Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy

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Bethesda, Maryland

This report updates the 1990 "National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy" and focuses on classification, pathophysiologic features, and management of the hypertensive disorders of pregnancy. Through a combination of 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." The recommendations to use Korotkoff phase V for determination of diastolic pressure and to eliminate edema as a criterion for diagnosing preeclampsia are discussed. In addition, the use as a diagnostic criterion of blood pressure increases of 30 mm Hg systolic or 15 mm Hg diastolic with blood pressure <140/90 mm Hg has not been recommended, because available evidence shows that women with blood pressures fitting this description are not more likely to have adverse outcomes. Management distinctions are made between chronic hypertension that is present before pregnancy and hypertension that occurs as part of the pregnancy-specific condition of preeclampsia, as well as management considerations for women with comorbid conditions. A discussion of the pharmacologic treatment of hypertension during 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. (Am J Obstet Gynecol 2000;183:S1-S22.)

Key words: Eclampsia, hypertension, preeclampsia, pregnancy, treatment

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

The purpose of this "Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy" is to provide guidance to practicing clinicians on management of (1) patients with hypertension who become pregnant and (2) patients in whom hypertensive disorders develop 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. Through a combination of evidence-based medicine and consensus, this 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."[2]

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**See Appendix at end of article for list of working group members and member organizations.*
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Evidence base

The studies that provided evidence to support the recommendations given in the 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 "The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" and originally

adapted from Last and Abramson,[3] is used in the reference list of 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 follow-up,* also known as *cohort studies,* including historical cohort studies and long-term follow-up

X: *cross-sectional population studies,* also known as *prevalence studies*

Pr: *previous review* or position statements

C: *clinical interventions* (nonrandomized studies)

These explanatory abbreviations are appended to some of the references in the reference section of the document.

Classification of the hypertensive disorders of pregnancy

The most important consideration in the classification of diseases in which blood pressure rises abnormally is differentiation of 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 related to vasospasm and activation of the coagulation cascade. Although our understanding of this syndrome has increased, the criteria used to identify the disorder remain subject to confusion and controversy. This confusion doubtless reflects the fact that preeclampsia is a syndrome, which means 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 Committee on Terminology in 1972.[5] This decision was prompted by the opinion that this classification was both simple and widely used 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 remains largely the same.

Several groups, including the American College of Obstetricians and Gynecologists,[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 given here. 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 blood pressures,[7] and to add systemic changes to proteinuria as diagnostic markers.[8] Of these changes 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—Korotkoff phase IV (muffling)[6, 7] or Korotkoff phase V (disappearance).[4, 8] We chose Korotkoff phase V 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 as a potential cause of maternal morbidity. As might be expected, the impacts of the two conditions on mother and fetus are different, as are the management strategies. Attempts to differentiate the two conditions have led to confusion in terminology worldwide. We have modified the American College of Obstetricians and Gynecologists classification slightly by adding the term "gestational hypertension" for the woman who has hypertension without proteinuria during pregnancy, reserving "transient hypertension of pregnancy" for a definitive diagnosis made post partum. According to this terminology women with increased blood pressure are divided into the groups discussed in the following Classification section.

Classification

- Chronic hypertension
- Preeclampsia-eclampsia
- Preeclampsia superimposed on 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 post partum (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 ≥140 mm Hg systolic or ≥90 mm Hg diastolic. Hypertension that is diagnosed for the first time during pregnancy and that does not resolve post partum is also classified as chronic hypertension.

Preeclampsia-eclampsia. The pregnancy-specific syndrome usually occurs after 20 weeks' gestation (or earlier in the case of 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 >140 mm Hg systolic or >90 mm Hg diastolic in a woman who was normotensive before 20 weeks' gestation. In the absence of proteinuria the disease is highly suspected when increased blood pressure appears accompanied by the following symptoms: headache, blurred vision, and abdominal pain, or by abnormal laboratory test results, specifically low platelet counts and abnormal liver enzyme values.

In the past it has been recommended that an incre-

ment of 30 mm Hg systolic or 15 mm Hg diastolic blood pressure be used as a diagnostic criterion, even when absolute values remain <140/90 mm Hg. This definition has not been included in our criteria, because the only available evidence shows that women with blood pressures fitting this description are not likely to have 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 ≥6 mg/dL) are also present.

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

Proteinuria is defined as the urinary excretion of ≥0.3 g protein in a 24-hour specimen. This will usually correlate with ≥30 mg/dL (≥1+ reading on dipstick) 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 concentrations in preeclampsia (which may be either higher or lower),[16-18] it is recommended that the diagnosis be based on a 24-hour urine sample if at all possible or that it be based on a timed collection corrected for creatinine excretion if the former procedure 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 follow-up:

- Blood pressure is ≥160 mm Hg systolic or ≥110 mm Hg diastolic.
- Proteinuria of ≥2.0 g in 24 hours is seen (2+ or 3+ on qualitative examination). The proteinuria should occur for the first time during pregnancy and regress after delivery.
- Serum creatinine level is increased (>1.2 mg/dL unless known to be previously elevated).
- Platelet count is <100,000 cells/mm^3, there is evidence of microangiopathic hemolytic anemia (with increased lactic acid dehydrogenase concentration), or both.
- Hepatic enzyme activities (either alanine aminotransferase, aspartate aminotransferase, or both) are elevated.
- Patient reports persistent headache or other cerebral or visual disturbances.
- Patient reports persistent epigastric pain.

