypertensive medication use during the second trimester or third trimester of the pregnancy was significantly associated with an increased risk of SGA (OR, 1.53; 95% CI, 1.17–1.99) (30). Another important issue regarding treatment of maternal hypertension during pregnancy is the risk of teratogenicity attributable to drugs. There is conflicting evidence; two population-based studies suggest that exposure to any antihypertensive medication may be associated with an increased risk of fetal cardiac abnormalities (31, 32), but these findings were not corroborated by others (30, 33).

Many limitations exist to these population-based studies, including the small numbers of malformations overall; furthermore, it is not possible to discern whether these are specific medication effects, effects of elevated BP, or, alternatively, effects of low BP secondary to treatment. Although the increased number of malformations are modest, these data support the general strategy of being cautious when prescribing any drug during pregnancy, particularly during the first trimester, and emphasize the need for additional, well-conducted prospective trials to clarify risks and benefits. Therefore, in the absence of strong evidence supporting use of antihypertensive therapy for mild to moderate chronic hypertension during pregnancy, initiation of therapy is not suggested unless BP approaches 160 mm Hg systolic or higher or 105 mm Hg diastolic or higher, or both).

TASK FORCE RECOMMENDATION

- For pregnant women with chronic hypertension and BP less than 160 mm Hg systolic or 105 mm Hg diastolic and no evidence of end-organ damage, it is suggested that they not be treated with pharmacologic antihypertensive therapy.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Blood pressure targets for antihypertensive treatment—Minimal data address the ideal target BP once antihypertensive therapy is initiated in pregnant women with chronic hypertension. Two pilot randomized trials that included women with either mild to moderate chronic or gestational hypertension were included in a Cochrane review (256 women) that compared "tight" (systolic BP less than 130 mm Hg and diastolic BP less than 80 mm Hg) BP with "less tight" (systolic BP less than 140 mm Hg and diastolic BP less than 90 mm Hg) BP control (34–37). No significant adverse outcomes were identified, and the evidence was insufficient to determine optimal BP control needed to improve maternal and fetal or neonatal outcomes.

TASK FORCE RECOMMENDATION

- For pregnant women with chronic hypertension treated with antihypertensive medication, it is suggested that BP levels be maintained between 120 mm Hg systolic and 80 mm Hg diastolic, and 160 mm Hg systolic and 105 mm Hg diastolic.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Treatment of women receiving antihypertensive therapy prior to pregnancy—In women who enter pregnancy with well-controlled or mild hypertension with medication, there are minimal data to guide decisions as to continuing or discontinuing therapy. A review of 298 women in whom medication dosage was reduced or stopped reported no increase in preeclampsia, abruptio placentae, and perinatal death compared with untreated groups (8). A recent case–control study also found no difference in preeclampsia or eclampsia with discontinuation of antihypertensive drugs in the first trimester (37). Although decision making must be individualized, discontinuing medications during the first trimester and restarting them if BP approaches the severe range is reasonable practice. For women with end-organ damage, such as chronic renal disease or cardiac disease, BP goals are lower (systolic BP less than 140 mm Hg and diastolic BP less than 90 mm Hg) to avoid progression of disease during pregnancy and associated complications. As noted previously, end-organ damage of the kidney and heart should be assessed before pregnancy or during early pregnancy, or both. A detailed review of the medical history as well as baseline assessment of renal function (serum creatinine, creatinine clearance, and urinary protein excretion) and cardiac function (echocardiography or electrocardiography) is useful, and women should be monitored closely if medications are withdrawn. This is clearly a case in which an informed discussion with the pregnant patient should guide the choice of therapy or no therapy.

Types of Antihypertensive Medication

When choosing an antihypertensive medication to use for the treatment of chronic hypertension in pregnancy, an important consideration is the goal of therapy, which is either 1) acute lowering of severe hypertension in the hospital setting (Table 7-1) or 2) chronic treatment of BP to keep levels below the severe range, often in the outpatient setting (Table 7-2).

Drugs for urgent lowering of blood pressure. Thirty-five randomized controlled trials that involved 3,573 women were included in a Cochrane systematic review that compared antihypertensive medications with each other for acute lowering of severely elevated BP in pregnancy (19). Most of these trials included only women with preeclampsia or gestational hypertension in the third trimester and excluded women with known chronic hypertension or previous antihypertensive therapy use. Hydralazine, labetalol, and calcium channel blockers are among the medications that were compared with each other. Based on the findings of the systematic review, evidence is inadequate to demonstrate the superior safety or efficacy of any of these medications (19). Therefore, the authors conclude that the choice of antihypertensive medication should depend on the potential adverse effects and contraindications as well as the individual clinician's experience and familiarity with a particular drug (19). Given the unlikelihood of future trials focusing specifically on acute treatment of pregnant women with chronic hypertension, it is reasonable to extrapolate management recommendations based on these data. Intravenous labetalol, intravenous hydralazine, or oral nifedipine are reasonable first-line agents for acute lowering of BP in the hospital setting (Table 7-1). There is theoretical concern that the combined use of nifedipine and intravenous magnesium sulfate can result in hypotension and neuromuscular blockade. One review concluded that the combined use of these drugs does not increase such risks (38); however, given the plausibility of the mechanism (both are calcium antagonists), careful monitoring of women receiving both is advisable. In view of these data, in women requiring antihypertensive medications for severe hypertension, the choice and route of administration of drugs should be based primarily on the physician's familiarity and experience, adverse effects and contraindications to the prescribed drug, local availability, and cost.

Drugs for continuous management. Oral agents are used for outpatient treatment of pregnant women with chronic hypertension (39). Randomized controlled trials of drug therapy have focused on methyldopa (included in five trials) (20–22, 24, 26) and labetalol (included in one trial) (26). The largest trial that included pregnant women with chronic hypertension randomized 263 women to labetalol, methyldopa, or no treatment; there were no differences in outcomes or safety (29). Commonly used oral agents for chronic hypertension management in pregnancy are summarized in Table 7-2.

Methyldopa, a centrally acting alpha-2 adrenergic agonist, remains a commonly used drug mainly because of the long history of use in pregnancy and childhood safety data. Blood pressure control is gradual, over 6–8 hours, as a result of the indirect mechanism of action. Methyldopa has been prospectively studied specifically in chronic hypertension compared with placebo (20–22, 24, 26), as well as in a mixed group of hypertensive women (40–42). There are no apparent adverse effects on uteroplacental or fetal hemodynamics or on fetal well-being (26, 43).

TABLE 7-1. Antihypertensive Agents Used for Urgent Blood Pressure Control in Pregnancy ⇦

Drug	Dose	Comments
Labetalol	10–20 mg IV, then 20–80 mg every 20–30 min to a maximum dose of 300 mg or Constant infusion 1–2 mg/min IV	Considered a first-line agent Tachycardia is less common and fewer adverse effects Contraindicated in patients with asthma, heart disease, or congestive heart failure
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 min or Constant infusion 0.5–10 mg/h	Higher or frequent dosage associated with maternal hypotension, headaches, and fetal distress—may be more common than other agents
Nifedipine	10–20 mg orally, repeat in 30 minutes if needed; then 10–20 mg every 2–6 hours	May observe reflex tachycardia and headaches

Abbreviations: IM, intramuscularly; IV, intravenously.

TABLE 7-2. Common Oral Antihypertensive Agents in Pregnancy ⇦

Drug	Dosage	Comments
Labetalol	200–2,400 mg/d orally in two to three divided doses	Well tolerated Potential bronchoconstrictive effects Avoid in patients with asthma and congestive heart failure
Nifedipine	30–120 mg/d orally of a slow-release preparation	Do not use sublingual form
Methyldopa	0.5–3 g/d orally in two to three divided doses	Childhood safety data up to 7 years of age May not be as effective in control of severe hypertension
Thiazide diuretics	Depends on agent	Second-line agent
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers		Associated with fetal anomalies Contraindicated in pregnancy and preconception period

Birth weight, neonatal complications, and development at 1 year were similar in infants exposed to methyldopa in utero compared with no therapy (44, 45). A follow-up study of children at 7 years of age did not show any difference in neurocognitive development or intelligence compared with controls (46). Serious adverse effects include hepatic dysfunction and necrosis as well as hemolytic anemia. Methyldopa may be less effective in preventing severe hypertension based on the Cochrane analysis of a subset of studies compared with β-blocker and calcium channel blocker classes combined (OR, 0.75; 95% CI, 0.59–0.94) (27).

Labetalol, a nonselective β-blocker with vascular alpha receptor-blocking ability, is commonly used in pregnancy. In women with chronic hypertension, there were no significant differences in perinatal outcomes when compared with placebo or methyldopa (26, 42). Based on comparisons with placebo or other antihypertensive agents for mild to moderate hypertension in pregnancy, labetalol is a reasonable choice in women with chronic hypertension (27). Adverse effects include lethargy, fatigue, sleep disturbances, and bronchoconstriction. Labetalol should be avoided in women with asthma, heart disease, or congestive heart failure. Beta-blockers alone have been used extensively in pregnancy and are effective in lowering BP (27). However, β-blockers may be associated with an increase in SGA infants (RR, 1.34; 95% CI, 1.01–1.79) compared with placebo or no treatment (47).

Calcium channel blockers are a class of drugs that has not been extensively studied in pregnant women with chronic hypertension. Extrapolation from the comparison trials for mild to moderate hypertension in pregnancy, in which nifedipine was the most commonly prescribed calcium channel blocker, indicates no increase in adverse perinatal outcomes (26, 48). Furthermore, nifedipine does not appear to adversely affect uterine or umbilical blood flow (49, 50).

Diuretics are generally considered second-line drugs for the treatment of hypertension in pregnancy (51). Theoretical concern has been raised regarding the potential for diuretics to cause intravascular volume depletion and thereby lead to fetal growth restriction. However, this is not supported based on data from a meta-analysis of nine randomized trials as well as a Cochrane systematic review of diuretics for the prevention of preeclampsia (52, 53). Thus, diuretics may be used in pregnancy with dose adjustments to minimize adverse effects and risks such as hypokalemia. They may be especially useful in women with known salt-sensitive hypertension, particularly in the setting of reduced renal function.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers used in the second and third trimesters of pregnancy are associated with fetal abnormalities (including renal failure, oligohydramnios, pulmonary hypoplasia, calvarial abnormalities, and fetal growth restriction) as well as postdelivery effects such as oliguria and anuria (54). Serious concerns also have been raised regarding first-trimester exposure and congenital anomalies. Based on a review of 29,096 Tennessee Medicaid records, 209 infants were exposed to ACE inhibitors in the first trimester with an RR for congenital malformations of 2.71 (95% CI, 1.72–4.27) compared with women not taking antihypertensive drugs (55). Cardiac and central nervous system anomalies were most common. In the Kaiser Northern California database, first-trimester

ACE inhibitor use was associated with a higher rate of cardiac malformations compared with normal controls (adjusted OR, 1.54; 95% CI, 0.9–2.62), but not significantly higher than women with chronic hypertension with or without other medications (adjusted OR, 1.14; 95% CI, 0.65–1.98).

