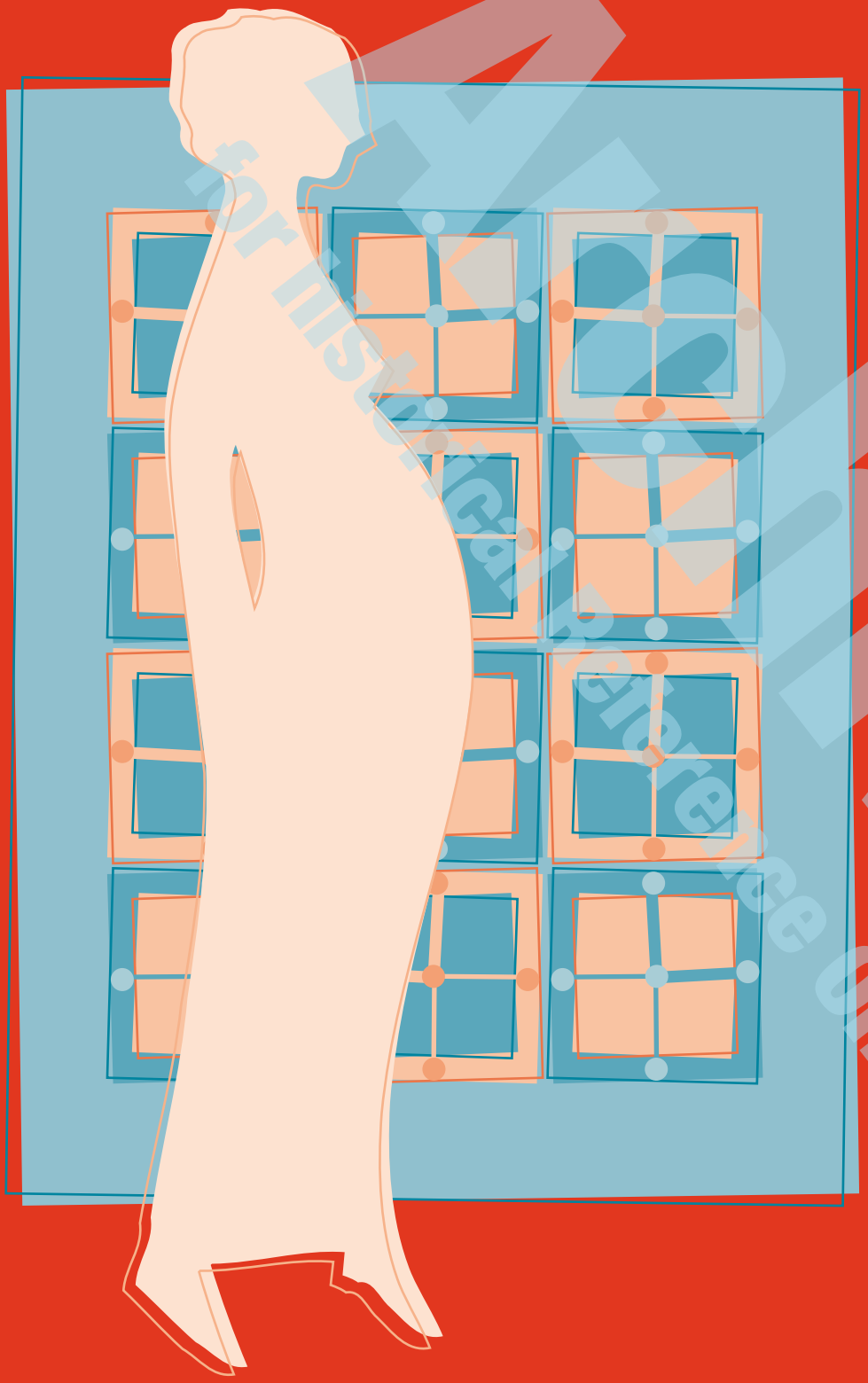
National High Blood Pressure Education Program



Working Group Report on High Blood Pressure in Pregnancy

NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

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American Academy of Insurance Medicine

American Academy of Neurology

American Academy of Ophthalmology

American Academy of Physician Assistants

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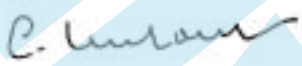
National Heart, Lung, and Blood Institute

National Institute of Diabetes and Digestive and Kidney Diseases

FOREWORD

This report updates the 1990 *National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy* and focuses on classification, pathophysiology, and management of the hypertensive disorders of pregnancy. Using evidence-based medicine and consensus, this report updates contemporary approaches to hypertension control during pregnancy by expanding on recommendations made in the *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)*. The recommendations to use K5 for determining diastolic pressure and to eliminate edema as a criterion for diagnosing preeclampsia are discussed. In addition, the use of blood pressure increases of 30 mm Hg systolic or 15 mm Hg diastolic as a diagnostic criterion has not been recommended, as available evidence shows that women in this group are not likely to suffer increased adverse outcomes. Management considerations are made between chronic hypertension that is present before pregnancy and those occurring as part of the pregnancy-specific condition preeclampsia, as well as management considerations in women with comorbid conditions. A discussion of the pharmacologic treatment of hypertension in pregnancy includes recommendations for specific agents. The use of low-dose aspirin, calcium, or other dietary supplements in the prevention of preeclampsia is described, and expanded sections on counseling women for future pregnancies and recommendations for future research are included. Once again we thank Dr. Ray Gifford, Jr., and his committee for volunteering their time to produce this important report. We hope it helps the busy clinician prevent and manage a very important problem.



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INTRODUCTION

Hypertensive disorders during pregnancy are the second leading cause, after embolism, of maternal mortality in the United States, accounting for almost 15 percent of such deaths.[1] Hypertensive disorders occur in 6 to 8 percent of pregnancies and contribute significantly to stillbirths and neonatal morbidity and mortality.[1] Expectant mothers with hypertension are predisposed to the development of potentially lethal complications, notably abruptio placentae, disseminated intravascular coagulation, cerebral hemorrhage, hepatic failure, and acute renal failure. The etiology of most cases of hypertension during pregnancy, particularly preeclampsia, remains unknown.

The purpose of the *National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy* is to provide guidance to practicing clinicians on managing (1) patients with hypertension who become pregnant and (2) patients who develop hypertensive disorders during gestation. The members of the working group recognize that the responsible clinician's judgment of the individual patient's needs remains paramount. Therefore, this national guideline should serve as a tool to be adapted and implemented in individual situations. Using evidence-based medicine and consensus, the report updates contemporary approaches to hypertension control during pregnancy. This report expands and updates recommendations made in *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)*.[2]

Evidence Base

The studies that provided evidence supporting the recommendations for treatment sections of this report were classified and reviewed by the members of the working group and staff. The following classification of references used in *JNC VI* and originally adapted from Last and Abramson[3] will be used in this report:

M Meta-analysis; an analysis of a compendium of experimental studies

Ra Randomized controlled trials; also known as experimental studies

Re Retrospective analyses; also known as case-control studies

F Prospective followup; also known as cohort studies, including historical cohort studies and long-term followup

X Cross-sectional population studies; also known as prevalence studies

Pr Previous review or position statements

C Clinical interventions (nonrandomized)

These explanatory symbols are appended to some of the references in the reference section of the document and to some of the citations in the text.

Classification of the Hypertensive Disorders of Pregnancy

The most important consideration in the classification of diseases in which blood pressure rises abnormally is differentiating hypertensive disorders that antedate pregnancy from a potentially more ominous disease peculiar to pregnancy: preeclampsia. Preeclampsia is a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and activation of the coagulation cascade. Although our understanding of this syndrome has increased, the criteria used to identify the disorder remain a subject of confusion and controversy. This doubtless reflects the fact that preeclampsia is a syndrome and that attempts at definition use arbitrarily selected markers rather than changes of pathophysiologic importance. The editors of the 1990 version of this document[4] elected to modify minimally the criteria presented by the American College of Obstetricians and Gynecologists (ACOG) Committee on Terminology in 1972.[5] This decision was prompted by the opinion that this classification was simple and used widely and that much of what was understood about the prevalence of these disorders and their outcomes was based on data generated with this classification. Our current opinion is largely the same.

Several groups, including the ACOG,[1] the Australasian Society for the Study of Hypertension in Pregnancy,[6] and the Canadian Hypertension Society,[7] have published classification schemes and diagnostic criteria that differ from one document to the other and contrast with those below. They include recommendations to eliminate edema from diagnostic criteria, to abandon the use of changes in blood pressure as diagnostic,[1,7] to use only diastolic pressures,[7] and to add systemic changes to proteinuria as diagnostic markers.[8] Of these, we determined that only the elimination of edema and changes in blood pressure as diagnostic criteria can be justified on the basis of available data. There were also differences in designating the Korotkoff sound that determines diastolic blood pressure—K4, muffling[6,7] or K5, disappearance.[4,8] We chose K5 because substantial data now support its use.[9–13]

In chronic hypertension, elevated blood pressure is the cardinal pathophysiologic feature, whereas in preeclampsia, increased blood pressure is important primarily as a sign of the underlying disorder and is a potential cause of maternal morbidity. As might be expected, the impact of the two conditions on mother and fetus is different, as is their management. Attempts to differentiate the two conditions have led to confusion in terminology worldwide. We have modified the ACOG classification slightly by adding the term "gestational hypertension" for the woman who has hypertension without proteinuria during pregnancy, reserving "transient hypertension" for a definitive diagnosis made postpartum. According to this terminology, women with increased blood pressure are divided into the groups discussed below:

Classification

- Chronic hypertension
- Preeclampsia-eclampsia
- Preeclampsia superimposed upon chronic hypertension
- Gestational hypertension: (1) transient hypertension of pregnancy if preeclampsia is not present at the time of delivery and blood pressure returns to normal by 12 weeks postpartum (a retrospective diagnosis) or (2) chronic hypertension if the elevation persists.