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

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

Preeclampsia superimposed on chronic hypertension. There is ample evidence that preeclampsia may occur in women who are already hypertensive (who have chronic hypertension) and that in such cases the prognoses for mother and fetus are 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' gestation), new-onset proteinuria, defined as the urinary excretion of ≥0.3 g protein in a 24-hour specimen, is present.
- In women with hypertension and proteinuria before 20 weeks' gestation any of the following are seen:
  —sudden increase in proteinuria,
  —sudden increase in blood pressure in a woman whose hypertension has previously been well controlled
  —thrombocytopenia (platelet count <100,000 cells/mm^3),
  —increase in alanine aminotransferase or aspartate aminotransferase 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 diagnosis covers women with the preeclampsia syndrome who have not yet manifested proteinuria as well as women who do not have the preeclampsia syndrome. The hypertension may be accompanied by other signs of the syndrome, which influences management. The final determination that the woman does not have the preeclampsia syndrome can be made only post partum. If preeclampsia has not developed and blood pressure has returned to normal by 12 weeks post partum, the diagnosis of transient hypertension of pregnancy can be assigned. If blood pressure elevation persists, the woman is considered to have chronic hypertension. Note that the diagnosis of gestational hypertension is used during pregnancy only until a more specific diagnosis can be assigned post partum.

Clinical implications of classification. The clinical spectrum of preeclampsia ranges from mild to severe. In most cases progression through this spectrum is slow, and the

disorder may never proceed beyond mild preeclampsia. In other cases the disease progresses more rapidly, changing from mild to severe within 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 inflammatorylike 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 the fact that preeclampsia is more than hypertension; it is a systemic syndrome, and several of its nonhypertensive complications may be life-threatening even 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 for 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 saclike flaccid vessels, which eventually accommodate a 10-fold 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 that trophoblastic invasion of the uterine spiral arteries is incomplete in women in whom preeclampsia eventually develops, with 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, human leukocyte antigen 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 tissues from pregnancies complicated by preeclampsia may express less or different human leukocyte antigen 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, decreased prevalences after heterologous blood transfusions and 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 in preeclampsia, as well as evidence of increased natural killer cells and neutrophil activation.[27]

Pathophysiology of the maternal manifestations of preeclampsia

Blood pressure in preeclampsia. Women with preeclampsia do not usually demonstrate frank hypertension until the second half of gestation, but vasoconstrictive influences may be present earlier. For instance, alterations in vascular reactivity may be detected by gestational week 20, and numerous surveys suggest that women in whom preeclampsia eventually develops have blood pressures falling slightly higher in the normal range (eg, diastolic levels >70 mm Hg) as early as the second trimester,[28] as 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 the normotensive gravid woman manifests a decreased pressor responsiveness to several vasoactive peptides and amines, especially to angiotensin II. The vessels of women with preeclampsia, however, become hyperresponsive to these hormones, and in the case of angiotensin II 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 may be labile and may be accompanied by a blunting and even reversal of normal circadian blood pressure rhythms.[34] Blood pressure normalizes post partum, usually within the first few days of the puerperium; however, the return to normal 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 vasodilatory and vasoconstrictive prostanoids, because there is evidence to suggest decrements and increments in the productions of prostacyclin and thromboxane, respectively.[36-38] More recently investigators have postulated that the vasoconstrictive potential of pressor substances (eg, angiotensin II and endothelin) is magnified in preeclampsia as a consequence of a decreased activity of nitric oxide synthase and decreased production of nitric oxide–dependent or

nitric oxide–independent endothelium-derived relaxing factor.[39-43] Also under investigation is the role of endothelial cells (the site of prostanoid, endothelin, and endothelium-derived relaxing factor production), which in preeclampsia may be dysfunctional, perhaps as a result of inflammatory cytokines (eg, tumor necrosis factor α) 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, with the decrements in cardiac performance representing a ventricle contracting normally 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, primarily as a result of 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 and renal blood flow decrease in preeclampsia, the former more than the latter, leading to a decrease in filtration fraction.[31] The decrement is usually modest (25%), even when morphologic changes are pronounced. Because renal function normally rises 35% to 50% 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 to the increased urinary calcium excretion observed during normal pregnancy.[67] Alterations in calcium regulatory hormones, including reduced plasma levels of 1,25-dihydroxyvitamin D[53] and increased plasma levels of 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, which is believed to be due in part to extravasation of albumin into the interstitium. In addition, central venous pressure and pulmonary capillary wedge pressure are often low or in the low normal range. 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 glomerular filtration rate and several volume-sensitive hormones fail to explain this observation. Filtered sodium level, although decreased with respect to the level in normal pregnancy, is still above the level 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 concentration is reported to be increased.[70, 71]