Based on the currently available data, the task force recommends discontinuation of ACE inhibitors and angiotensin-receptor blockers, as well as associated classes of medications such as the renin inhibitors and mineralocorticoid receptor antagonists, during pregnancy (33). Because 50% of pregnancies are unplanned, these medications should be avoided in women of reproductive age. If these medications are unavoidable or strongly indicated (eg, proteinuric renal disease), then women should be counseled regarding risks and effective contraception recommended. In select and rare cases in which there is a compelling reason to continue ACE inhibitors until conception, extensive counseling of risk and benefits is warranted.

TASK FORCE RECOMMENDATIONS

- For the initial treatment of pregnant women with chronic hypertension who require pharmacologic therapy, labetalol, nifedipine, or methyldopa are recommended above all other antihypertensive drugs.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women with uncomplicated chronic hypertension in pregnancy, the use of ACE inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

- For women of reproductive age with chronic hypertension, the use of ACE inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists is not recommended unless there is a compelling reason, such as the presence of proteinuric renal disease.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Prevention of superimposed preeclampsia. Various nutritional modifications, addition of supplemental vitamins, and medications have been evaluated in large randomized controlled trials designed to prevent preeclampsia. The task force could locate few studies that have been performed exclusively in women with chronic hypertension; however, hypertensive women have been included as subgroups in trials of high-risk women.

Meta-analysis and systematic reviews have demonstrated that the use of antiplatelet agents (eg, low-dose aspirin) is associated with a small but statistically significant reduction (17%) in preeclampsia (56). Women considered to be at high risk (including those with chronic hypertension) may experience a benefit as great as a 25% reduction (95% CI, 34–15% reduction) (57). Small effects (approximately a 10% reduction) on fetal outcomes (fetal survival or preterm birth) also were observed. Another meta-analysis suggested that benefits were greater when low-dose aspirin was initiated earlier in pregnancy (58).

Calcium supplementation also has been extensively studied for the prevention of preeclampsia. A Cochrane meta-analysis of 13 studies (more than 15,000 women) concluded that calcium supplementation of 1 g or greater was associated with an approximate 50% reduction in BP and development of preeclampsia (17). The effect was greatest for high-risk women (five trials, 587 women; risk ratio [RR], 0.22; 95% CI, 0.12–0.42) and those with low baseline calcium intake (eight trials, 10,678 women; RR, 0.36; 95% CI, 0.20–0.65). Preterm birth was reduced modestly (RR, 0.76; 95% CI, 0.60–0.97) and among women at high risk of developing preeclampsia recruited to four small trials (568 women; RR, 0.45; 95% CI, 0.24–0.83). Additional preventive strategies that have been tested, primarily in low-risk women, have not been shown to reduce the rate of preeclampsia or improve maternal and fetal outcomes.

- For women with chronic hypertension who are at a greatly increased risk of adverse pregnancy outcomes (history of early-onset preeclampsia and preterm delivery at less than 34 0/7 weeks of gestation or preeclampsia in more than one prior pregnancy), initiating the administration of daily low-dose aspirin (60–80 mg) beginning in the late first trimester is suggested.*

  Quality of evidence: Moderate
  Strength of recommendation: Qualified

*Meta-analysis of more than 30,000 women in randomized trials of aspirin to prevent preeclampsia indicates a small reduction in the incidence and morbidity of preeclampsia and reveals no evidence of acute risk, although long-term fetal effects cannot be excluded. The number of women to treat to have a therapeutic effect is determined by prevalence. In view of maternal safety, a discussion of the use of aspirin in light of individual risk is justified.

Fetal Surveillance for Women With Chronic Hypertension

The risk of fetal growth restriction is higher in pregnant women with chronic hypertension. In patients with mild chronic hypertension, the incidence of SGA infants is 8–15.5%, but in women with severe chronic hypertension, the incidence may be as high as 40% (1, 8, 59). Fetuses with growth restriction are at an increased risk of perinatal morbidity (60).

Ideally, identification of fetal growth restriction should allow obstetric interventions to decrease perinatal risks. Two methods primarily used to screen for fetal growth restriction are 1) measurement of fundal height and 2) ultrasonographic estimation of fetal weight. Fundal height measurements are more suitable in women who are at low risk of fetal growth restriction. The sensitivity for fundal height measurement to detect fetal growth restriction is inadequate for high-risk women (61). In pregnancies at high risk of fetal growth restriction based on maternal disease such as hypertension, the preferred method for screening is ultrasonography. Based on observational data, the best predictor of fetal growth restriction is serial ultrasonographic assessments of either fetal weight or abdominal circumference (62). The optimal timing and frequency of examinations is not known. The timing and frequency of ultrasonography for fetal growth is based on the clinical scenario, such as prior obstetric history, severity of hypertension, and coexisting morbidities.

It remains unclear whether the antenatal detection of fetal growth restriction decreases perinatal mortality. In a systematic review of more than 27,000 low-risk women, screening compared with no screening with ultrasonography after 24 weeks of gestation did not improve perinatal outcomes (63). In high-risk pregnancies, no data exist to address this issue. Based on expert opinion, early detection and appropriate management of fetal growth restriction is expected to decrease the stillbirth rate by 20% (64).

TASK FORCE RECOMMENDATION

- For women with chronic hypertension, the use of ultrasonography to screen for fetal growth restriction is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Doppler velocimetry studies of the fetoplacental unit can be used antenatally to detect increased placental resistance and fetal vascular response. Umbilical artery Doppler velocimetry is often used in conjunction with antenatal testing to determine the optimal timing of delivery in a fetus with growth restriction. Absent end-diastolic flow and reversed end-diastolic flow are indicative of fetal compromise. If umbilical artery Doppler velocimetry is abnormal, timing of the delivery is based on the gestational age and the severity of the Doppler velocimetry abnormality.

In a systematic review of 10,156 high-risk pregnancies from 18 randomized studies, the use of umbilical artery Doppler testing compared with either no Doppler or nonstress test (NST) alone reduced perinatal mortality by 29% (RR, 0.71; 95% CI, 0.52–0.98) without increasing rates of induction of labor (RR, 0.89; 95% CI, 0.80–0.99) or cesarean delivery (RR, 0.92; 95% CI, 0.84–0.97). Studies incorporated into this analysis were not of high quality and were not limited to patients with hypertension with or without fetal growth restriction (65).

TASK FORCE RECOMMENDATION

- If evidence of fetal growth restriction is found in women with chronic hypertension, fetoplacental assessment to include umbilical artery Doppler velocimetry as an adjunct antenatal test is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Fetal antenatal surveillance with either an NST, biophysical profile (BPP), or a modified BPP may be beneficial in reducing perinatal morbidity and mortality in high-risk pregnancies (66). In patients with chronic hypertension, data for the specific time to initiate antenatal testing, the testing interval, and the most effective antenatal test to use are lacking. Based on observational studies in populations at high risk of intrauterine fetal demise, antepartum fetal surveillance with either is often recommended to decrease perinatal morbidity. Patients with chronic hypertension at highest risk of perinatal mortality have either fetal growth restriction or superimposed preeclampsia.

A systematic review of NSTs compared with no or concealed NSTs in 2,105 high-risk women from six randomized or quasi-randomized trials showed no difference in perinatal mortality (RR, 2.05; 95% CI, 0.95–4.42) or potentially preventable deaths (RR, 2.46; 95% CI, 0.96–6.30) (65). When BPPs were compared with NSTs or modified BPPs in a systematic review of five trials that involved 2,974 high-risk women, there was no significant difference in perinatal deaths between the groups (RR, 1.33; 95% CI, 0.60–2.98) (67).

TASK FORCE RECOMMENDATION

- For women with chronic hypertension complicated by issues such as the need for medication, other underlying medical conditions that affect fetal outcome, any evidence of fetal growth restriction, and superimposed preeclampsia, antenatal fetal testing is suggested.

  Quality of evidence: Low
  Strength of recommendation: Qualified

Intrapartum Management

The optimal delivery time to reduce maternal and fetal morbidity and mortality in women with chronic hypertension, with or without maternal or fetal complications, has not been studied. Trials that have been conducted included women with hypertensive disorders of pregnancy, such as gestational hypertension and preeclampsia with or without preexisting hypertension. Hypertensive disorders of pregnancy affect a heterogeneous population, but data are often extrapolated to women with chronic hypertension.

In women with chronic hypertension and without any obstetric complications, a small clinical trial suggests that the risk of adverse perinatal outcomes is similar to women without chronic hypertension (59). Findings in a population-based cohort study suggest that the optimal timing for women with uncomplicated hypertension is between 38 weeks of gestation and 39 weeks of gestation (68). Delivery in this gestational age group optimizes fetal outcomes while decreasing neonatal morbidity. In a systematic review of 22 studies that involved almost 30 million infants, late preterm birth is associated with increased neonatal complications and death within the first year of life (69). Without a known maternal or fetal benefit but with known risk of neonatal complications, delivery before 38–39 weeks of gestation is not warranted in patients with only isolated, uncomplicated chronic hypertension (70).

TASK FORCE RECOMMENDATION

- For women with chronic hypertension and no additional maternal or fetal complications, delivery before 38 0/7 weeks of gestation is not recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Superimposed Preeclampsia

Definition and Diagnosis

Superimposed preeclampsia refers to women with chronic hypertension who develop preeclampsia. Distinguishing superimposed preeclampsia from benign gestational increases in BP and proteinuria that are often observed in women with chronic hypertension can be quite challenging. Given the higher risk of adverse pregnancy outcomes with superimposed preeclampsia, overdiagnosis may be preferable, with the goal of increasing vigilance and preventing catastrophic maternal and fetal outcomes. Alternatively, a more specific and stratified approach based on severity and predictors of adverse outcome may be useful in guiding clinical management and avoiding unnecessary preterm births.

Based on these considerations, the task force proposes that superimposed preeclampsia be stratified into two groups to guide management: 1) superimposed preeclampsia and 2) superimposed preeclampsia with severe features.