Chronic Hypertension

Chronic hypertension is defined as hypertension that is present and observable before pregnancy or that is diagnosed before the 20th week of gestation. Hypertension is defined as a blood pressure equal to or greater than 140 mm Hg systolic or

90 mm Hg diastolic. Hypertension that is diagnosed for the first time during pregnancy and that does not resolve postpartum is also classified as chronic hypertension.

Preeclampsia-Eclampsia

The pregnancy-specific syndrome usually occurs after 20 weeks of gestation (or earlier with trophoblastic diseases such as hydatidiform mole or hydrops). It is determined by increased blood pressure (gestational blood pressure elevation) accompanied by proteinuria. *Gestational blood pressure elevation* is defined as a blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic in a woman normotensive before 20 weeks. In the absence of proteinuria the disease is highly suspect when increased blood pressure appears accompanied by the symptoms of headache, blurred vision, and abdominal pain, or with abnormal laboratory tests, specifically, low platelet counts and abnormal liver enzymes.

In the past it has been recommended that an increment of 30 mm Hg systolic or 15 mm Hg diastolic blood pressure be used as a diagnostic criterion, even when absolute values are below 140/90 mm Hg. This definition has not been included in our criteria because the only available evidence shows that women in this group are not likely to suffer increased adverse outcomes.[14,15] Nonetheless, it is the collective clinical opinion of this panel that women who have a rise of 30 mm Hg systolic or 15 mm Hg diastolic blood pressure warrant close observation, especially if proteinuria and hyperuricemia (uric acid [UA] greater than or equal to 6 mg/dL) are also present.

Diastolic blood pressure is determined as the disappearance of sound (Korotkoff 5). Measuring the blood pressure successively may result in very different readings. It is recommended that gestational blood pressure elevation be defined on the basis of at least two determinations. The repeat blood pressure should be performed in a manner that will reduce the likelihood of artifact and/or patient anxiety.[2] For database studies, the measurements of increased blood pressure should be no more than 1 week apart.

Proteinuria is defined as the urinary excretion of 0.3 g protein or greater in a 24-hour specimen. This will usually correlate with 30 mg/dL ("1+ dipstick") or greater in a random urine determination with no evidence of urinary tract infection. However, because of the discrepancy between random protein determinations and 24-hour urine protein in preeclampsia (which may be either higher or lower),[16–18] it is recommended that the diagnosis be based on a 24-hour urine if at all possible or a timed collection corrected for creatinine excretion if this is not feasible.

Preeclampsia always presents potential danger to mother and baby. Other conditions may increase blood pressure and even result in proteinuria; thus, as the certainty of the diagnosis increases, the requirements for careful assessment and consideration for delivery also increase. The following findings increase the certainty of the diagnosis of the preeclampsia syndrome and indicate such followup:

- Blood pressure of 160 mm Hg or more systolic, or 110 mm Hg or more diastolic.
- Proteinuria of 2.0 g or more in 24 hours (2+ or 3+ on qualitative examination). *The proteinuria should occur for the first time in pregnancy and regress after delivery.*
- Increased serum creatinine (>1.2 mg/dL unless known to be previously elevated).
- Platelet count less than 100,000 cells/mm^3 and/or evidence of microangiopathic hemolytic anemia (with increased lactic acid dehydrogenase).
- Elevated hepatic enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]).
- Persistent headache or other cerebral or visual disturbances.
- Persistent epigastric pain.

Eclampsia is the occurrence, in a woman with preeclampsia, of seizures that cannot be attributed to other causes.

Edema occurs in too many normal pregnant women to be discriminant and has been abandoned as a marker in this and other classification schemes.[1,7,8]

Preeclampsia Superimposed Upon Chronic Hypertension

There is ample evidence that preeclampsia may occur in women already hypertensive (i.e., who have chronic hypertension) and that the prognosis for mother and fetus is much worse than with either condition alone. Distinguishing superimposed preeclampsia from worsening chronic hypertension tests the skills of the clinician. For clinical management, the principle of high sensitivity and unavoidable overdiagnosis is appropriate. The suspicion of superimposed preeclampsia mandates close observation, with delivery indicated by the overall assessment of maternal-fetal well-being rather than any fixed end point. The diagnosis of superimposed preeclampsia is highly likely with the following findings:

- In women with hypertension and no proteinuria early in pregnancy (<20 weeks), new-onset proteinuria, defined as the urinary excretion of 0.3 g protein or greater in a 24-hour specimen.
- In women with hypertension and proteinuria before 20 weeks' gestation.
- Sudden increase in proteinuria.
- A sudden increase in blood pressure in a woman whose hypertension has previously been well controlled.
- Thrombocytopenia (platelet count <100,000 cells/mm^3).
- An increase in ALT or AST to abnormal levels.

Gestational Hypertension

The woman who has blood pressure elevation detected for the first time after midpregnancy, without proteinuria, is classified as having gestational hypertension. This nonspecific term includes women with the preeclampsia syndrome who have not yet manifested proteinuria as well as women who do not have the syndrome. The hypertension may be accompanied by other signs of the syndrome, which will influence management. The final differentiation that the woman does not have the preeclampsia syndrome is made only postpartum. If preeclampsia has not developed and blood pressure has returned to normal by 12 weeks postpartum, the diagnosis of transient hypertension of pregnancy can be assigned. If blood pressure elevation persists, the woman is diagnosed as having chronic hypertension. Note that the diagnosis of gestational hypertension is used during pregnancy only until a more specific diagnosis can be assigned postpartum.

Clinical Implications of Classification

The clinical spectrum of preeclampsia ranges from mild-to-severe forms. In most women, progression through this spectrum is slow, and the disorder may never proceed beyond mild preeclampsia. In others, the disease progresses more rapidly, changing from mild to severe in days or weeks. In the most serious cases, progression may be fulminant, with mild preeclampsia evolving to severe preeclampsia or eclampsia within days or even hours. Thus, for clinical management, preeclampsia should be overdiagnosed, because a major goal in managing preeclampsia is the prevention of maternal and perinatal morbidity and mortality, primarily through timing of delivery.

Pathophysiology

Preeclampsia is a syndrome with both maternal and fetal manifestations. The maternal disease is characterized by vasospasm, activation of the coagulation system, and perturbations in many humoral and autacoid systems related to volume and blood pressure control. Oxidative stress and inflammatory-like responses may also be important in the pathophysiology of preeclampsia. The pathologic changes in this disorder are primarily ischemic in nature and affect the placenta, kidney, liver, and brain. Of importance, and distinguishing preeclampsia from chronic or gestational hypertension, is that preeclampsia is more than hypertension; it is a systemic syndrome, and several of its "nonhypertensive" complications can be life-threatening when blood pressure elevations are quite mild.

Pathogenic Mechanisms

The cause of preeclampsia is not known. Many consider the placenta the pathogenic focus for all manifestations of preeclampsia because delivery is the only definitive cure of this disease. Thus research has focused on the changes in the maternal blood vessels that supply blood to the placenta.

Early in gestation the spiral arteries (the terminal branches of the uterine artery) are transformed from thick-walled, muscular vessels to sac-like flaccid vessels, which eventually accommodate a tenfold increase in uterine blood flow. This transformation involves invasion of the spiral arteries by endovascular trophoblast cells of the placenta.[19–22] There is evidence in women destined to develop preeclampsia that trophoblastic invasion of the uterine spiral arteries is incomplete, the vessels remaining thick-walled and muscular.[20,22,23] The cause of this may be a failure of cytotrophoblast cells to express the adhesion molecules necessary for normal remodeling of the maternal spiral arteries.[21,22] Failure of the spiral arteries to remodel is postulated as the morphologic basis for decreased placental perfusion in preeclampsia, which may ultimately lead to early placental hypoxia.

Research on how alterations in the immune response at the maternal interface might lead to preeclampsia addresses the link between placental and maternal disease. A nonclassical human leukocyte antigen (HLA), HLA G, is expressed in normal placental tissue and may play a role in modulating the maternal immune response to the immunologically foreign placenta.[24,25] Placental tissue from preeclamptic pregnancies may express less or different HLA G proteins,[26] resulting in breakdown of maternal tolerance to the placenta. Additional evidence for alterations in immunity in pathogenesis includes the disease's prominence in nulliparous gestations with subsequent normal pregnancies, a decreased prevalence after heterologous blood transfusions, long cohabitation before successful conception, and observed pathologic changes in the placental vasculature in preeclampsia that resemble allograft rejection.[27] Finally, there are increased levels of inflammatory cytokines in the placenta and maternal circulation, as well as evidence of increased "natural killer" cells and neutrophil activation in preeclampsia.[27]

Pathophysiology of the Maternal Manifestations of Preeclampsia

Blood Pressure in Preeclampsia

Women with preeclampsia do not usually develop frank hypertension until the second half of gestation, but vasoconstrictor influences may be present earlier. For instance, alterations in vascular reactivity may be detected by gestational week 20, and numerous surveys suggest that women destined to develop preeclampsia have slightly higher "normal" blood pressure (e.g., diastolic levels >70 mm Hg) as early as the second trimester,[28] confirmed by ambulatory blood pressure monitoring techniques.[29,30]