Superimposed preeclampsia is likely when any of the following are present:

- A sudden increase in BP that was previously well controlled or escalation of antihypertensive medications to control BP
- New onset of proteinuria or a sudden increase in proteinuria in a woman with known proteinuria before or early in pregnancy

The diagnosis of superimposed preeclampsia with severe features is established when any of the following are present:

- Severe-range BP despite escalation of antihypertensive therapy
- Thrombocytopenia (platelet count less than 100,000/microliter)
- Elevated liver transaminases (two times the upper limit of normal concentration for a particular laboratory)
- New-onset and worsening renal insufficiency
- Pulmonary edema
- Persistent cerebral or visual disturbances

Clinicians should recognize that there is often ambiguity in the diagnosis of superimposed preeclampsia and that the clinical spectrum of disease is broad. Furthermore, women with superimposed preeclampsia can progress and develop end-organ

involvement and adverse outcomes. Therefore, increased surveillance but not intervention (eg, delivery) is warranted even if the diagnosis is suspected and not definitive. Future investigation is needed to further refine the diagnosis, potentially including markers that are predictive of adverse outcome.

Initial Evaluation of Women With Superimposed Preeclampsia

Initial evaluation of women with superimposed preeclampsia should occur in a hospital setting to confirm the diagnosis, evaluate maternal–fetal status, and monitor for progressive worsening of the disease. The clinical workup should include questions about symptoms associated with preeclampsia (neurologic symptoms, epigastric or right upper quadrant pain, nausea and vomiting, vaginal bleeding, and fetal movement). Serial BP measurements should be obtained. Physical examination should be performed with attention to signs of preeclampsia and associated complications. Proteinuria should be assessed by a protein/creatinine ratio or 24-hour urine collection. Laboratory evaluation should also include a complete blood count with platelets, liver transaminases, lactic dehydrogenase, and creatinine assessment. Uric acid assessment also may be helpful if uric acid concentrations are known from early pregnancy because hyperuricemia is associated with adverse outcomes in superimposed preeclampsia and also with early renal dysfunction, which may be present with chronic hypertension (71, 72). Ideally, these laboratory results are compared with baseline information obtained in early pregnancy. If abnormalities are of new-onset, then the diagnosis of superimposed preeclampsia; end-organ involvement; or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome can be confirmed. If abnormalities are long-standing or of unknown duration, results should be cautiously interpreted before a definitive diagnosis is established. Although not included in the diagnostic criteria for superimposed preeclampsia, fetal growth and well-being should be assessed when superimposed preeclampsia is suspected. Additional testing or interventions or both may be warranted if there are concerns regarding fetal status.

Antihypertensive Treatment for Superimposed Preeclampsia

Clinical trials that have evaluated antihypertensive therapy that included women with chronic hypertension have not specifically addressed lowering BP once the diagnosis of superimposed preeclampsia is established. Therefore, recommendations regarding antihypertensive treatment in this group are extrapolated from the evidence based on chronic hypertension in pregnancy and preeclampsia. Pharmacologic antihypertensive therapy should be used for women with hypertension (systolic BP 160 mm Hg or higher or diastolic BP 105 mm Hg or higher) or at even lower levels if there is evidence of end-organ involvement to prevent acute maternal cerebrovascular and coronary events (19). Treatment of women with systolic BP 140–160 mm Hg or diastolic BP 90–105 mm Hg has not been shown to be beneficial in decreasing adverse perinatal outcomes but reduces progression to severe hypertension (27). Initiation of antihypertensive medications or an increase in dosages because of worsening BP in the setting of superimposed preeclampsia should occur in the hospital setting while monitoring for worsening maternal–fetal status. Acute lowering of severe hypertension may be accomplished by intravenous or oral medications (intravenous labetalol, intravenous hydralazine, or oral nifedipine) (Table 7-1). Long-term treatment of BP that maintains levels below the severe range generally involves the use of oral agents such as labetalol, nifedipine, or methyldopa as initial agents (Table 7-2).

Antepartum Management of Superimposed Preeclampsia

General considerations in the antepartum management of women with superimposed preeclampsia include the administration of antenatal corticosteroids and use of magnesium sulfate for seizure prophylaxis. Ongoing management and timing of delivery is based on gestational age and the severity of disease.

Antenatal Corticosteroids

Women with superimposed preeclampsia diagnosed before 37 weeks of gestation are at increased risk of preterm delivery. Therefore, antenatal corticosteroids should be administered at less than 34 weeks of gestation for fetal lung maturity benefit to decrease neonatal morbidity and mortality (73).

TASK FORCE RECOMMENDATION

- For women with superimposed preeclampsia who receive expectant management at less than 34 0/7 weeks of gestation, the administration of corticosteroids for fetal lung maturity benefit is recommeded.

  Quality of evidence: High
  Strength of the recommendation: Strong

Magnesium Sulfate for Seizure Prophylaxis

Eclampsia is associated with maternal mortality in the range of 0.3–1% and serious morbidity, including renal failure, pulmonary edema, aspiration pneumonia, stroke, and cardiopulmonary arrest (74). There also is evidence of long-term maternal sequelae, such as persistence of white-matter lesions and impaired cognitive function (75, 76). Magnesium sulfate has been shown to be superior to a number of other agents for the prevention of seizures in women with preeclampsia.

The frequency of eclampsia in women with chronic hypertension and superimposed preeclampsia is not well defined but ranges from 0% to 2.4% as reported in observational and small retrospective studies (77, 78). Currently, no data appear to specifically address the use of magnesium sulfate for seizure prophylaxis for the subgroup of women with superimposed preeclampsia. Therefore, evidence from the general preeclampsia literature must be used to guide management. For women with chronic hypertension and superimposed preeclampsia with severe features, the task force recommends the administration of intrapartum–postpartum parenteral magnesium sulfate to prevent eclampsia. In the absence of data that specifically address superimposed preeclampsia without any severe features, the collective opinion of the task force is against the use of magnesium sulfate for seizure prophylaxis during labor and delivery in this subgroup. However, signs and symptoms that have traditionally been considered premonitory to eclampsia (eg, neurologic symptoms, clonus, and right upper quadrant pain), as well as worsening clinical course to severe disease, should be considered in the decision to initiate magnesium during labor and delivery.

TASK FORCE RECOMMENDATION

- For women with chronic hypertension and superimposed preeclampsia with severe features, the administration of intrapartum–postpartum parenteral magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Timing and Indications for Delivery

Indications for and timing of delivery in superimposed preeclampsia are based on gestational age, severity of disease, progression of disease, and ongoing assessment of maternal and fetal well-being. With any attempts to prolong pregnancy, the potential fetal–neonatal benefits must be weighed against maternal and fetal morbidity and mortality.

Gestational age of 37 weeks or older. Delivery is suggested for superimposed preeclampsia diagnosed at term (37 weeks of gestation or more). Neonatal outcomes are favorable, and continuation of pregnancy incurs risk to the woman and her fetus (70).

Gestational age of less than 37 weeks. In the absence of severe features and with reassuring fetal status, expectant management with ongoing close maternal and fetal surveillance is reasonable. There is a paucity of data to support outpatient management of superimposed preeclampsia. However, if an outpatient approach is undertaken, maternal adherence to home BP monitoring, reporting of symptoms, physician visits one to two times a week, weekly laboratory testing, and fetal surveillance are important. Women with superimposed preeclampsia with worsening disease, severe features, or concern for fetal well-being should be monitored as inpatients (see the following section "Management of Superimposed Preeclampsia With Severe Features").

Optimal delivery timing between 34 weeks of gestation and 37 weeks of gestation in superimposed preeclampsia without any evidence of severe features or worsening disease is unclear. A retrospective cohort study that used a perinatal database found no difference in perinatal outcomes between superimposed preeclampsia and preeclampsia; however, there was a higher rate of delivery at less than 34 weeks of gestation (17.3% versus 8.7%; $P<0.001$), cesarean delivery (46.2% versus 36.3%; $P<0.001$), and neonatal intensive care unit admission (16.3% versus 11.4%; $P<0.002$) (79). These data indicate a higher risk of intervention-related events and morbidity among women with superimposed preeclampsia compared with women with preeclampsia, thus raising the issue of potentially unnecessary iatrogenic preterm births with superimposed preeclampsia. If extrapolated from the general preeclampsia literature, delivery for severe preeclampsia (expectantly managed) is suggested at 34 weeks of gestation and at 37 weeks of gestation for preeclampsia without severe features (70, 80, 81). The task force suggests that superimposed preeclampsia with severe features be managed in a manner similar to severe preeclampsia and superimposed preeclampsia without severe features be managed in a manner similar to preeclampsia without severe features. Future research and investigation is needed to better delineate the risk–benefit balance of pregnancy continuation between 34 weeks of gestation and 37 weeks of gestation among women with superimposed preeclampsia. If the disease has remained stable without evidence of progression or severe features, delivery at 37 weeks of gestation is suggested.

TASK FORCE RECOMMENDATION

- For women with superimposed preeclampsia without severe features and stable maternal and fetal conditions, expectant management until 37 0/7 weeks of gestation is suggested.

  Quality of evidence: Low
  Strength of the recommendation: Qualified

Management of Superimposed Preeclampsia With Severe Features

Before 34 weeks of gestation, management options for superimposed preeclampsia with severe features are as follows: immediate delivery after maternal stabilization, short-term prolongation to achieve steroid benefit for the fetus, or long-term prolongation (expectant management) to increase gestational age and improve neonatal outcomes. Given the paucity of clinical trials and prospective studies in women with superimposed preeclampsia, the indications and timing of delivery are based on indirect evidence from the management of preeclampsia (11). Two randomized trials that included 133 women and a number of observational studies provide the basis for management of severe preeclampsia (80–82). Because of the significant maternal–fetal or maternal–neonatal morbidity, immediate delivery after maternal stabilization is recommended if any of the following are present: uncontrollable severe hypertension, eclampsia, pulmonary edema, disseminated intravascular coagulation, new or increasing renal dysfunction or both, abruptio placentae, or nonreassuring fetal status. Many of these studies do not clearly differentiate between immediate delivery and an attempt to achieve some level of steroid benefit (80, 83). Given the neonatal benefit of antenatal corticosteroids and some data supporting the expectant management of HELLP syndrome and fetal growth restriction (80, 83–85), it is reasonable to delay delivery in a subset of women with severe disease to achieve the benefits of antenatal corticosteroid use (48 hours). Women with neurologic or epigastric pain symptoms, HELLP syndrome or partial HELLP syndrome, thrombocytopenia, elevated liver transaminases, or fetal growth restriction are potential candidates for short-term pregnancy prolongation with close inpatient monitoring and readily available tertiary obstetric, neonatal, and anesthesia services. Delivery is recommended if there is worsening of maternal or fetal status. Parenteral magnesium sulfate is recommended for seizure prophylaxis.

For women with superimposed preeclampsia diagnosed before 34 weeks of gestation, published data regarding expectant management beyond the 48 hours to achieve steroid benefit are limited. Thus, management is based on extrapolation of indirect evidence from management of severe preeclampsia, as well as direct evidence from retrospective studies of expectant management of superimposed preeclampsia. Expectant management beyond the 48 hours of antenatal corticosteroid administration in two randomized trials of severe preeclampsia at less than 34 weeks of gestation was associated with significant prolongation of pregnancy, reduction in neonatal respiratory distress syndrome, fewer days in the neonatal intensive care units, and higher birth weight with reasonable maternal safety in the expectantly managed group (80–82). Women with severe preeclampsia were candidates for expectant management if BP was controlled, there was no evidence of severe end-organ involvement, and fetal status was reassuring without growth restriction.

The subgroup of women with superimposed preeclampsia diagnosed before 34 weeks of gestation is typically excluded from studies focusing on the expectant management of preeclampsia, and if included, their outcomes are generally not reported separately (81, 82, 86, 87). Prospective studies of women with chronic hypertension allude to expectant management of women with superimposed preeclampsia, but this issue is not clearly addressed. For example, in a prospective cohort of 861 women with chronic hypertension enrolled in the Vitamins in Preeclampsia Trial, the incidence of superimposed preeclampsia was 22%, and 51% of these women gave birth before 37 weeks of gestation (77). The average antenatal inpatient stay was 7.3 days, suggesting that an expectant management approach was taken in at least a subset of patients with superimposed preeclampsia. A retrospective case series of expectant management of preeclampsia specifically reported on a subset of 29 women with superimposed preeclampsia (88). Compared with women with severe preeclampsia in this series, women with superimposed preeclampsia had similar latency periods (8.4 days versus 8.5 days) and no difference in the rates of abruptio placentae, oliguria, or HELLP syndrome.

Another retrospective review focused on women with superimposed preeclampsia at a single institution in the United States who were expectantly managed beyond 48 hours to achieve steroid benefit and gave birth before 37 weeks of gestation (78). In this series of 41 women, the median gestational age at diagnosis was 31.6 weeks, and the mean time from diagnosis to delivery was 9.7 days, with a wide range of 2–34 days. There were no perinatal deaths, and adverse outcomes included two cases of abruptio

placentae, one pulmonary edema, one case of progression to HELLP syndrome, and an average neonatal intensive care unit stay of 17.9 days. Although these studies are small and fraught with limitations, they suggest that the rate of adverse outcomes and latency periods are comparable with those observed with expectant management of preterm severe preeclampsia (80). Thus, expectant management in women with superimposed preeclampsia before 34 weeks of gestation in the hospital setting, as espoused with preterm severe preeclampsia, appears reasonable. Prospective studies are needed to quantify the risks and benefits of this approach.

For women with superimposed preeclampsia with severe features undergoing expectant management before 34 weeks of gestation, inpatient management is recommended with delivery at 34 weeks of gestation. This is based on the morbidity associated with severe preeclampsia and the approach taken in randomized clinical trials (80, 82, 83). As with the expectant management of severe preeclampsia, parenteral magnesium sulfate is recommended during the initial evaluation and stabilization period (generally 24 hours) before expectant management.

As with severe preeclampsia, if superimposed preeclampsia with severe features is newly diagnosed after 34 weeks of gestation, delivery should be accomplished after stabilization of maternal status.

TASK FORCE RECOMMENDATIONS

- Delivery soon after maternal stabilization is recommended irrespective of gestational age or full corticosteroid benefit for women with superimposed preeclampsia that is complicated further by any of the following:
  - uncontrollable severe hypertension
  - eclampsia
  - pulmonary edema
  - abruptio placentae
  - disseminated intravascular coagulation
  - nonreassuring fetal status

  Quality of evidence: Moderate
  Strength of the recommendation: Strong

- For women with superimposed preeclampsia with severe features at less than 34 0/7 weeks of gestation with stable maternal and fetal conditions, it is recommended that continued pregnancy be undertaken only at facilities with adequate maternal and neonatal intensive care resources.

  Quality of evidence: Moderate
  Strength of evidence: Strong

- For women with superimposed preeclampsia with severe features, expectant management beyond 34 0/7 weeks of gestation is not recommended.

  Quality of evidence: Moderate
  Strength of the recommendation: Strong

Management of Women With Chronic Hypertension in the Postpartum Period

Women with chronic hypertension before and during pregnancy will usually require treatment with antihypertensive medications in the postpartum period, even if they were not treated during pregnancy. Because the American College of Obstetricians and Gynecologists encourages all women to breastfeed their infants, antihypertensive medications that are safe for breastfeeding (ie, they tend not to be secreted into breast milk) should be prescribed.

The task force is not aware of clinical trials that specifically address management of postpartum hypertension in women with any form of hypertension in pregnancy. Blood pressure in the postpartum period is often higher compared with antepartum levels, particularly in the first 1–2 weeks (89, 90). Medication should be adjusted to maintain BP in a safe range (less than 160 mm Hg systolic and 100 mm Hg diastolic). Use of nonsteroidal antiinflammatory agents should be avoided in the postpartum period in women with chronic hypertension, particularly those with superimposed preeclampsia. Extensive documentation exists that nonsteroidal antiinflammatory agents increase BP and sodium retention in patients who are not pregnant. Although use of these medications have not been investigated in the postpartum period, alternative strategies are recommended.

Magnesium sulfate is indicated if there are signs and symptoms of persistent or new-onset superimposed preeclampsia, such as severe headache, visual disturbances, shortness of breath, and signs of HELLP syndrome. Older women, women with comorbidities (obesity, diabetes, or kidney disease), and those with an onset of hypertension at an earlier gestational age may be at greater risk of prolonged elevations in BP postpartum (89). It also has been observed that eclampsia and adverse cerebrovascular events associated with pregnancy are more likely to occur in the postpartum period (90). The role of BP control in preventing these outcomes has not been well studied; however, antihypertensive medications may be used more liberally in the postpartum period, and if cerebral symptoms are present, BP should be lowered. If hypertension in the postpartum period remains severe despite adequate doses of two antihypertensive

medications, the woman should be referred to a hypertension specialist to rule out secondary causes.

Breastfeeding

Good clinical practice suggests that women with chronic hypertension should be encouraged to breastfeed, although the task force is not aware of clinical trials that have assessed either maternal or fetal outcomes in this patient population. Many, if not most, types of antihypertensive medications are detectable, albeit at low concentrations, in breast milk.

In general, drugs that are bound to plasma proteins are not transferred to breast milk. Lipid-soluble drugs may achieve higher concentrations compared with water-soluble drugs. Methyldopa is considered safe, and concentrations in breast milk are low. Several β-blockers are concentrated in breast milk, with atenolol and metoprolol resulting in high concentrations, and propranolol and labetalol resulting in low concentrations. Both captopril and enalapril concentrations in breast milk have been reported as low, and many consider these drugs to be safe for breastfeeding; however, in women who require high doses, other agents are appropriate. There are only limited reports of calcium channel blockers and their transfer into breast milk; no adverse effects have been reported. Although the concentration of diuretics in breast milk is usually low, these agents may reduce the quantity of milk production and interfere with the ability to successfully breastfeed. The task force is unaware of clinical trials that evaluate outcomes of children exposed to antihypertensive medications in breast milk.

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CHAPTER 8

Later-Life Cardiovascular Disease in Women With Prior Preeclampsia

Several large epidemiologic studies demonstrate that all women with a history of preeclampsia have an increased risk of cardiovascular (CV) diseases later in life. For many years, the older literature was misinterpreted to suggest that women with preeclampsia only in a first pregnancy were not at increased risk. However, more recent studies with larger numbers of participants and longer follow-up indicate an increased risk of later-life CV disease even with preeclampsia in a first pregnancy (1). This risk is much greater if the woman has recurrent preeclampsia (2), gave birth preterm (less than 37 weeks of gestation), or had a pregnancy with fetal growth restriction (1, 3, 4), with risk rates at least equaling the CV risk with obesity or smoking (5). In 2011, the American Heart Association added preeclampsia to its list of risk factors for CV disease (6). Prepregnancy risk factors and preeclampsia may both contribute to the development of long-term CV disease risk (7). Preeclampsia, particularly when associated with preterm delivery, should be considered as a strong risk factor for CV disease (data exist to support that it is quantitatively similar in magnitude to the increase in the risk of having diabetes) (7). These individuals are at increased risk of hypertension and CV disease (myocardial infarction, stroke, and congestive heart failure) (3) and, therefore, should be advised to 1) maintain ideal body weight; 2) engage in aerobic exercise regularly (five times per week); 3) eat a diet high in fiber, vegetables, and fruits and low in fat (the Dietary Approaches to Stop Hypertension diet); and 4) avoid tobacco. Evaluation for risk of later-life CV disease requires health care provider and patient consideration (Box 8-1).

TASK FORCE RECOMMENDATION

- For women with a medical history of preeclampsia who gave birth preterm (less than 37 0/7 weeks of gestation) or who have a medical history of recurrent preeclampsia, yearly assessment of blood pressure, lipids, fasting blood glucose, and body mass index is suggested.*

  Quality of evidence: Low
  Strength of recommendation: Qualified

*Although there is clear evidence of an association between preeclampsia and later-life CV disease, the value and appropriate timing is not yet established. Health care providers and patients should make this decision based on their judgment of the relative value of extra information versus expense and inconvenience.

BOX 8-1. Evaluation for Risk Factors ⇦

- How many pregnancies have you had?
- How many miscarriages have you had?
- Were any of your babies born early (more than 3 weeks before your due date)?
  – How many?
  – Did this occur spontaneously or were the babies delivered early because you were ill?
- Did you have preeclampsia in any of your pregnancies?
  – Which pregnancy?
  – How many times?
  – Was the baby delivered early because you had preeclampsia?
  – How many weeks before your due date was the baby delivered?
- Did you have high blood pressure in any pregnancy?
  – Did you have protein in your urine in that pregnancy?
  – Do you have a family history of preeclampsia? Is there a history of preeclampsia in your partner's family?
- Did you have gestational diabetes?
  – Were you treated with insulin or blood glucose-lowering pills?
- What were the birth weights of your babies, and how many weeks before your due date were they delivered?
- Do you have a medical history of high blood pressure or chronic kidney disease?

Modified from Roberts JM, Catov JM. Pregnancy is a screening test for later life cardiovascular disease: now what? Research recommendations. Womens Health Issues 2012;22:e123–8.

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CHAPTER 9

Patient Education

Many millions of dollars have been spent on clinical and laboratory research in an effort to discover the pathogenesis of prophylactic measures for and optimal treatment of preeclampsia. Although these goals are of the utmost importance, a more effective use of currently available information and resources may reduce the burden of morbidity and mortality that arises in association with preeclampsia. Health services interventions, including patient education, may not only help to reduce this burden, particularly among populations at greatest risk (eg, those with low health literacy or at highest risk of developing preeclampsia), but also may reach that goal at a relatively low cost. Patient and health care provider education is key to the successful recognition and management of preeclampsia. Health care providers need to inform women during the prenatal and postpartum periods of the signs and symptoms of preeclampsia and stress the importance of contacting health care providers if these are evident. This can be accomplished without increasing patient anxiety (1).