High blood pressure in preeclampsia is due mainly to a reversal of the vasodilation characteristic of normal pregnancy, replaced by marked increases in peripheral vascular resistance.[31,32] Normally, the vasculature of normotensive gravidas manifests a decreased pressor responsiveness to several vasoactive peptides and amines, especially to angiotensin II (AII). The vessels of women with preeclampsia, however, become hyperresponsive to these hormones, and in the case of AII, such changes may occur months before the appearance of overt disease,[33] although this has not been observed by all investigators.[30] Hypertension in preeclampsia can be labile and may be accompanied by a blunting and even reversal of normal circadian blood pressure rhythms.[34] Blood pressure normalizes postpartum, usually within the first few days of the puerperium, but may take as long as 2 to 4 weeks, especially in severe cases.[35]

The mechanisms underlying vasoconstriction and altered vascular reactivity in preeclampsia remain obscure. Research has focused on changes in the ratio of vasodilating and vasoconstricting prostanoids, since there is evidence suggesting decrements and increments in the production of prostacyclin and thromboxane, respectively.[36–38] More recently, investigators have postulated that the vasoconstricting potential of pressor substances (e.g., AII and endothelin) is magnified in preeclampsia as a consequence of a decreased activity of nitric oxide (NO) synthase and decreased production of NO-dependent or -independent endothelium relaxing factor (EDRF).[39–43] Also under investigation is the role of endothelial cells (the site of prostanoid, endothelin, and EDRF production), which in preeclampsia may be dysfunctional, due perhaps to inflammatory cytokines (e.g., TNF alpha) and increased oxidative stress.[44–51] Other factors postulated to play a role in preeclamptic hypertension are the sympathetic nervous system,[52] calciotropic hormones,[53,54] insulin,[55–58] and magnesium metabolism.[59]

The Heart

The heart is usually unaffected in preeclampsia, the decrements in cardiac performance representing a normally contracting ventricle against a markedly increased afterload.[31,60] Cardiac decompensation may complicate this disorder; however, this is most often due to the presence of preexisting heart disease.[61]

The Kidney

The renal lesion that is characteristic of preeclampsia is termed "glomerular endotheliosis."[62–65] The glomeruli are enlarged and swollen but not hypercellular, due primarily to hypertrophy of the intracapillary cells (mainly endothelial but mesangial as well), which encroach on the capillary lumina, giving the appearance of a bloodless glomerulus.

Both glomerular filtration rate (GFR) and renal blood flow decrease in preeclampsia, the former more so than the latter, leading to a decrease in filtration fraction.[31] The decrement is usually modest (25 percent) even when morphological changes are pronounced. Since renal function normally rises 35 to 50 percent during pregnancy, creatinine levels in women with preeclampsia may still be below the upper limits of normal for pregnancy (0.8 mg/dL). Renal insufficiency is rarely severe, but acute tubular or cortical necrosis has been linked to preeclampsia.[66] Fractional urate clearance decreases, producing hyperuricemia, which is an important marker of preeclampsia.[31] Proteinuria may appear late in the clinical course and tends to be nonselective.[31] Preeclampsia is associated with hypocalciuria, in contrast with the increased urinary calcium excretion observed during normal pregnancy.[67] Alterations in calcium regulatory hormones, including reduced plasma levels of $1,25(OH)_2D_3$,[53] and increased parathyroid hormone[54] are also present.

Sodium excretion may be impaired in preeclampsia, although this is variable.[68] Some of the severest forms of the disease occur in the absence of edema. Even when edema is marked, plasma volume is lower than that of normal gestation, and there is evidence of hemoconcentration, believed to be due in part to extravasation of albumin into the interstitium. In addition, central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) are often low or low normal. The reductions in intravascular volume and the lack of evidence for elevations in central pressures, along with decrements in placental perfusion, are major reasons to avoid diuretic therapy in women with preeclampsia.[62]

The cause of the impaired renal sodium excretion is unclear; the changes in GFR and several volume-sensitive hormones fail to explain this observation. Filtered sodium, though decreased compared with that in normal pregnancy, is still above that

measured in nonpregnant women. Suppression of the renin angiotensin system is a well-documented feature of preeclampsia[69] and may be a consequence rather than a cause of impaired sodium excretion. Atrial natriuretic hormone is reported to be increased.[70,71]

The Coagulation System

Thrombocytopenia, rarely severe, is the most commonly found hematologic abnormality in preeclampsia. Circulating fibrin degradation products occasionally may be elevated, and unless the disease is accompanied by placental abruption, plasma fibrinogen levels are unaffected.[72] However, antithrombin III levels are lower and cellular fibronectin levels higher in women with preeclampsia compared with normal pregnant women—observations consistent with vascular endothelial injury.[73,74]

Platelet counts below 100,000 cells/mm^3 signal serious disease, and if delivery is delayed, levels may continue to fall precipitously. Although platelet counts have not been correlated with maternal hemorrhagic complications, very low platelet counts would be expected to increase the risk of bleeding.

The cause of the thrombocytopenia is also unclear. It has been ascribed to platelet deposition at sites of endothelial damage[72] and to an immunologic process.[75] There is no firm evidence that the fetuses born to women with severe preeclampsia-eclampsia will develop thrombocytopenia, despite severe maternal thrombocytopenia.[76]

The Liver

The pathologic changes in the liver in preeclampsia have been well described in the autopsy studies of Sheehan and Lynch.[77] They include periportal hemorrhages, ischemic lesions, and fibrin deposition. Liver damage accompanying preeclampsia may range from mild hepatocellular necrosis with serum enzyme abnormalities (aminotransferase and lactate dehydrogenase) to the ominous hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, with markedly elevated enzyme levels and even subcapsular bleeding or hepatic rupture. The latter syndrome represents serious disease and is associated with significant maternal morbidity.[78,79]

The Central Nervous System

Eclampsia, the convulsive phase of preeclampsia, remains a significant cause of maternal mortality. Other central nervous system manifestations include headache and visual disturbances including blurred vision, scotomata, and, rarely, cortical blindness. Occasionally, focal neurologic signs may develop, which should prompt radiologic investigation.

The pathogenesis of eclampsia remains disputed and has been attributed both to coagulopathy and fibrin deposition, as well as hypertensive encephalopathy. The latter explanation is difficult to reconcile with the clinical observations that many women develop convulsions with only mild or moderate hypertension. However, vasoconstriction in eclampsia may be selective, and the results of studies using ultrasonographic Doppler techniques suggest that severe cerebral vasospasm may occur even when peripheral vasoconstriction is less evident.[80,81]

The best descriptions of gross and microscopic pathology in eclampsia remain those of Sheehan and Lynch,[77] in which most autopsies were performed within 1 to 2 hours of death, eliminating most of the postmortem changes that usually confound interpretation of brain pathology. There are varying degrees of hemorrhages and petechiae, vasculopathy with vessel wall damage and fibrinoid necrosis (possibly related to chronic hypertension), ischemic brain damage, and microinfarcts.[77,82]

Women with eclampsia have been evaluated with computerized axial tomography (CAT) and magnetic resonance imaging (MRI) techniques.[83,84] Some studies have been relatively normal, and others describe a variety of abnormalities, most of which are usually transient. Lesions consistent with cerebral edema and hemorrhage, as well as hypodense areas believed to represent localized edema induced perhaps by hypoxia, have been described in the CAT scans.[85] Hemorrhage and edema have also been documented by MRI, and of interest are reports of changes in the posterior hemispheres or in the vascular watershed areas, findings consistent with global ischemia induced by vasospasm.[86] Predominance of posterior lesions may explain the increased incidence in preeclampsia-eclampsia of visual disturbances.

Differential Diagnosis

Decisions regarding hospitalization and delivery that have significant impact on maternal and fetal health are often based on whether the patient is believed to have preeclampsia or a more benign form of high blood pressure, such as chronic or gestational hypertension. The correct diagnosis is important when counseling patients regarding future pregnancies. (See the Prepregnancy Counseling section.)

The period in gestation when hypertension is first documented is helpful in determining the correct diagnosis. Documentation of hypertension before conception, or before gestational week 20, favors a diagnosis of chronic hypertension (either essential or secondary). High blood pressure presenting at midpregnancy (weeks 20 to 28) may be due either to early preeclampsia (rare before 24 weeks), transient hypertension, or unrecognized chronic hypertension. Concerning the latter, blood pressure normally falls in the initial trimesters, and this "physiologic" decrement may even be exaggerated in patients with essential hypertension, masking the diagnosis in pregnancy. Hypertension may be noted later in pregnancy, however, as part of the normal third trimester rise in blood pressure or when superimposed preeclampsia occurs.

Laboratory Tests

Laboratory tests recommended to diagnose or manage hypertension in pregnancy serve primarily to distinguish preeclampsia from either chronic or transient hypertension. They are also useful in assessing the severity of disease, particularly in the case of preeclampsia, which is usually associated with laboratory abnormalities that deviate significantly from those of normal pregnant women. These same measurements are usually normal in women with uncomplicated chronic or transient hypertension.