Little is understood about how to best educate women about preeclampsia and provide them with the information needed to seek prompt and appropriate care. What is known is that the population, in general, has difficulty understanding even basic health information, and preeclampsia, specifically, is a poorly understood complication of pregnancy (2). Education techniques that are appropriate for patients with poor literacy skills have been researched and described in the literature. These can be applied to patient education about preeclampsia with the goal of ensuring that the best possible outcomes are achieved with the resources currently available.

Importance of Patient Education

In the developed world, the frequency of adverse maternal and perinatal events related to preeclampsia remains markedly lower than in developing countries, largely because of the greater number of available resources and routine hypertension and proteinuria screening (3–5). Interventions for women with disease include increased monitoring, magnesium sulfate, antihypertensive medications, corticosteroids for fetal lung maturation, and delivery. To maximally benefit from these resources, however, women must first seek medical care in a timely fashion.

The possibility that women do not seek timely care may be increased if they have a poor understanding of the signs and symptoms of preeclampsia. Several recent studies emphasized the potential value of educating patients to report and their health care providers to act on signs and symptoms of severe preeclampsia that commonly precede eclampsia, hypertensive encephalopathy, pulmonary edema, or stroke (6–11). This hypothesis is further supported by studies of women in whom preeclampsia was diagnosed, received timely and proper surveillance, and had fewer adverse events

than those with delayed diagnosis (12). Regardless of literacy level and understanding of preeclampsia, this knowledge deficit appears to be modifiable because women who acknowledge receiving information about the disease demonstrate greater preeclampsia-specific knowledge (2).

Beyond improving outcomes, it is the ethical responsibility of the health care system and the health care providers who work within that system to ensure that patients have been educated about the implications and complications of a specific health state, including pregnancy. According to the American Medical Association, "Patients have the right to understand healthcare information that is necessary for them to safely care for themselves, and to choose among available alternatives. Health care providers have a duty to provide information in simple, clear and plain language and to check that the patients have understood the information before ending the conversation" (13).

Patient Education Strategies

Although few would debate the importance of patient education, the question still remains as to how best to provide such education about preeclampsia. The solution is complex because it is estimated that approximately one half of the American population has a limited capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (14, 15). In addition, an overall paucity of published research addresses patient education in the context of pregnancy. Consequently, models for successful interventions that address health-related outcomes are found outside the context of pregnancy. In 2007, the American Medical Association Foundation published a monograph summarizing research related to health literacy. The publication also provided recommendations on how health care providers can effect change in the practice environment as it relates to patient education when considering a population with limited health literacy (16). A summary of recommendations is listed in Box 9-1.

Predicting who is affected by inadequate health literacy skills is challenging because the problem is ubiquitous, spanning all races and income and education levels. Certainly, an obstetric care provider can relay both the symptoms of preeclampsia in nonmedical language (Box 9-1) and the appropriate actions that should be taken should those symptoms arise; however, if that message is relayed in a manner that is poorly understood by the patient, it is of little to no value. Hence, any educational intervention should be created so that patients with even limited literacy skills can understand and act on the information.

It is not only important that medical care providers offer easy-to-understand and straightforward verbal communication, but also that appropriate aids are used for women to take with them that offer visual reminders at home. These should be written at no greater than a fifth-grade or sixth-grade reading level, be graphic-based, and be culturally sensitive (16–21). For example, relaying to a patient that she should notify her health care provider if she experiences right upper quadrant pain, headache, or visual alterations may be confusing to the patient and her family. The health care provider should instead explain that the patient should notify her health care provider if she has pain in her stomach, has a headache, or sees spots. The health care provider could then point to the areas of concern (abdomen, head, and eyes) and provide a graphic-based tool intended to relay the same concept (22, 23). A group of researchers found that after distributing a card depicting pictures of preeclampsia signs and symptoms to women in certain Jamaican parishes, women from these parishes had lower rates of preeclampsia-related morbidity than women from

BOX 9-1. Key Components of Effective Health Communication and Patient Education ⇦

- Do not assume a patient's literacy level or understanding based on her appearance.
- In both oral and written communication, use plain, nonmedical language.
- Speak slowly.
- Organize information into two or three components.
- Ask the patient to "teach back" information to confirm understanding.

Data from Nielsen-Bohlman L, Panzer AM, Kindig DA, editors. Health literacy: a prescription to end confusion. Committee on Health Literacy, Board on Neuroscience and Behavioral Health, Institute of Medicine. Washington, D.C.: The National Academies Press; 2004. p. 345.

parishes who had not received the card (22). The health care provider should also ask the patient to "teach back" the information to confirm the patient's understanding. An example would include, "We have gone over a lot of information. In your own words, can you tell me what we discussed today? What would make you call your health care provider or come to the hospital?" This should take the place of close-ended questions such as, "Did you understand the material discussed today?" (16).

Grouping information together and then checking for understanding—"chunk and check"—also is a way to provide information that is easier to understand and remember. When applying this concept to preeclampsia, a health care provider could break down the conversation by explaining the syndrome, its implications, the associated symptoms, and the appropriate actions that should be used if a patient experiences symptoms. Each of these broad ideas could include two or three details (Box 9-2). The health care provider should check for understanding using the teach-back method before moving on to the next idea (16).

Mobile applications are increasingly being used to reach diverse populations. More than 85% of Americans own a cell phone, and 72% of cell phone users send or receive text messages (24). Text4Baby, a text-messaging program that sends out timed prenatal and postpartum information to registered mobile phones, recently reported positive results since its launch in February 2010 (25). Time spent in the patient reception area can be used to convey information by way of TV monitors and print material written at the fifth-grade to sixth-grade reading level. Group prenatal care, often called "centering pregnancy," has been found to be effective in conveying information and improving perinatal outcomes at no added cost (26).

Patient Education Barriers

There are several barriers that may preclude a health care provider's ability to educate patients about preeclampsia (Box 9-3). The amount of time available for each prenatal visit is limited, and a great deal of information has to be relayed in a typical prenatal appointment. It is important to note that many of the aforementioned techniques actually require little time. If they are spread out over several visits starting as early as 15 weeks of gestation, but no later than 20 weeks of gestation, and reviewed several times during the course of the pregnancy, it would only take a few minutes to discuss this information. In some settings, health care systems have successfully used a centering pregnancy model, whereby women are grouped together by due dates for prenatal education and support (27–29). Some may believe that providing a patient with information about preeclampsia will produce unnecessary anxiety. There is evidence to the contrary because failure to educate patients about preeclampsia may cause women to experience greater fear because of lack of information (1).

Evidence suggests that health care providers who fail to inform patients about preeclampsia may do so because the health care provider is underinformed. A 2002 survey of obstetrician–gynecologists revealed

BOX 9-2. Chunk-and-Check ⇦

What is it?

Definition of preeclampsia in layman's terms: "Preeclampsia is a serious disease related to high blood pressure. It can happen to any pregnant woman."

Why should you care?

Explanation of risks to the patient and her infant, emphasizing the seriousness of responding in a timely manner: "There are risks to you: seizures, stroke, organ damage, or death; and to your baby: premature birth or death."

What should you pay attention to?

Explanation of potentially concerning signs and symptoms accompanied by graphics and simply written description: "Symptoms include…"

What should you do?

Explanation of appropriate actions that should be taken if a patient experiences symptoms: "If you experience any concerning symptoms, call you health care provider right away. Finding preeclampsia early is important for you and your baby."

BOX 9-3. Most Commonly Reported Barriers to Providing Preeclampsia Education ⇦

- Health care providers have too many important issues to address and not enough time.
- Information overload is causing women to be too anxious about their pregnancies.
- Materials that are written simply, available in other languages, and affordable, are not available.
- Health care providers are unsure about what information needs to be provided that will affect outcomes.

great disparities in their knowledge and clinical management of hypertensive disorders of pregnancy (30). Health care providers need to understand that preeclampsia without severe features can progress quickly and unexpectedly; that proteinuria is not always present, even in severe forms of preeclampsia; that women remain at risk of preeclampsia postpartum; and that a woman's symptoms should not be dismissed without a proper assessment. This is corroborated by thousands of patient experiences reported to the Preeclampsia Foundation (31). Many clinicians and patients are unaware that preeclampsia can still occur after delivery. Postpartum hypertension or preeclampsia either is a new-onset condition or is secondary to persistence or exacerbation of hypertension in women with previous gestational hypertension, preeclampsia, or chronic hypertension (32). In cases of late postpartum eclampsia, researchers found that almost all of the patients had at least one prodromal symptom, and one half had more than one symptom that heralded the seizure. However, only 33% of women sought care for their symptoms, suggesting that proper patient education may have led to better outcomes (9).

In addition, it should be recognized that many of the pamphlets developed with the intention of educating women about issues related to obstetrics and gynecology may be written at a higher readability level than that recommended for the general public (33). Therefore, those who provide obstetric care cannot assume that all available patient literature will be effective. The limited number of appropriately written materials available to educate women about preeclampsia is a perceived and underresearched barrier to providing patient education about preeclampsia (23).

When women know how to recognize the signs and symptoms and they understand the information offered, they have the opportunity to report symptoms more promptly, request appropriate investigations and follow-up, reduce their fear and anxiety, and adhere to prescribed management. This all leads to improved pregnancy outcomes.

TASK FORCE RECOMMENDATION

- It is suggested that health care providers convey information about preeclampsia in the context of prenatal care and postpartum care using proven health communication practices.

  Quality of evidence: Low
  Strength of recommendation: Qualified

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CHAPTER 10

State of the Science and Research Recommendations

An important charge of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy was to review the state of the science and to develop corresponding research recommendations relating to management of hypertension during pregnancy. The last such formal review of scientific data dates back to the National High Blood Pressure Education Program's presentation in 2000 (1). Summarized as follows is the progress of research from 2000 through 2012, with suggested areas in which focused investigations are needed or should continue.

Fundamental Advances in the Understanding of Preeclampsia

Preeclampsia, at least early-onset preeclampsia, is believed to evolve in two stages (2–7). The first stage (less than 20 weeks of gestation) involves poor placentation, at which time there are neither signs nor symptoms of the disorder. The second stage involves the consequences of poor placentation, probably evoked by relative placental hypoxia and hypoxia reperfusion, resulting in a damaged syncytium and limited fetal growth, with these and other events leading to the clinical findings of preeclampsia. The link between the relatively hypoxic placenta and the maternal syndrome includes a cascade of secondary effector mechanisms, including altered proangiogenic and antiangiogenic factor balance, increased maternal oxidative stress, and endothelial and immunological dysfunction (5, 6). Further elucidation of these mechanisms will hopefully lead to a more complete understanding of the pathophysiology of preeclampsia and to specific and successful therapeutic intervention.