Efforts to identify an ideal screening or predictive test for preeclampsia have not been successful to date.[7] Several parameters, such as midpregnancy blood pressure, ambulatory blood pressure monitoring, serum ß-hCG, AII sensitivity, urinary calcium excretion, urinary kallikrein, uterine artery Doppler, plasma fibronectin, and platelet activation, have been shown to be statistically valid early markers of disease; however, they have not been demonstrated to have sufficient predictive value or practical utility for application to individual patients.[87]

High-Risk Patients Presenting With Normal Blood Pressure

Pregnant women whose gestations are considered "high risk" for preeclampsia (e.g., history of increased blood pressure before conception or in a previous gestation, especially before week 34, or when the subject is multiparous; women with diabetes, collagen vascular disease, or underlying renal vascular or renal parenchymal disease; and those with a multifetal pregnancy) will benefit from a database of laboratory tests performed in early gestation.[88,89] Tests that by later comparison will help establish an early diagnosis of preeclampsia (pure or superimposed) include hematocrit, hemoglobin, and platelet count as well as serum creatinine and uric acid levels. Observation of 1 plus protein by routine urine analysis, documented by a clean-catch specimen, should be followed by a 24-hour collection for measurement of protein as well as creatinine content (to determine accuracy of collection and to permit calculation of the creatinine clearance). High-risk patients require accurate dating and assessment of fetal growth. If conditions are not optimal for clinical dating, sonographic dates should be established as early in pregnancy as possible. A baseline sonogram for evaluating fetal growth should be considered at 25 to 28 weeks in these circumstances.

Patients Presenting With Hypertension Before Gestation Week 20

Most women presenting with hypertension before gestation week 20 have, or will develop, essential hypertension; their management is discussed in the next section. Some may be already under the care of primary physicians and screened for secondary hypertension. Young women with preexisting or early gestational hypertension are among the population in which secondary hypertension is more apt to be found (e.g., renal disease, renovascular hypertension, primary aldosteronism, Cushing syndrome, and pheochromocytoma). Thus, further evaluation with noninvasive testing may be warranted, especially when there is suspicion of those forms of secondary hypertension that are associated with more maternal and fetal complications.

The same database described above (high-risk women presenting with normal blood pressure) is helpful in determining whether further increments in pressure in the third trimester represent the "physiologic" increments or the onset of superimposed preeclampsia. Since these fetuses are at higher risk for the development of intrauterine growth restriction, early baseline sonography for dating and fetal size is also indicated for these patients.

Patients Presenting With Hypertension After Midpregnancy

Table 1 summarizes the laboratory tests that are recommended in the evaluation of women with hypertension after midpregnancy and the rationale for testing them biweekly or more often if clinical circumstances lead to hospitalization of the patient. Not only do such tests help to distinguish preeclampsia from chronic and transient hypertension, but they are useful in assessing disease progression and severity. It is important to recognize that in women with preeclampsia, one or more abnormalities may be present even when blood pressure elevation is minimal. If there is a life-threatening abnormality such as coagulopathy or abnormal hepatic or renal function, it may be necessary to terminate the pregnancy despite only mild hypertension. (See the section on Management of Preeclampsia.)

TABLE 1. Laboratory Evaluation and Its Rationale for Women Who Develop Hypertension After Midpregnancy

Test	Rationale
Hemoglobin and hematocrit	Hemoconcentration supports diagnosis of preeclampsia and is an indicator of severity. Values may be decreased, however, if hemolysis accompanies the disease.
Platelet count	Thrombocytopenia suggests severe preeclampsia.
Quantification of protein excretion	Pregnancy hypertension with proteinuria should be considered preeclampsia (pure or superimposed) until it is proved otherwise.
Serum creatinine level	Abnormal or rising serum creatinine levels, especially in association with oliguria, suggest severe preeclampsia.
Serum uric acid level	Increased serum uric acid levels suggest the diagnosis of preeclampsia.
Serum transaminase levels	Rising serum transaminase values suggest severe preeclampsia with hepatic involvement.
Serum albumin, lactic acid dehydrogenase, blood smear, and coagulation profile	For women with severe disease, these values indicate the extent of endothelial leak (hypoalbuminemia), presence of hemolysis (latic acid dehydrogenase level increase, schizocytosis, spherocytosis), and possible coagulopathy, including thrombocytopenia.

Chronic Hypertension in Pregnancy

Prepregnancy Counseling

Women with hypertension should be evaluated before pregnancy to define the severity of their hypertension and to facilitate planning for potential lifestyle changes that a pregnancy may require. As recommended in *JNC VI*,[2Pr] the diagnosis should be confirmed by multiple measurements and may incorporate home or other out-of-office blood pressure readings. If hypertension is confirmed and particularly if it is severe (stage 3: systolic pressure ≥ 180 mm Hg or diastolic pressure ≥ 110 mm Hg), a woman should be evaluated for potentially reversible causes. Angiotensin-converting enzyme inhibitors and AII receptor antagonists should be discontinued. (For a discussion of drug therapy, see the next section.)

Women with a history of hypertension for several years should be evaluated for target organ damage including left ventricular hypertrophy, retinopathy, and renal disease. If damage is present, the woman should be advised that pregnancy may exacerbate the condition. Women with chronic hypertension are at higher risk for adverse neonatal outcomes independent of the development of preeclampsia, if proteinuria is present early in pregnancy.[88F] The risks of fetal loss and accelerated deterioration of maternal renal disease are increased if serum creatinine is above 1.4 mg/dL at conception, although it may be difficult to separate the effects of the pregnancy from progression of the underlying renal disease.[90F,91F] In patients with impaired renal function, relative risk of fetal loss has been reported to be increased tenfold when hypertension is present and not controlled at conception, compared with pregnancy without hypertension or with well-controlled hypertension.[92F,93Re]

Chronic hypertension before pregnancy requires planning for lifestyle changes. For example, pregnant women with hypertension may need to restrict their activities at work and home and refrain from vigorous exercise. Although regular exercise is beneficial for hypertensive individuals who are not pregnant and may be safe for normotensive pregnant women,[94F,95F] there are no data on safety in the setting of chronic hypertension and pregnancy. In view of the theoretical concerns with maintaining adequate placental blood flow in hypertensive women who are at increased risk for preeclampsia, our recommendation is to discourage aerobic exercise in hypertensive pregnant women until more data are available. Weight reduction during pregnancy, even in obese women, is not recommended. Although obesity may be a risk factor for superimposed preeclampsia, there is no evidence that limiting weight gain reduces its occurrence. Although the evidence is sparse in pregnant women, many experts recommend restriction of sodium intake to the same 2.4 g sodium intake recommended for essential hypertension. Women who already follow a more restricted sodium intake may continue to follow that dietary approach.

The use of alcohol and tobacco during pregnancy should be strongly discouraged. Both have a deleterious effect on the fetus and the mother. Excessive consumption of alcohol can cause or aggravate maternal hypertension. Tobacco is associated with a substantive risk for placental abruption and fetal growth restriction.

Treatment of Chronic Hypertension

The majority of women with chronic hypertension in pregnancy have Stage 1 to 2 hypertension (defined as systolic blood pressure of 140 to 179 mm Hg or diastolic blood pressure of 90 to 109 mm Hg) and are at low risk for cardiovascular complications within the short timeframe of pregnancy. Among women with Stage 1 to 2 preexisting essential hypertension and normal renal function, most pregnancies will have good maternal and neonatal outcomes. These women are candidates for nondrug therapy because, to date, there

is no evidence that pharmacologic treatment results in improved neonatal outcomes.[96Ra,97Ra] Since blood pressure usually falls during the first half of pregnancy, hypertension may be easier to control with less or no medication.

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. Although it may be beneficial for the mother with hypertension to reduce her blood pressure, lower pressure may impair uteroplacental perfusion and thereby jeopardize fetal development.[98,99M] Although it is not generally agreed whether antihypertensive therapy is beneficial or detrimental to pregnancy outcome, several studies offer some clinical guidance. Over the past 30 years, at least seven studies have compared antihypertensive therapy with either no medication or a placebo in pregnant women with mild chronic hypertension.[100Pr] Higher fetal losses during the second trimester were noted among untreated women in several early trials, but this finding was not confirmed. Indeed, overall prevalence rates of these adverse outcomes were very low. Rey and Couturier retrospectively evaluated the course of 298 pregnant women with chronic hypertension whose antihypertensive medications had been discontinued or whose doses were reduced early in pregnancy.[101F] Treatment did not decrease the frequency of superimposed preeclampsia, preterm delivery, abruptio placentae, or perinatal death when compared with untreated groups. Much uncertainty about the benefits of lowering blood pressure in pregnant women with mild chronic hypertension stems from published trials that are too small to detect modest reductions in obstetrical complications.

Evidence from several studies indicates the effectiveness of antihypertensive drugs in preventing exacerbation of chronic hypertension to severe hypertension during pregnancy.[96Ra,100Pr] These trials have included heterogeneous populations of women with preexisting hypertension and gestational hypertension, different thresholds for treatment by gestational age, and the presence or absence of proteinuria, and they often included multiple treatment agents.

Most of the increased risk associated with chronic hypertension occurs in the setting of superimposed preeclampsia.[88F] Preeclampsia is more common in women with chronic hypertension and complicates almost 25 percent of such pregnancies. The incidence is even higher if the high blood pressure is associated with renal insufficiency, the presence of hypertension for at least 4 years, and a history of hypertension in a previous pregnancy.[88F,90F,91F] The incidence of placental abruption is markedly increased in the presence of superimposed preeclampsia.[102Pr]

On the basis of available data, some centers currently manage women with chronic hypertension by stopping antihypertensive medications under close observation.[101F,103Pr] In patients with hypertension for several years, with evidence of target organ damage, or on multiple antihypertensive agents, medications may be tapered on the basis of blood pressure readings but should be continued if needed to control blood pressure. End points for reinstituting treatment include exceeding threshold blood pressure levels of 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic or the presence of target organ damage such as left ventricular hypertrophy or renal insufficiency. Methyldopa is preferred by most practitioners. Alternatively, women who are well controlled on antihypertensive therapy before pregnancy may be kept on the same agents (with the exception of angiotensin-converting enzyme inhibitors, AII receptor antagonists) during pregnancy.

Antihypertensive Drug Selection

While the goal of treating chronic hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus, especially in regard to acute and long-range neurologic effects. Methyldopa is preferred by many physicians as first-line therapy, on the basis of reports of stable uteroplacental blood flow and fetal hemodynamics,[104F] and one followup study after 7.5 years, in a limited number of infants, showed no long-term adverse effects on development of children exposed to methyldopa in utero.[105F] Methyldopa causes somnolence in many individuals. If this agent cannot be tolerated, alternatives such as labetalol are selected based on more limited clinical experience. If methyldopa is ineffective, alternatives can be substituted (see below) based on rational considerations of mechanisms of action. In the latter respect, salt retention may cause

refractoriness to vasodilator therapy, in which case a diuretic added to the regimen restores blood pressure control and permits prolongation of the pregnancy.

Most of the published experience with other agents comes from trials using adrenergic-blocking drugs including beta-blockers and the alpha-beta-blocker labetalol.[106M] There is a suggestion that beta-blockers prescribed early in pregnancy, specifically atenolol, may be associated with growth restriction.[106M,107Re,108F,109Ra] On the other hand, none of these agents has been associated with any consistent ill effects; however, long-term followup studies are lacking.

Experience with calcium antagonists is limited, with most reported uses being late in pregnancy. A multicenter prospective cohort study of first trimester drug exposures reported no increase in major teratogenicity from these agents.[110F] A recent multicenter study randomizing patients to slow-release nifedipine or no treatment beginning in the second trimester reported neither benefits nor evidence of harm from nifedipine treatment.[97Ra]

The use of diuretic agents in pregnancy is controversial. The primary concern is theoretical. It is known that preeclampsia is associated with a reduction of plasma volume[111F] and that fetal outcome is worse in women with chronic hypertension who fail to expand plasma volume.[112Ra] Whether this is a cause-and-effect relationship is not clearly established. Nonetheless, women using diuretics from early pregnancy do not increase their blood volume to the degree usually occurring in normal pregnancy.[113Ra] Because of the theoretical concerns, diuretics are usually not used as first-line drugs. A meta-analysis of nine randomized trials involving more than 7,000 subjects receiving diuretics revealed a decrease in the tendency of the women to develop edema and/or hypertension[114M] and confirmed no increased incidence of adverse fetal effects. However, if their use is indicated, they are safe and efficacious agents, can markedly potentiate the response to other antihypertensive agents, and are not contraindicated in pregnancy except in settings where uteroplacental perfusion is already reduced (preeclampsia and intrauterine growth restriction). Although data concerning the use of diuretics in pregnant women with essential hypertension are sparse, this working group concluded that gestation does not preclude use of diuretic drugs to reduce or control blood pressure in women whose hypertension predated conception or manifested before midpregnancy.

Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy because of associations with fetal growth restriction, oligohydramnios, neonatal renal failure, and neonatal death.[115Pr,116,117Re,118] Although no data are available on human use of angiotensin II receptor antagonists, adverse effects are likely to be similar to those reported with angiotensin converting enzyme inhibitors, and these agents should be avoided.

There are no placebo-controlled trials examining the treatment of severe hypertension in pregnancy, and none are likely to be performed, because of ethical considerations. Early reports of experience with severe chronic hypertension in the first trimester described fetal loss of 50 percent and significant maternal mortality.[119F] Most of the poor outcomes were in pregnancies complicated by superimposed preeclampsia.[119F] Antihypertensive therapy is indicated for maternal benefit but may also permit prolongation of the pregnancy and thereby improve fetal maturity.

Pregnancy, Hypertension, and Renal Disease

Among pregnant women with mild renal disease (serum creatinine less than 1.4 mg/dL), fetal survival is moderately reduced, and the underlying disease does not generally worsen.[120Pr] Women with renal diseases that tend to progress should be encouraged to complete their childbearing while their renal function is well preserved. The presence of hypertension before conception or early in pregnancy increases the incidence of maternal and fetal complications, with a tenfold higher relative risk of fetal loss.[92F,121Re]

Moderate or severe renal insufficiency may accelerate during pregnancy and jeopardize fetal survival.[90F,91F,120Pr,121Re] Hypertension occurs in more than half of these pregnancies.[122Pr] A decrease in birthweight correlates directly with rising maternal serum creatinine concentration.[91F] As renal failure progresses, the hypertension has a component of volume overload and may require sodium restriction, use of loop diuretics, or dialysis.

Recognition of superimposed preeclampsia may be difficult because proteinuria commonly increases in women with glomerular disease during pregnancy. Chronic dialysis during pregnancy is associated with significant maternal morbidity, and conception should be discouraged. Infant survival rates are higher in pregnancies where dialysis is started after conception (74 to 80 percent) than in those women who conceived while on maintenance dialysis (40 to 50 percent),[123X,124Re] presumably because the former are women with greater residual renal function. Infant survival may improve with greater duration of dialysis each week. Although low birthweight and preterm delivery are the rule, prognosis appears to be improving.

Clinical Note: *Magnesium sulfate is hazardous in women with severe renal failure, and maintenance doses must be reduced.* The usual loading dose can be given as this distributes to total body water and is not influenced by renal function. Then magnesium should be administered at a gram per hour maintenance, with therapy guided by hourly to two hourly magnesium levels until steady state is reached. Phenytoin may be considered as an alternative. (See the Anticonvulsive Therapy section.)

Renal transplant recipients are advised to wait 1.5 to 2 years after successful transplantation to undertake pregnancy and only if renal function is stable with creatinine of 2.0 mg/dL or less.[122Pr,125Pr] Although pregnancies may be complicated, 92 percent of infants survive in those pregnancies that go beyond the first trimester. From the National Transplantation Pregnancy Registry, in 115 renal transplant patients who received cyclosporine, high risks to the newborn were reported in settings of maternal hypertension and serum creatinine levels greater than 1.5 mg/dL. Rates of prematurity approach 55 percent; thus, all pregnancies in transplant recipients are considered high risk.[126Re]

Treating Hypertension That Persists Postpartum

Women with chronic hypertension can develop encephalopathy, heart failure and pulmonary edema, and renal failure in the postpartum period. Risk factors include underlying cardiac disease, chronic renal disease, superimposed preeclampsia in the second trimester, placental abruption complicated by disseminated intravascular coagulation, and requirement for multiple antihypertensive agents.[127C,128F] Acute hypertensive changes induced by pregnancy usually dissipate rapidly, within the first several days after delivery. Resolution of hypertension is more rapid in patients with gestational hypertension and may lag in those with preeclampsia, especially those with longer duration of preeclampsia and greater extent of renal impairment.[35F] This delay in resolution may reflect the time needed for endothelial recovery.

Oral antihypertensive agents may be required after delivery to help control maternal blood pressure, in particular, for women who were hypertensive before pregnancy. If prepregnancy blood pressures were normal or unknown, it is reasonable to stop oral medication after 3 to 4 weeks and observe the blood pressure at 1- to 2-week intervals for 1 month, then at 3- to 6-month intervals for 1 year. If hypertension recurs, it should be treated.

Treating Hypertension During Lactation

Breastfeeding should be encouraged and can be done safely with certain limits on antihypertensive drug choices. In mildly hypertensive mothers who wish to breastfeed for a few months, the clinician may consider withholding medication, with close monitoring of blood pressure. After discontinuation of nursing, antihypertensive therapy can be reinstituted. For patients with more severe blood pressure elevation and taking a single antihypertensive agent, the clinician may consider reducing the dosage, then closely observing both the mother and the infant.

Little information is available regarding excretion of antihypertensive agents in human breast milk and effects on the newborn.[129Pr] Further, there are no data concerning long-term effects of these drugs on infants exposed through breastfeeding. The reader is referred to the text by Briggs and colleagues[130Pr] and recommendations of the Committee on Drugs of the American Academy of Pediatrics.[131Pr] The available data suggest that all studied agents are excreted into human breast milk, although differences in the milk/plasma ratio

are related to lipid solubility and extent of ionization of the drug at physiologic pH.[132Pr] No short-term adverse effects have been reported from exposure to methyldopa or hydralazine. Although the Committee on Drugs considers atenolol compatible with breastfeeding, this beta-blocker, as well as metoprolol and nadolol, appears to be concentrated in breast milk. This property is not shared by propranolol or labetalol; for that reason these agents have been recommended if a beta-blocker is indicated. No data on calcium-channel blockers and lactation have been reported. Diuretics may reduce milk volume and suppress lactation.[133,134] Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists should be avoided on the basis of reports of adverse fetal and neonatal renal effects. Given the scarcity of data, breastfed infants of mothers taking antihypertensive agents should be closely monitored for potential adverse effects.

Fetal Assessment in Chronic Hypertension

Much of the increased perinatal morbidity and mortality associated with chronic hypertension can be attributed to superimposed preeclampsia and/or fetal growth restriction. A plan of antepartum fetal assessment is directed by these findings. Efforts should, therefore, be directed at the early detection of superimposed preeclampsia and fetal growth restriction. If these are excluded, then extensive fetal antepartum testing is less essential.

An initial sonographic assessment of fetal size and dating should be performed at 18 to 20 weeks' gestation. Fetal growth should be carefully assessed thereafter. If this is not possible with usual clinical estimation of fundal height (e.g., maternal obesity or multiple examiners), sonographic assessment should be performed at 28 to 32 weeks and monthly until term. If there is evidence of growth restriction, fetal well-being should be assessed by nonstress tests or biophysical profiles as usual for the growth-restricted fetus. Similarly, if preeclampsia cannot be excluded, then fetal assessment as appropriate for the fetus of a woman with preeclampsia is mandatory. If the infant is normally grown and preeclampsia can be excluded, however, there is no indication for these studies.