Abnormal Implantation and Vasculogenesis

Although the underlying molecular mechanisms that lead to the preeclampsia syndrome are not clear, a major mechanism is believed to be placental insufficiency due to inadequate remodeling of the maternal vasculature perfusing the intervillous space. During normal pregnancy, fetally derived cytotrophoblasts invade the maternal uterine spiral arteries, replacing their endothelium, and differentiating into an endothelial-like phenotype (8). This complex process results in a conversion of the high-resistance, small-diameter vessels into high-capacitance, low-resistance vessels and ensures adequate delivery of maternal blood to the developing uteroplacental unit. In the woman destined to develop preeclampsia, poorly understood errors in this carefully orchestrated scheme lead to inadequate delivery of blood to the developing uteroplacental unit and increase the

degree of hypoxemia and oxidative and endoplasmic reticulum stress.

The exact mechanisms responsible for the abnormal trophoblast invasion and vascular remodeling in preeclampsia are unclear, but a series of studies have now appeared that are enhancing the understanding of these important adaptations and of potential mechanisms that may lead to maladaptations (2–7). In one study, researches provided evidence that Notch signaling may be a crucial component of the process whereby fetal trophoblast cells invade and remodel maternal blood vessels (9). They reported that failure of this physiologic transformation in the absence of *Notch2* is associated with reduced vessel diameter and placental perfusion. Their findings that perivascular and endovascular cytotrophoblasts often fail to express the Notch ligand, *JAG1,* in preeclampsia provides further evidence that defects in Notch signaling may be an important part of the pathogenesis of this pregnancy complication.

Other studies also have suggested that variability of immune system genes that code for major histocompatibility complex molecules and natural killer receptors also may affect human placentation (10). They reported that specific combinations of fetal major histocompatibility complex molecules and maternal natural killer receptor genes in humans correlate with the risk of preeclampsia, recurrent miscarriage, and fetal growth restriction. Researchers have begun to explore the similarities and differences between human and mice natural killer cells and potential trophoblast ligands with the aim of developing mouse models that will elucidate how natural killer cell–trophoblast interactions contribute to placentation.

Studies like the aforementioned studies, have established abnormalities in vasculogenic and angiogenic signaling pathways as important candidates to explain mechanisms by which placentation goes awry in preeclampsia, leading the task force to strongly recommend the need for more emphasis on the study of placentation during pregnancy and preeclampsia. Although genetic manipulation in mouse models can be an important tool in providing insights into the process of placentation, the placentas of these animals differ significantly from those in women, underscoring a critical need to perform such research in primates, where placentation is similar to that in humans. In addition, use of state-of-the-art technologies and experimental approaches such as genomic, proteomic, metabolomic, and microRNA analyses should provide new and important information regarding molecular pathways involved in the process of placentation.

Endothelial Activation and Dysfunction

The maternal vascular endothelium of women destined to develop preeclampsia appears to be an important target of factors that are presumably generated through placental ischemia and hypoxia (5, 6, 11). The vascular endothelium has many important functions, including control of smooth muscle tone through the release of vasoconstrictors and vasodilators and the regulation of anticoagulation, antiplatelet, and fibrinolytic functions by release of different soluble factors. Alterations in the circulating concentration of many markers of endothelial dysfunction have been reported in women that develop preeclampsia (5, 6, 11). This suggests that the disease is an endothelial cell disorder. The fact that this endothelial dysfunction can be demonstrated before overt disease supports a causal role.

Maternal status may influence the endothelial response to factors triggered by placental ischemia and hypoxia in preeclampsia. There is compelling evidence, for example, that obesity, a major epidemic in developed countries, including the United States, increases the risk of preeclampsia. A body mass index (calculated as weight in kilograms divided by height in meters squared) characteristic of obesity (greater than 39) increases this risk threefold (12). Despite this and many other studies linking obesity to preeclampsia, the pathophysiologic mechanisms whereby obesity increases the risk of developing preeclampsia are unclear. Thus, further research into how obesity and metabolic factors such as leptin, insulin, and free fatty acids, affect the various stages of preeclampsia is warranted.

Factors Linking Placental Ischemia and Hypoxia With the Maternal Syndrome

Angiogenic Factors

In response to placental hypoxia, the placenta is proposed to produce pathogenic factors that enter the maternal blood stream and are responsible for the endothelial dysfunction and other clinical manifestations of the disorder. A variety of molecules are released but amongst them, antiangiogenic and autoimmune or inflammatory factors have recently received the greatest attention (13, 14). In these respects, perhaps the most intensely studied pathway in the manifestation of preeclampsia is that related to vascular endothelial growth factor (VEGF) signaling. Vascular endothelial growth factor and placental growth factor (PlGF-1), besides their role in angiogenesis, also are important in the maintenance of proper endothelial cell function. This signaling pathway came to prominence with the discovery of elevated circulating and placental concentrations of the soluble form of the VEGF receptor Flt-1 (sFlt-1).

The soluble form of the VEGF receptor Flt-1 is a circulating soluble receptor for both VEGF and PlGF, that when increased in maternal plasma leads to less circulating free-VEGF and free-PlGF, thus preventing their availability to stimulate angiogenesis and maintain endothelial integrity. In the kidney, this inactivation of free-VEGF is believed to cause glomerular endotheliosis with consequent proteinuria (13, 14). Studies of the regulation of sFlt-1 in cell culture and placental tissue in vitro have demonstrated that sFlt-1 is released from placental villi and trophoblast cells in response to reduced oxygen tension similar to that seen in an ischemic placenta. A promising pilot study demonstrated that sFlt-1 could be removed from the maternal circulation by apheresis safely, and that this therapy reduced both blood pressure (BP) and proteinuria, with a trend toward increased gestational duration (15).

Although compelling data derived from animal and human studies suggest an important role for angiogenic imbalance in the pathophysiology of preeclampsia, there are many unanswered questions and many opportunities for future research. For example, the molecular mechanisms involved in the regulation of sFlt-1 production have yet to be fully elucidated. Moreover, although sFlt-1 appears to play an important role in the pathogenesis of preeclampsia, specific inhibitors of sFt-1 production are not available at this time. Thus, research into the discovery of inhibitors of sFlt-1, or ways to stimulate greater production of VEGF and PlGF, is of critical importance.

Immune Factors and Inflammation

One of the earliest and most persistent theories about the origins of preeclampsia was that it is a disorder of immunity and inflammation (16). Of interest is work that suggests the inflammatory response is triggered by particles shed from the syncytial surface of the human placenta ranging from large deported multinuclear fragments to subcellular components. These circulating particles are increased in preeclampsia. In this respect, researchers have proposed that the fragments include proinflammatory proteins that may contribute to the systemic inflammatory response in normal pregnancy and the exaggerated inflammatory response in preeclampsia (16). There is new evidence from the same researchers of a large hidden population of microvesicles and nanovesicles (including exosomes), not easily studied because of their small size (17). Using nanoparticle tracking analysis to measure the size and concentration of syncytiotrophoblast vesicles prepared by placental perfusion, they found that vesicles range in size from 50 nanometers to 1 micrometer with the majority being less than 500 nanometers, which includes both exosomes and microvesicles. They speculate that changes not only in the numbers, but also in the size (beneficial syncytiotrophoblast exosomes and harmful microvesicles), might be important in the maternal syndrome of preeclampsia.

Another area related to the immune component of preeclampsia is research relating to the agonistic antibody AT1-AA (18, 19). These autoantibodies, isolated more than a decade ago in women who had preeclampsia, have been studied more intensively recently, including their identification in the circulation of rats undergoing placental ischemia. These antibodies appear to be induced by the production of the cytokine, tumor necrosis factor (TNF)-α because infusion of TNF-α into pregnant rats also results in production of the antibody at concentrations comparable to that seen in pregnant women with preeclampsia and the Reduced Uterine Perfusion Pressure (RUPP) rat (20). It also has been demonstrated that infusion of AT1-AA directly into pregnant rats results in moderate hypertension. However, the pathogenic importance of these antibodies remains to be fully elucidated because their presence has been noted postpartum in a subset of patients who had preeclampsia with no discernible phenotype. Further studies are needed, including determining how these unique antibodies are produced and how they interact with the other pathogenic agents in preeclampsia to produce the clinical phenotype.

Endothelin

There is growing evidence to suggest an important role for endothelin-1 (ET-1) in the pathophysiology of preeclampsia. Given the myriad experimental models of preeclampsia (placental ischemia, sFlt-1 infusion, TNF-α infusion, and AT1-AA infusion) that have proved susceptible to ET_A antagonism, could the ET-1 system be a potential therapeutic target for the treatment of preeclampsia (21)? Because there is evidence that interfering with the ET_A receptor in early animal pregnancy may abort the pregnancy or lead to developmental anomalies, research here should focus later in gestation where ET_A-receptor antagonists might prove safe and efficacious, which is started when symptoms appear. Alternatively, development of ET_A-receptor antagonists, which do not cross the placental barrier, would be welcome. Researchers recently reported that a selective ET_A-receptor antagonist had limited access to the fetal compartment during chronic maternal administration late in pregnancy (22).

Nitric Oxide

Studies have suggested important roles for nitric oxide as a regulator of arterial pressure under various physi-

ologic and pathophysiologic conditions (6). Nitric oxide production is elevated in normal pregnancy, and these increments appear to play an important role in the vasodilatation of pregnancy. Thus, it was postulated that nitric oxide deficiency during preeclampsia might be involved in the disease process. Studies from several laboratories have found that chronic nitric oxide synthase inhibition in pregnant rats produces hypertension associated with peripheral and renal vasoconstriction, proteinuria, intrauterine growth restriction, and increased fetal morbidity, a pattern resembling the findings of preeclampsia (6). However, whether there is a reduction in nitric oxide production during preeclampsia is controversial. Much of the uncertainty originates from the difficulty in directly assessing the activity of the nitric oxide system in a clinical setting. Assessment of whole-body nitric oxide production by measurement of 24-hour nitrate–nitrite excretion has yielded variable results because of difficulties in controlling for factors such as nitrate intake, thus, the relative importance of nitric oxide deficiency in the pathogenesis of preeclampsia has yet to be fully elucidated.