PREECLAMPSIA

PREVENTION OF PREECLAMPSIA

The ability to prevent preeclampsia is limited by lack of knowledge of its underlying cause. Prevention has focused on identifying women at higher risk, followed by close clinical and laboratory monitoring to recognize the disease process in its early stages. These women can then be selected for more intensive monitoring or delivery. Although these measures do not prevent preeclampsia, they may be helpful for preventing some adverse maternal and fetal sequelae.

Use of Low-Dose Aspirin To Prevent Preeclampsia

Benefits of low-dose aspirin prophylaxis are unproven for most women, including nulliparas. The prevailing opinion is that women without risk factors do not benefit from treatment, despite earlier prospective studies that suggested that aspirin administration reduced the incidence of preeclampsia. The basis for this opinion is the results of eight large trials in different populations around the world. Overall, the results of these trials, which included more than 27,000 pregnant women, demonstrate minimal to no reduction in the incidence of preeclampsia with low-dose aspirin.[89Ra,135Ra,136Ra,137Ra,138Ra,139Ra,140Ra,141Ra,142Pr]

An important study on low-dose aspirin prophylaxis in 2,539 women at higher risk for preeclampsia was published recently by the National Institutes of Health (NIH).[89Ra] Included were four subgroups of women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestation, or preeclampsia in a previous pregnancy. The incidence of preeclampsia, perinatal death, preterm delivery, and fetal growth restriction was the same in the aspirin- and placebo-treated patients, with no significant differences in outcomes for any of the four subgroups at higher risk.

Calcium Supplementation

There are no data indicating that dietary supplementation with calcium will prevent preeclampsia in low-risk women in the United States. Certainly, a diet that provides 1,000 mg elemental calcium daily is recommended for general health.[143Pr] Whether an enriched calcium diet beyond this amount may have benefit is unproven.

Results from a large NIH trial in 4,589 healthy nulliparous women randomized at 13 to 21 weeks to 2 g elemental calcium daily or placebo indicate that calcium supplementation neither reduced the incidence or severity of preeclampsia nor delayed its onset.[144Ra] There were no differences in the prevalence of nonproteinuric hypertension. Even within the subgroup of women with the lowest quintile of dietary calcium intake, similar to that reported for women in many developing countries, no benefit of calcium supplementation was demonstrated.[145Ra,146Ra]

Still, randomized trials of calcium supplementation in nulliparous women considered at *high risk* demonstrated significant reductions in incidence of preeclampsia.[147Ra,148Ra,149Ra,150Ra,151Ra]

Other Dietary Supplements

Prophylactic magnesium supplementation has not been shown to be beneficial in preventing preeclampsia.[152Ra,153Ra]

The results of three randomized trials of fish oil supplementation in women at high risk for preeclampsia revealed no reduction in incidence of preeclampsia.[154Ra,155Ra,156Ra] A recent study showing the benefits of vitamins C and E to prevent preeclampsia was encouraging but needs further confirmation.[157Ra,158]

Management of Preeclampsia

Rationale for Treatment

The objectives of therapy for preeclampsia are based on a philosophy of management arising from the knowledge of the pathology, pathophysiology, and prognosis of the disorder for mother and baby. The following three important tenets underlie management schemes:

1. Delivery is always appropriate therapy for the mother but may not be so for the fetus. For maternal health, the goal of therapy is to prevent eclampsia as well as other severe complications of preeclampsia. These disorders are completely reversible and usually begin to abate with delivery. Thus, if only maternal well-being was considered, the delivery of all women with preeclampsia, regardless of the severity of preeclampsia or duration of gestation, would be appropriate. Conversely, delivery induction is not indicated for a preterm fetus with no evidence of fetal compromise in women with mild disease. There are two important corollaries of this statement. First, any therapy for preeclampsia other than delivery must have as its successful end point the reduction of perinatal morbidity and mortality. Second, the cornerstone of obstetric management of preeclampsia is based on whether the fetus is more likely to survive without significant neonatal complications in utero or in the nursery.
2. The pathophysiologic changes of severe preeclampsia indicate that poor perfusion is the major factor leading to maternal physiologic derangement and increased perinatal morbidity and mortality. Attempts to treat preeclampsia by natriuresis or by lowering blood pressure may exacerbate the important pathophysiologic changes.
3. The pathogenic changes of preeclampsia are present long before clinical diagnostic criteria are manifest. Several studies indicate that changes in vascular reactivity, plasma volume, and renal tubular function antedate—in some cases by weeks—the increases in blood pressure, protein excretion, and sodium retention. These findings suggest that irreversible changes affecting fetal well-being may be present before the clinical diagnosis. If there is a rationale for management other than delivery, it would be to palliate the maternal condition to allow fetal maturation and cervical ripening.

Nonpharmacological Management

Fetal Evaluation

Fetal surveillance is indicated for the woman with preeclampsia. (See the section on High-Risk Patients Presenting With Normal Blood Pressure.)

Nonstress testing (NST), ultrasound assessment of fetal activity and amniotic fluid volume (biophysical profile [BPP]), and fetal movement counts constitute the most common fetal surveillance techniques. If determination of pulmonary maturity would influence management, amniocentesis should be done to determine this before the interruption of pregnancy.

For all women with preeclampsia, daily fetal movement assessment is a useful screening assessment. More formal testing is indicated if movements are not normal. Formal testing (NST, BPP) should be performed periodically with even normal fetal activity. The frequency of formal testing will be dictated by the clinical condition. Although weekly to biweekly assessment will usually suffice, for women with severe preeclampsia who are being managed expectantly, daily testing is appropriate. (See Table 2.)

If possible fetal compromise is indicated by fetal surveillance, then decision-making for delivery requires judgment heavily weighted by fetal age.

Maternal Evaluation

Antepartum monitoring has two goals. The first is to recognize preeclampsia early; the second is to observe progression of the condition, both to prevent maternal complications by delivery and to determine whether fetal well-being can be safely monitored with the usual intermittent observations.

At present, clinical management of preeclampsia is directed by overt clinical signs and symptoms. Although rapid weight increase and facial edema may indicate the fluid and sodium retention of preeclampsia, they are neither universally present nor uniquely characteristic of preeclampsia.

TABLE 2. Fetal Monitoring in Gestational Hypertension and Preeclampsia

Gestational Hypertension (hypertension only without proteinuria, with normal laboratory test results, and without symptoms)
• Estimation of fetal growth and amniotic fluid status should be performed at diagnosis. If results are normal, repeat testing only if there is significant change in maternal condition. • Nonstress test (NST) should be performed at diagnosis. If NST is nonreactive, perform biophysical profile (BPP). If BPP value is eight or if NST is reactive, repeat testing only if there is significant change in maternal condition.
Mild Preeclampsia (mild hypertension, normal platelet count, normal liver enzyme values, and no maternal symptoms)
• Estimation of fetal growth and amniotic fluid status should be performed at diagnosis. If results are normal, repeat testing every 3 weeks. • NST, BPP, or both should be performed at diagnosis. If NST is reactive or if BPP value is eight, repeat weekly. Testing should be repeated immediately if there is abrupt change in maternal condition. • If estimated fetal weight by ultrasound is <10th percentile for gestational age or if there is oligohydramnios (amniotic fluid index ≤ 5 cm), then testing should be performed at least twice weekly.

These signs are, at most, a reason for closer monitoring of blood pressure and urinary protein. Early recognition of impending preeclampsia is based primarily on blood pressure increases in the late second and early third trimesters. Once blood pressure starts to rise (this may be the first sign of developing preeclampsia), a repeat examination within 1 to 3 days is recommended. In selected patients, blood pressure and urinary protein may be checked at home. In either case, the woman should be evaluated for symptoms suggestive of preeclampsia—headaches, blurred vision, right upper quadrant or epigastric pain—and should undergo laboratory testing for platelet count, renal function, and liver enzymes. Quantification of a 12- to 24-hour urine sample for proteinuria is recommended. (See Table 1.) These measures determine how fast the condition is progressing to ensure that it is not following a fulminant course. The frequency of subsequent observations is determined by the initial observations and the ensuing clinical progression. If the condition appears stable, weekly observations may be appropriate. The initial appearance of proteinuria is an especially important sign of progression and dictates frequent observations.

Often, hospitalization is initially recommended for women with new-onset preeclampsia. After maternal and fetal conditions are serially assessed, subsequent management may be continued in-hospital, at a day-care unit, or at home on the basis of the initial assessment. Prolonged hospitalization for the duration of pregnancy allows rapid intervention in case of fulminant progression to hypertensive crisis, eclampsia, or abruptio placentae.[159Pr] These complications are rare in compliant women who have mild hypertension, minimal proteinuria, no symptoms, and normal platelet counts and serum liver enzyme levels. Recently, ambulatory management at home or at a day-care unit has been evaluated as an option for monitoring women with mild gestational hypertension or preeclampsia remote from term. A number of observational[160F,161F,162F,163F,164F] and randomized studies[165F,166Ra,167Ra] suggest a place for ambulatory management of selected women. If day care or home management is selected, it should include frequent maternal and fetal evaluation and access to health care providers.[159Pr] If worsening of preeclampsia is diagnosed, as determined by laboratory findings, symptoms, and clinical signs, hospitalization is indicated.

Hospitalization for the duration of pregnancy is indicated for preterm onset of severe gestational hypertension or preeclampsia. The decision to prolong the pregnancy in these women is determined day by day. The women should receive intensive maternal and fetal surveillance, usually at a tertiary

care facility.[168F,169Ra,170Ra] Laboratory studies are performed at frequent intervals and include serial determinations of platelet count, serum liver enzyme levels, renal function, and urinary protein. Assiduous attention is given for worsening hypertension; evidence of central nervous system involvement that includes severe headache, disorientation, or visual symptoms; and hepatic involvement indicated by epigastric pain and tenderness.

Antepartum Management of Preeclampsia

There is little to suggest that any therapy alters the underlying pathophysiology of preeclampsia. Therapeutic efforts that may be palliative, slow progression of the disorder, and permit continuation of pregnancy have not been shown to reverse the underlying disorder. Restricted activity is a usual and reasonable recommendation for women with preeclampsia, although its efficacy is not clearly established. Strict sodium restriction and diuretic therapy appear to have no role in management. Finally, results of several randomized trials suggest that antihypertensive therapy for women with gestational hypertension or preeclampsia does not improve perinatal outcomes.[97Ra,100Pr,171Ra]

Indications for Delivery

Delivery is the only definitive treatment for preeclampsia, and some suggested indications are listed in Table 3. All women with this diagnosis should be considered for delivery at 40 weeks' gestation. Delivery may be indicated for women with mild disease and a favorable cervix for induction at 38 weeks' gestation and should be considered in women who have severe preeclampsia beyond 32 to 34 weeks' gestation. At gestational week 33 to 34, the fetus may benefit from corticosteroid administration.

Prolonged antepartum management in women with severe preeclampsia is possible in a select group of women with fetal gestational age between 23 and 32 weeks. In some women, preeclampsia improves after hospitalization and treatment with magnesium sulfate and antihypertensive agents given acutely.[96Ra,169Ra,170Ra] Such management may prolong pregnancy, with a decrease in perinatal morbidity and mortality. It should be attempted only in centers equipped to provide close maternal and fetal surveillance.[172Pr] Delivery in these preterm pregnancies is indicated by worsening maternal symptoms, laboratory evidence of end-organ dysfunction, or fetal deterioration.

Route of Delivery

Vaginal delivery is preferable to caesarean delivery for women with preeclampsia, thus avoiding the added stress of surgery to multiple physiologic aberrations. Acute palliation for several hours does not increase maternal risk if performed appropriately. Labor induction should be carried out aggressively once the decision for delivery is made. In gestation remote from term in which delivery is indicated and with fetal and maternal

TABLE 3. Indications for Delivery in Preeclampsia*

Maternal	Fetal
Gestational age ≥ 38 weeks	Severe fetal growth restriction
Platelet count <100,000 cells/mm^3	Nonreassuring fetal testing results
Progressive deterioration in hepatic function	Oligohydramnios
Progressive deterioration in renal function	
Suspected abruptio placentae	
Persistent severe headaches or visual changes	
Persistent severe epigastric pain, nausea, or vomiting	

* Delivery should be based on maternal and fetal conditions as well as gestational age.

conditions stable enough to permit pregnancy to be prolonged 48 hours, glucocorticoids can be safely administered to accelerate fetal pulmonary maturity. (See Table 3.)

The aggressive approach to induction includes a clear end point for delivery, usually within 24 hours of the decision to induce labor. Most experts recommend a trial of induction regardless of cervical condition. If vaginal delivery cannot be effected within a reasonable time, caesarean delivery is considered and is also performed for other usual obstetrical indications.

Neuraxial (epidural, spinal, and combined spinal-epidural) techniques offer many advantages for labor analgesia and can be safely administered to the preeclamptic parturient. Dilute epidural infusions of local anesthetic plus opioid produce adequate sensory block without motor block or clinically significant sympathectomy. When neuraxial techniques are used for cesarean delivery, however, there is a possibility of extensive sympatholysis with profound hypotension which may lead to decreased cardiac output and further diminished uteroplacental perfusion. This may be more likely with single-shot spinal anesthesia, which although considered acceptable by some experts, is still considered by others to be relatively contraindicated in women with severe preeclampsia. A recent analysis, however, suggests that spinal anesthesia can be used safely in the severely preeclamptic patient undergoing cesarean section, since the magnitude of maternal blood pressure declines appear to be similar after spinal or epidural anesthesia.[173Re] Hypotension can usually be avoided by meticulous attention to anesthetic technique and careful volume expansion. In one unblinded study of 80 women with severe preeclampsia randomized to receive epidural, combined spinal-epidural, or general anesthesia, all three regimens appeared equally safe.[174Ra]

With general anesthesia, significant hypertension may occur at the time of laryngoscopy and tracheal intubation and again during emergence and extubation. These responses can usually be blocked by appropriate pretreatment with hydralazine, nitroglycerin, or labetalol. Airway edema may be seen in the preeclamptic patient and may increase the risks of a "difficult airway" situation leading to failed intubation and ventilation. Because general anesthesia poses considerably greater risk to parturients than regional anesthesia,[175X] the risk of a failed intubation must be weighed against the risk of transient hypotension when deciding between general and regional anesthesia for cesarean section in the severely preeclamptic/eclamptic patient. Although neuraxial techniques have become the preferred method to provide labor analgesia or anesthesia for cesarean section in women with severe preeclampsia-eclampsia, they are relatively contraindicated in the presence of coagulopathy. Early consultation with an anesthesiologist is suggested for parturients with severe preeclampsia.

Anticonvulsive Therapy

Anticonvulsive therapy is usually indicated either to prevent recurrent convulsions in women with eclampsia or to prevent convulsions in women with preeclampsia. There is universal agreement that women with eclampsia should receive anticonvulsive therapy.[176Ra] Several randomized studies indicate that parenteral magnesium sulfate reduced the frequency of eclampsia more effectively than phenytoin in a mixed group of gestational hypertensive and preeclamptic women.[177Pr,178M] Parenteral magnesium sulfate is given during labor, delivery, and for variable durations postpartum. There is not clear agreement concerning the use of prophylactic magnesium sulfate for women with preeclampsia.[179Ra] The results of two large randomized trials showed that parenteral magnesium sulfate reduces the frequency of eclampsia in women with either pregnancy-induced hypertension or severe preeclampsia.[179Ra,180Ra] Although parenteral magnesium sulfate should be given peripartum to women with severe preeclampsia, its benefits with mild gestational hypertension or preeclampsia remain unclear. A multicenter randomized trial to answer this question is urgently needed. Precautions regarding the use of magnesium sulfate during pregnancy in women with renal failure are discussed in the section on Pregnancy, Hypertension, and Renal Disease.

Invasive Hemodynamic Monitoring

Some investigators recommend the use of invasive hemodynamic monitoring in managing women with severe preeclampsia-eclampsia. It has been used to monitor fluid therapy during plasma volume expansion;[181Re] in managing women with pulmonary edema, persistent oliguria unresponsive to fluid challenge, and intractable severe

hypertension; and in some patients receiving epidural anesthesia.[182Pr] There is no published evidence that the use of invasive hemodynamic monitoring is indicated for the purposes mentioned above.

Treatment of Acute Hypertension

Antihypertensive therapy is indicated when blood pressure is dangerously high or rises suddenly in women with preeclampsia, especially intrapartum. Antihypertensive agents can be withheld as long as maternal pressure is only mildly elevated. Some experts would treat persistent diastolic levels of 105 mm Hg or higher. Others would withhold treatment until diastolic blood pressure levels reach 110 mm Hg.[103Pr] In adolescents whose diastolic pressures were recently below 75 mm Hg, treating persistent levels of 100 mm Hg or higher may be considered. When treatment is required, the ideal drug that reduces pressures to a safe level should act quickly, reduce pressure in a controlled manner, not lower cardiac output, reverse uteroplacental vascular constriction, and result in no adverse maternal or fetal effects. The medications used to treat hypertensive crises in pregnancy, and their route of administration, are summarized in Table 4. Details of their pharmacology and safety are discussed elsewhere.[183Pr]

The most commonly used drug is hydralazine, administered as either intravenous (IV) or intramuscular (IM), which, if given cautiously, is successful in most instances. It has been shown to be effective against preeclamptic hypertension.[184F,185Re] Although this drug is sometimes given as an intravenous infusion, the pharmacokinetics (maximal effect at 20 minutes, duration of action 6 to 8 hours) indicate intermittent bolus injections are more sensible. A 5 mg bolus is given intravenously over 1 to 2 minutes. After 20 minutes, subsequent doses are dictated by the initial response. Once the desired effect is obtained, the drug is repeated as necessary (frequently in several hours).[185Re] Parenteral labetalol has been shown to be effective for the treatment of acute severe hypertension in pregnancy.[106M,184F] The drug may be used as intravenous bolus injections of 20 mg or 40 mg, or as continuous intravenous infusion of 1 mg/kg as needed. Labetalol is usually used as a second-line drug. It should be avoided in women with asthma and in those with congestive heart failure.