Oxidative and Endoplasmic Reticulum Stress

Oxidative stress also has been implicated in preeclampsia because increased concentration of several oxidative stress markers also have been reported systemically in women with preeclampsia, among these peroxynitrites (23, 24). Peroxynitrite concentrations in vascular endothelium were much higher in women with preeclampsia compared with women with normal pregnancies, concurrent with decreased concentrations of superoxide dismutase and nitric oxide synthase (25). There also is evidence of increased oxidative stress during gestation in the RUPP rat hypertensive model, suggesting a link between placental ischemia and hypoxia with the production of reactive oxygen species (6). Treating this model with two different antioxidants, 1) vitamin C and 2) vitamin E, had no effect on the gestational hypertension. The superoxide dismutase mimetic drug, tempol, however, led to significant attenuation of the hypertensive response. In a related study, administration of the reduced form of nicotinamide adenine dinucleotide phospate oxidase inhibitor, apocynin, also significantly attenuated RUPP-induced gestational hypertension, implicating that enzyme as an important source of pathogenic reactive oxygen species in the RUPP animal (6). Failure of the drug to fully normalize BP, however, leaves open the possibility that alternative reactive oxygen species production pathways are at work in the RUPP model. Further studies into the mechanism of reactive oxygen species production in animal models of preeclampsia should help shed further light into the importance of oxidative stress in the pathophysiology of preeclampsia and perhaps allow the identification of useful antioxidant strategies. It remains to be seen whether reactive oxygen species production is a primary or secondary cause of preeclampsia pathophysiology, and how effective manipulation of the system will be in the search for effective therapies.

There also appears to be an excess of endoplasmic reticulum stress in placentas from women with early-onset preeclampsia (26). Endoplasmic reticulum stress activates a number of signaling pathways aimed at restoring homeostasis. Researchers have proposed that this homeostatic mechanism fails and apoptotic pathways are activated to alter placental function in women who develop preeclampsia (26). In addition chronic, low concentrations of endoplasmic reticulum stress during the second trimester and third trimester may result in a growth restricted phenotype. They also propose that higher concentrations of endoplasmic reticulum stress lead to activation of proinflammatory pathways that may contribute to maternal endothelial cell activation. Although endoplasmic reticulum stress is known to occur in preeclampsia, the importance of this abnormality in the pathophysiology has yet to be fully elucidated.

Hemeoxygenase

It also appears that the stress response gene, hemeoxygenase-1 (HO-1), and its catalytic product, carbon monoxide also may be involved in the pathogenesis of preeclampsia (27). Genetic or pharmacologic blockade of HO-1 in pregnant animals lead to preeclampsia-like phenotypes (27). It also appears that induction of the HO-1 gene may be involved and, thus, this too is an area in which to explore therapeutic approaches. There are several lines of evidence that HO-1 and its catalytic products may protect against the progression of preeclampsia by interfering at sites in the pathway that links placental hypoxia and hypertension (28–30). Of interest, in this respect, are studies suggesting that combustion products of tobacco, such as carbon monoxide, reduce the risk of preeclampsia by more than 35% (29). In addition, TNF-α mediated cellular damage in placental villous explants can be prevented by up-regulating HO-1 enzyme activity (28). Heme oxygenase pathways have also been shown to inhibit the release of sFlt-1 in several in vitro models (30). Induction of the HO-1 enzyme or chronic administration of HO-1 metabolites have also been reported to ameliorate hypertension in several animal models of hypertension that involve BP regulatory factors similar to that observed in women with preeclampsia. More

compelling evidence that supports the concept that HO-1 and its catalytic products may protect against the progression of preeclampsia are data that indicate that chronic administration of an HO-1 enzyme inducer (cobalt protoporphyrin IX chloride) or carbon monoxide releasing molecule-A1 significantly attenuates hypertension in response to placental ischemia (31). These findings, taken together, make heme oxygenase a potential target for studies to improve the treatment of preeclampsia. In this respect, the cardiovascular (CV) drugs, statins, have been shown to stimulate HO-1 expression and inhibit sFlt-1 release in vivo and in vitro; thus, they have the potential to ameliorate early-onset preeclampsia. The pavaStatin to Ameliorate Early Onset Pre-eclampsia trial is underway to address this and, if positive, its outcome could lead to therapeutic intervention to prolong affected pregnancies.

Summary of Fundamental Research Recommendations by the Task Force

As noted, there has been enormous progress toward understanding the pathophysiology of preeclampsia during the past two decades, but many unresolved and critical questions remain. The full elucidation of the molecular and cellular mechanisms involved in the various stages of the disease process will hopefully lead to a more complete understanding of the etiology of preeclampsia and eventually lead to successful therapeutic intervention through the targeted disruption of new and novel pathways. As follows are basic science research recommendations to attempt to resolve some of these unsolved questions over the next several years:

- More research on the study of placentation, including immunological abnormalities and abnormalities of angiogenic signaling pathways during pregnancy and preeclampsia, is needed.
- Continued research on the role of genetic and epigenetic factors in preeclampsia is warranted.
- Research on the molecular mechanisms involved in the regulation of proangiogenic and antiangiogenic factors also is needed.
- Research into the discovery of novel inhibitors of sFlt-1 is of critical importance.
- Further development of animal models is needed.

Advances in Clinical Research

Clinical research stimulated by and performed following the last National High Blood Pressure Education Program report also has led to important advances in the management of preeclampsia. Cogent examples are the clinical trials of magnesium sulfate to prevent and treat eclampsia that resolved decades of controversy. Obstetricians in the United Sates used magnesium sulfate for almost 70 years with little attention from other parts of the world and with scorn from the neurological community. However, studies in the past two decades have now established that magnesium sulfate can be used safely, including administering it in developing countries. Magnesium sulfate therapy was shown to be superior to phenytoin or diazepam for treating eclampsia and is more effective than phenytoin or placebo for preventing preeclampsia (32–34). This has had a major effect on modifying treatment outside the United States. In the United States magnesium sulfate is accepted as the drug of choice but the answer to the question of whom to treat remains unclear. In Chapter 5 "Management of Preeclampsia and HELLP Syndrome," the available data are reviewed and recommendations are made to guide rational use of the drug.

At times empirically guided, but also guided by research results, a plethora of potential predictive tests have been examined. None of these have been shown to be clinically useful, although current investigations using combinations of tests has engendered cautious optimism that clinically useful ways to predict preeclampsia may be on the horizon (35, 36). In this respect, the use of combinations of analytes and biophysical testing (eg, uterine artery Doppler velocimetry) has encouraging preliminary results (35).

Prevention is another critical focus of clinical studies. Several strategies have been tested, retested, or reanalyzed with, at best, minimal evidence of success. The latest entry into prevention testing was the use of antioxidant vitamins. The presence of oxidative stress in preeclampsia has been evident for many years in multiple tissues (although there has been some controversy) (37, 38). By the late 1990s the evidence seemed sufficient to warrant a trial of the antioxidants vitamin C and vitamin E, to modify the pathophysiology of preeclampsia. In a small pilot study, performed in England, vitamin C and vitamin E were administered in pharmacologic doses (far exceeding those present in prenatal vitamins) with the intent of reducing evidence of endothelial activation (39). Antioxidant vitamin treatment was associated not only with reduced endothelial activation and reduced oxidative stress, but also with a significant reduction in the frequency of preeclampsia. The findings stimulated large trials in England, Canada, Australia, and the United States and in developing countries. Both low-risk and high-risk women were studied. However, none of the studies

demonstrated any evidence of a beneficial effect (40). Whether the lack of success was due to timing, dosage, or the particular antioxidant used is not known, but it is clear that the use of vitamin C and vitamin E in unselected low-risk or high-risk women is not indicated for the prevention of preeclampsia.

The findings with vitamin C and vitamin E mirror the findings of studies that used low-dose aspirin and calcium to prevent preeclampsia. In all studies, these agents were successful in initial small studies, but that success was not validated in larger trials (41–45). The most likely explanation for this discrepancy is that the small studies are underpowered and reflect publication bias. That is, small studies that are successful are reported, whereas small studies that do not succeed are not likely to be reported and published. There are other interesting possibilities. One treatment may not be effective for all cases of preeclampsia. Thus, successes in small studies in homogenous populations are not substantiated in larger studies, which characteristically are not only larger but also more heterogeneous because they are usually performed in several centers. This was a consideration in the studies of calcium to prevent preeclampsia where the early small successful trials largely took place in developing countries where many women had low calcium intake, whereas the large unsuccessful trial was conducted in the United States where the vast majority of women had adequate calcium intake (40, 41). The World Health Organization tested this possibility in a study in which calcium was supplemented in pregnant women from populations known to have a low calcium intake (46). There was no reduction in the incidence of preeclampsia with calcium treatment. However, the frequency of severe adverse outcomes, including eclampsia and severe hypertension was lower. Further, treatment reduced a composite outcome of adverse maternal outcomes. Although the body of the calcium studies supports the concept of prevention with a particular agent being pertinent in some, but not all, populations, it also indicates calcium supplementation is not useful in a population with adequate calcium intake as occurs in the United States.

An attempt was made to evaluate the efficacy of low-dose aspirin by meta-analysis of approximately 35,000 women who had been included in trials of aspirin to prevent preeclampsia. There was no evidence of significant reduction in preeclampsia in any of the large individual trials. However, in the meta-analysis of this large number of participants, there was a significant reduction in the frequency of preeclampsia, premature births, and perinatal mortality with low-dose aspirin therapy (47). Based on the calcium success, it could be postulated that there might be a subset of women with preeclampsia in whom low-dose aspirin therapy would be effective. This was studied using an approach termed "individual patient meta-analysis" in which the data from studies are brought together for reanalysis. In this study, it was not possible to identify any subset of patients in whom therapy was uniquely effective (48). The study did confirm the significant effects of aspirin therapy reported in standard meta-analysis to prevent preeclampsia, and to reduce prematurity and perinatal mortality. However, the effects of aspirin were not clinically useful in these analyses because the usual prevalence of preeclampsia in low-risk populations was 2–3%; therefore, 500 women would need to be treated in order to prevent one case of preeclampsia. However, it is important to remember that as the prevalence of a disease increases, the number of patients necessary to treat for a successful outcome reduces. Thus, in individuals who have preexisting risk factors that increase preeclampsia prevalence to 20%, it would only require treating 50 patients to prevent one case of preeclampsia. For this reason the task force suggests low-dose aspirin prophylaxis in patients at high risk of preeclampsia. Specifically, low-dose aspirin is recommended beginning late in the first trimester for women with a medical history of preeclampsia in more than one prior pregnancy or in whom preeclampsia in a prior pregnancy resulted in the birth of an infant at less than 34 weeks of gestation. These women have a prevalence of preeclampsia of at least 40%. Thus, approximately 20 women would need to be treated to prevent one case of preeclampsia. Additionally, the treatment of 35,000 women with low-dose aspirin in the numerous previous trials indicated no acute adverse outcomes for the woman or her infant. However, there is no information on the long-range safety of the drug. Based on this information, it would seem reasonable to discuss the possibility of low-dose aspirin therapy with an individual woman at less extreme risk, pointing out the potential benefit to her and the established safety of the drug acutely, but also the unknown long-term safety. The decision for therapy would then be based on the importance of these particular factors to the particular woman.

Another possibility that arises from the failure of predictors to predict preeclampsia and therapy based on well-established pathophysiology to prevent preeclampsia is that preeclampsia may actually be more than one disease. This possibility certainly is supported by clinical and epidemiologic data, which indicate profoundly different effects of the disorder in different women and at different times in pregnancy and differ-

ent long-term CV outcome with early-onset preeclampsia and late-onset preeclampsia (49). Thus, the task force encourages attempts to identify subtypes of preeclampsia as one of the targets for future research. The analogy of diabetes in which the disease is recognized as insulin-resistant or is insulinopenic with each subset that requires different therapy indicates the value of this approach.

In a clinical trial performed in the Netherlands, investigators examined whether in women with mild preeclampsia or mild gestational hypertension (hypertension, but no proteinuria) it is safer for them to give birth at 37 weeks of gestation or it is safer to observe them (50). The study showed a reduction in adverse maternal outcomes with delivery at 37 weeks of gestation compared with observation. There was no increase in neonatal morbidity. For this reason the task force recommends delivery at 37 weeks of gestation in women with mild preeclampsia and mild gestational hypertension. Nonetheless, this study should be replicated in a U.S. population.

A problem inherent in this recommendation must be resolved by future research. There is abundant evidence that gestational hypertension is not simply a mild form of preeclampsia. Twenty five percent of women in whom gestational hypertension is diagnosed at 34 weeks of gestation will later develop proteinuria and thus preeclampsia (51). It also is likely that another portion of the women have preeclampsia without developing proteinuria by the time they give birth. Another portion of women with gestational hypertension have chronic hypertension that was masked by the decrease of BP in early pregnancy. However, it is also evident there is another group of women with mild gestational hypertension in whom there is no risk other than hypertension. This is evident from studies of women with mild gestational hypertension in whom, as the components of the syndrome of preeclampsia decrease (eg, no evidence of hyperuricemia or an increase in cellular fibronectin), the likelihood of adverse outcomes is reduced until it is difficult to differentiate their outcome from that of normotensive women (52, 53). Thus, a target for research recommended by the task force is to develop tests that can be performed on women with gestational hypertension to predict the likelihood that they have or will proceed to preeclampsia or adverse outcome.

For many years, it has been evident that women with preeclampsia have an increased risk of CV disease later in life. Recent epidemiological studies indicate this to be an approximate twofold increase for all women with a history of preeclampsia (54). However, women with preeclampsia who give birth before 34 weeks of gestation have an 8–10-fold increased risk, and women with recurrent preeclampsia have an increase in death from CV disease earlier in life than women who only have preeclampsia in their first pregnancies (55). It seems most likely that the increase in CV disease in later life in women with preeclampsia is due to common risk factors for both conditions although a component of residual injury from preeclampsia cannot be completely excluded. The American Heart Association recognized the relationship of preeclampsia and later-life CV disease in its recent guidelines (56). These guidelines list a pregnancy history as a part of the assessment of CV risk for women. They also state that preeclampsia and gestational diabetes should be part of the risk score for CV disease. The challenge is to determine how to use this information (57). This raises the idea that a history of preeclampsia might suggest that these women be tested for CV disease earlier than age 40 years.

In reviewing the recommendations that the task force has prepared, it becomes evident that there are few clinical issues for which there is strong evidence. Therefore, the task force has prepared the following lists of research recommendations to attempt to resolve some of these problems in the near future.

Task Force Recommendations for Clinical Research

Prediction and Risk Stratification

- Prospective clinical trials should be performed to demonstrate the clinical utility of biomarkers or their combinations with biophysical variables that can directly affect management decisions as follows:
  - Ways to differentiate women destined to develop preeclampsia from those who will not at a period during gestation when available interventions will improve outcome.
  - Clarification if such markers or BP thresholds can identify an increased risk of perinatal morbidity in subsets of women
  - Clarification if uric acid level assessment will serve as a biomarker given its ease and minimal cost of its measurement.
- There is evidence that subsets of preeclampsia exist characterized by gestational age onset, gestational age at delivery, the presence or absence of fetal growth restriction, or the long-term risk of maternal CV disease. Additional research is needed to help verify and characterize the subsets of the disease in a manner that helps clarify morbidity and mortality risks as well as specific management options.

- Additional evaluation is needed to show whether the magnitude of 24-hour protein excretion discriminates the ongoing risk of morbidity in preeclampsia, and, if so what the ideal cutoff needs to be.
- Future research on more novel technologies, such as plasma or urine metabolite profiles and circulating microRNAs, may prove to not only be useful for understanding the pathogenesis of the disease, but also in the development of novel therapies.
- Identify biophysical variables or biomarkers (or combinations) that distinguish women with mild gestational hypertension who will not have adverse outcomes with a negative predictive value sufficient to allow follow-up and management as a low-risk patient.
- All of these recommended studies should focus not only on clinical usefulness but how they directly affect obstetrician's management decisions, improve health outcomes, and reduce costs to the health care system.

Therapy and Prevention of Preeclampsia, Eclampsia, and HELLP Syndrome

- Research collaboration between investigators, the pharmaceutical industry, and governmental agencies should be encouraged to develop novel therapies for the treatment of preeclampsia.
- The role of potent corticosteroids to prevent progression and accelerate recovery from HELLP syndrome requires further study in a large randomized prospective clinical trial that is appropriately structured to include only patients who do not require corticosteroids for fetal indications (greater than 34 weeks of gestation).
- Research should be directed at determining the most appropriate antihypertensive treatment for persistent postpartum hypertension.
- The optimal use of diuretics in the postpartum management of patients with preeclampsia, eclampsia, and HELLP syndrome requires study and clarification to augment current management schemes.
- The administration of potent corticosteroids appears to benefit patients with cerebral edema. The potential role of any of these agents to benefit patients with eclampsia or patients developing cerebral edema or posterior reversible encephalopathy syndrome deserves investigation.
- Major perinatal morbidity with HELLP syndrome occurring before 23–24 weeks of gestation has not been improved with any current management scheme used because delivery is usually mandated. Work is needed to develop effective therapeutic interventions to safely prolong pregnancy to viability of the fetus without endangering maternal welfare.
- Therapy to effectively treat patients with preeclampsia that fails to improve or resolve postpartum using standard therapy requires more extensive investigation and standardization.
- A Clinical Trials Network for the performance of preeclampsia-focused research should be considered for implementation.

Management of Preeclampsia, Eclampsia, and HELLP Syndrome

- More research should be performed to determine the most appropriate antihypertensive treatment for persistent postpartum hypertension.
- Randomized trials to determine optimum delivery timing in women with mild gestational hypertension and preeclampsia should be repeated in U.S. populations.
- Maternal mortality data should be assessed to better identify causes of death in hypertensive pregnant women.
- Some cases of eclampsia appear to be manifestations of posterior reversible encephalopathy syndrome. It should be determined whether or not women with preeclampsia and milder cerebrovascular symptoms (headache or visual disturbances) also have posterior reversible encephalopathy syndrome.
- Identification of early posterior reversible encephalopathy syndrome and prevention of its progression might prevent eclampsia. Studies are needed to determine if posterior reversible encephalopathy syndrome can be detected without a magnetic resonance imaging examination and whether any intervention such as magnesium sulfate, steroids, diuretics, or other agents can be targeted to patients at greatest risk.
- Management of eclampsia occurring before 34 weeks of gestation requires further investigation to determine if delay of delivery for 24–72 hours may significantly improve perinatal outcome without adversely affecting maternal outcome.

- How often to evaluate patients in the postpartum period with severe forms of preeclampsia following hospital discharge remains unclear. Protocols to evaluate possible management schemes are desirable to undertake so that best practices can be determined and implemented.
- Nifedipine use for BP control in the patient with preeclampsia receiving magnesium sulfate requires further study to determine the limits of safety for use of both drugs concurrently.
- Persistent moderate hypertension several days into the puerperium in patients with a severe form of preeclampsia requires study as to which antihypertensive agents are best to administer and how best to monitor and assess their effectiveness.
- A subset of patients with HELLP syndrome present with evidence of renal compromise early in the course of the disease. The factors leading to this and the optimal management of the adversely affected kidneys in these patients requires further investigation.
- The role of umbilical artery Doppler velocimetry and its effect on perinatal morbidity and mortality in the complicated pregnancies without IUGR, including pregnancies complicated by hypertension, diabetes, and other disorders associated with placental abnormalities requires further investigation.

Mechanistic Clinical Research

- Research is needed to identify the mechanisms that account for the increased risk of CV disease in women with a medical history of preeclampsia.
- Research on the molecular mechanisms involved in the regulation of proangiogenic and antiangiogenic factors is needed.
- Research on the mechanisms whereby obesity affects placentation is warranted.
- Research on the mechanisms whereby chronic hypertension increases the risk of developing preeclampsia is needed.
- Further studies of the renal abnormalities in preeclampsia are warranted to better explain the basis for the decreased glomerular filtration rate and strategies to reverse the renal pathology and decreasing glomerular filtration rate.

Long Range Follow-Up of Women Who Have Had Preeclampsia

- Studies are needed to determine the best immediate and remote postpartum follow-up procedures in relation to the increased remote CV disease in women who have had preeclampsia. The following questions need to be answered:
  - When and how often they should be evaluated?
  - What tests should be performed?
  - Can risk be stratified with considerations in addition to early-onset, severe, recurrent preeclampsia?
  - Are there women with normal pregnancy outcomes with increased risk of CV disease who can be identified by assessments of metabolic and vascular changes during pregnancy?
- More research on fetal programming of CV diseases (in utero influences on the development of CV issues later in life) is needed.
- Studies of the psychologic effect of preeclampsia are needed.

Chronic Hypertension

- Current data regarding teratogenicity of drugs that decrease angiotensin production or their actions have been questioned. This combined with the problem of stopping therapy in some women with hypertensive preeclampsia, dictates more research to determine the effects of renin angiotensin system inhibitors during early pregnancy on fetal outcomes.
- More clinical evidence is needed to guide the management of hypertension during pregnancy. Specifically, it is not known whether lowering moderate chronic hypertension (greater than 150 mm Hg systolic and 95 mm Hg diastolic; less than 160 mm Hg systolic and 110 mm Hg diastolic) confers either maternal or fetal risk or benefit during pregnancy. Clinical trials should evaluate specific BP targets, using specific antihypertensive agents, and evaluating meaningful clinical outcomes such as preterm birth, IUGR, and severe maternal disease, including eclampsia and HELLP syndrome.

Education

- Evaluation of the effect of prenatal education for women with low literacy on pregnancy outcomes is needed.

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