The use of oral nifedipine has been described in a limited number of women with acute severe hypertension during pregnancy.[186F] Details of these reports are summarized elsewhere.[100Pr] Nifedipine acts rapidly, causing significant reduction in arterial blood pressure within 10 to 20 minutes of oral administration. Although it has favorable hemodynamic effects,[186F] physicians should be advised that rapidly acting nifedipine (in capsules containing the liquid form) has never been approved by the Food and Drug Administration for treating hypertension or hypertensive emergencies. The JNC VI[2Pr] has recommended that it not be used for this purpose because it has been associated with fatal and nonfatal untoward cardiovascular events, especially in older patients.[187Pr] Of the 16 case reports reviewed by Grossman and colleagues,[187Pr, 188] one was a 37-year-old pregnant woman whose blood pressure was reduced from 150/118 to 90/55, precipitating the need for caesarean section because of fetal distress. Care should be exercised when using nifedipine or any calcium antagonist with magnesium sulfate.[189,190Pr,191]

In the rare case, sodium nitroprusside may be indicated after the failure of hydralazine, nifedipine, and labetalol for acute hypertensive emergency.

TABLE 4. Treatment of Acute Severe Hypertension in Preeclampsia*

BP ≥ 160 mm Hg systolic and/or ≥ 105 mm Hg diastolic if sustained

- Hydralazine: Start with 5 mg IV or 10 mg IM. If blood pressure is not controlled, repeat at 20-minute intervals (5 to 10 mg depending on response). Once BP control is achieved, repeat as needed (usually about 3 hours). If no success by 20 mg IV or 30 mg IM total, consider another drug.
- Labetalol: Start with 20 mg IV as a bolus; if effect is suboptimal, then give 40 mg 10 minutes later and 80 mg every 10 minutes for two additional doses. Use a maximum of 220 mg. If desired blood pressure levels are not achieved, switch to another drug. Avoid giving labetalol to women with asthma or congestive heart failure.
- Nifedipine: Start with 10 mg orally and repeat in 30 minutes if necessary. *See precautions, in Treatment of Acute Hypertension section.* (Short-acting nifedipine is not approved by FDA for managing hypertension.)
- Sodium nitroprusside is rarely needed for hypertension not responding to the drugs listed above and/or if there are clinical findings of hypertensive encephalopathy. Start at a rate of 0.25 µg/kg/min to a maximum dose of 5 µg/kg/min. Fetal cyanide poisoning may occur if used for more than 4 hours.

*** Side effects:** See *Physicians Desk Reference* (53rd edition).

Caution: Sudden and severe hypotension can result from the administration of any of these agents, especially short-acting oral nifedipine. The goal of blood pressure reduction in emergency situations should be a gradual reduction of blood pressure to the normal range. (See *Treatment of Acute Hypertension section.*)

Clinical Note: In managing hypertensive emergencies, the IV route is safer than oral or IM administration because it is easier to combat inadvertent hypotension by stopping an IV injection or infusion than it is to stop intestinal or intramuscular absorption of an orally or IM-administered drug.

Postpartum Counseling and Followup

Women who develop hypertension during pregnancy should be carefully reevaluated during the immediate postpartum months and counseled with respect to future gestations and remote cardiovascular risks as well. Any laboratory abnormality or physical finding that has not returned to normal before postdelivery discharge should be reassessed at postpartum followup. The expectation is that hypertension and other signs or symptoms of organ dysfunction associated with preeclampsia will have remitted by the 6-week postpartum examination, but if abnormalities persist, the patients should be reexamined 6 weeks later, when persisting pathology will probably be chronic.

Counseling for Future Pregnancies

Women who have had preeclampsia are more prone to hypertensive complications in subsequent pregnancies. Risk is best established for nulliparas with a history of preeclampsia, the magnitude of the recurrence rate increasing the earlier the disease manifested during the index pregnancy. For instance, when preeclampsia presents clinically before gestational week 30, the recurrence rate may be as high as 40 percent.[192F,193F] Preeclampsia reappearance rates may also be population-specific. For example, in white woman with well-defined disease after gestational week 36, recurrence is barely 10 percent,[194Pr] but it may be substantially greater in black patients.[192F] The recurrence rate for women with one episode of HELLP is almost 5 percent.[195F]

Recurrence rates are higher for those experiencing preeclampsia as multiparas compared with nulliparous women.[196Re] Risk is also increased in multiparas who conceive with a new father even when their first pregnancy was normotensive, the incidence being intermediate between that of primiparous women and monogamous multiparous women who have not had a preeclamptic pregnancy.[196Re]

Of interest are data indicating that women with early-onset severe preeclampsia harbor metabolic abnormalities or risk factors associated with vascular thrombosis. These include activated protein C resistance (Factor V Leiden), antiphospholipid antibodies, hyperhomocysteinemia, and protein S deficiency.[197F,198F,199,200Re] Therefore, patients with a history of early-onset severe preeclampsia should be evaluated for evidence of prior thromboembolic diseases and, if they have such a history, should be tested for the above-described abnormalities (which when present jeopardize not only future pregnancies but the patients' general health as well).

Remote Cardiovascular Prognosis

Preeclampsia-Eclampsia

The remote prognosis of women experiencing preeclampsia or eclampsia is best summarized as follows: The more certain the diagnosis is preeclampsia alone (e.g., nulliparity, especially if complicated by eclampsia or confirmed by renal biopsy), the lower the prevalence of remote cardiovascular disorders. Prevalence of remote hypertension, however, is increased in nulliparous women with preeclampsia or eclampsia manifesting hypertension in subsequent gestations, multiparas who develop the disorder, and women with severe early-onset disease of any parity. The literature further suggests that preeclampsia-eclampsia, by itself, is not a cause of essential hypertension. In essence, it is the hypertension in subsequent gestations, presence of preeclampsia in a multipara, or early-onset disease in any pregnancy that signals that the disease has occurred in a patient with an increased probability of essential hypertension later in life.[89Ra,192F,193F,194Pr,201F]

In summary, it is reasonable to counsel patients as follows: If preeclampsia occurred late in an initial gestation, there is no evidence of remote cardiovascular risk, but subsequent pregnancies will help us define risk more accurately. Women with early-onset disease, multiparous women with preeclampsia or only hypertension, and those manifesting gestational hypertension in any pregnancy are at increased cardiovascular risk—information of importance for long-term health care strategies. The best news, however, is that women experiencing normotensive births have a reduced risk for remote hypertension.

Recommendations for Future Research

A Research Diagnosis of Preeclampsia

The clinical definitions used in this document aim to protect both mother and fetus from adverse outcome. They were purposely chosen to have a high sensitivity rather than specificity because overdiagnosis is a safe strategy that ensures closer scrutiny of the patient and avoids morbidity. In the process, however, many women receiving the clinical diagnosis do not, in reality, have true preeclampsia. The use of patients labeled preeclamptic by the clinical definition may lead to erroneous findings in studies designed to determine outcome and epidemiologic associations. Thus, more stringent criteria must be used for selecting cases for research in preeclampsia. Specifically, cases should be documented to be normotensive before pregnancy or 12 weeks after pregnancy.

Studies of nulliparous women are important in order to distinguish unique pathologic features of preeclampsia from other preexisting or future pathophysiology, which is often present in multiparas who appear to develop the disorder. There are situations in which studies of multiparas are useful, mainly those designed to understand factors that predispose to preeclampsia (and that should eventually provide targets to prevent the disease or improve management strategies). Included here are subsets of patients such as those with a variety of metabolic disorders and women with a history of early-onset preeclampsia.[193]

Other Research Needs

Studies To Establish Appropriate Diagnostic Criteria for Preeclampsia

Large prospective multicenter trials designed to detect markers that uniquely predict and/or specifically accompany the preeclamptic syndrome and are absent from other hypertensive disorders are needed. Ideally, the clinical diagnosis of preeclampsia would be based on sensitive and specific diagnostic tests derived directly from the causative mechanism of the disease. No such tests exist, and none is likely until we understand the pathogenesis of the syndrome more completely. Lacking such tests, clinical diagnosis should be based on the relationship of findings to outcomes or those findings' ability to predict development of frank clinical preeclampsia. Estimates of the prevalence of preeclampsia at different threshhold values of blood pressure or change in pressure, and the magnitude of overlap using the different criteria, *must be developed*. Ideally, receiver-operating characteristic curves should be defined for both absolute blood pressure and change over baseline so that the most appropriate criterion values can be chosen and the need for revising current definitions assessed. Use of current estimates of qualitative and quantitative protein excretion should be analyzed similarly, and these prospective studies should also be designed to determine the predictive value of other signs and symptoms to diagnose preeclampsia when proteinuria is absent (e.g., platelets, liver function, abdominal and neurologic symptoms, markers of endothelial activation[58]). Such data may help improve both the clinical and research diagnoses of preeclampsia.

A substantial subset of the desired data, at least for blood pressures if not for other tests, may be obtained by reanalyzing the original data sets of the large prospective trials of aspirin or calcium supplementation for prophylaxis. That may be the most cost-effective approach in the short term.

Clinical Trials Regarding Prevention and Management of the Hypertensive Complications

There are few trials to guide choices of antihypertensive agents in pregnancy, and all appear to have one or more major flaws. Large multicenter randomized trials, carefully designed to determine the

teratogenicity of any prescribed medication and other aspects of fetal jeopardy as well as maternal well-being, are needed. Such studies should include substantial periods of neonatal followup. Given both their importance and costs, such trials can rarely rely on industry funding; they require Government support.

Attempts To Identify Subsets of Women With the Preeclampsia Syndrome

Efforts should be made to recognize different subsets of women with preeclampsia and to examine them separately for both outcome and pathophysiology. This approach has increased our understanding of other complex syndromes (e.g., type 1 and type 2 diabetes). Criteria for determining subsets could include gestational age at delivery, association with intrauterine growth restriction, as well as research into the genetic predisposition of preeclampsia including both population genetics and biochemical markers for women at risk for preeclampsia. Such studies should identify women at adverse risk for maternal and fetal outcome as a result of preeclampsia.

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