The coagulation system. Thrombocytopenia, rarely severe, is the most commonly found hematologic abnormality in preeclampsia. Circulating levels of fibrin degradation products are occasionally elevated, and plasma fibrinogen levels are unaffected unless the disease is accompanied by abruptio placentae.[72] However, antithrombin III levels are lower and cellular fibronectin levels are higher in women with preeclampsia than in women with normal pregnancies—observations consistent with vascular endothelial injury.[73, 74]

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

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

The liver. The pathologic changes in the liver associated with preeclampsia ere well described in the autopsy studies of Sheehan and Lynch.[77] These changes include periportal hemorrhages, ischemic lesions, and fibrin deposition. Liver damage accompanying preeclampsia may range from mild hepatocellular necrosis with abnormalities in serum enzyme levels (aminotransferase and lactate dehydrogenase activities) to the ominous HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, with markedly elevated liver 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 to fibrin deposition, as well as to hypertensive encephalopathy. This last explanation is difficult to reconcile with the clin-

ical observations that many women with convulsions have only mild or moderate hypertension. Vasoconstriction in eclampsia may be selective, however, and studies with Doppler ultrasonographic techniques suggest that severe cerebral vasospasm may occur even when peripheral vasoconstriction is less evident.[80, 81]

The best descriptions of gross and microscopic pathologic features in eclampsia remain those of Sheehan and Lynch,[77] in which most autopsies were performed within 1 to 2 hours of death, thus eliminating most of the postmortem changes that usually confound interpretation of brain pathologic conditions. 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 computed tomographic and magnetic resonance imaging techniques.[83, 84] Some studies have shown relatively normal results, whereas others have described 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 perhaps induced by hypoxia, have been described in the computed axial tomographic scans.[85] Hemorrhage and edema have also been documented by magnetic resonance imaging, 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 of visual disturbances in preeclampsia-eclampsia.

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 Counseling sections).

The period during 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 detected at midpregnancy (gestational weeks 20-28) may be due to either early preeclampsia (rare before 24 weeks' gestation), transient hypertension, or unrecognized chronic hypertension. With respect to the last, blood pressure normally falls in the initial trimesters, and this physiologically appropriate decrement may even be exaggerated in patients with essential hypertension, masking the diagnosis during 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 during 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 test results that deviate significantly from those of women with normal pregnancies. 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 level of the β subunit of human chorionic gonadotropin, angiotensin II sensitivity, urinary calcium excretion, urinary kallikrein concentration, uterine artery Doppler ultrasonography, plasma fibronectin level, 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 (eg, women with history of increased blood pressure before conception or in a previous gestation, especially before gestational week 34, or multiparity; women with diabetes, collagen vascular disease, or underlying renal vascular or renal parenchymal disease; and women with multifetal pregnancy) will benefit from a database of laboratory tests performed during early gestation.[88, 89] Tests that through later comparison will help establish an early diagnosis of preeclampsia (pure or superimposed) include hematocrit, hemoglobin concentration, platelet count, and serum creatinine and uric acid levels. Observation of 1+ protein by routine urinalysis, documented by a clean-catch specimen, should be followed up with a 24-hour collection for measurement of protein and creatinine contents (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, ultrasonographic dates should be established as early in pregnancy as possible. A baseline sonogram for evaluation of fetal growth should be considered at 25 to 28 weeks' gestation in these circumstances.

Patients presenting with hypertension before gestational week 20. Most women who have hypertension before gestational week 20 have or will acquire 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 hyperten-

Table I. Laboratory evaluation and its rationale for women in whom hypertension develops 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 leakage (hypoalbuminemia), presence of hemolysis (lactic acid dehydrogenase level increase, schizocytosis, and spherocytosis), and possible coagulopathy, including thrombocytopenia.

sion are among the population in which secondary hypertension is more apt to be found (eg, 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 database described previously for high-risk women with normal blood pressure is helpful in determining whether further increments in pressure during the third trimester represent the physiologically usual increments or the onset of superimposed preeclampsia. Because these fetuses are at higher risk for the development of intrauterine growth restriction, early baseline ultrasonography for gestational dating and fetal size determination is also indicated for these patients.

Patients presenting with hypertension after midpregnancy. Table I summarizes the laboratory tests that are recommended in the evaluation of women with hypertension after midpregnancy and the rationale for testing these women 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, 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).

Chronic hypertension in pregnancy

Prepregnancy counseling. Women with hypertension should be evaluated before pregnancy to determine the severity of the hypertension and to facilitate planning for potential lifestyle changes that a pregnancy may require. As recommended in "The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,"[2] 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 angiotensin II 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.[88] The risks of fetal loss and accelerated deterioration of maternal renal disease are increased if serum creatinine is >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.[90, 91] Among patients with impaired renal function in whom hypertension is present and not controlled at conception relative risk of fetal loss has been reported to be increased 10-fold with respect to that in pregnancy without hypertension or with well-controlled hypertension.[92, 93]

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,[94, 95] there are no data on safety in the setting of chronic hypertension and pregnancy. In view of the theoretic concerns with maintenance of adequate placental blood flow in women with hypertension who are at increased risk for

preeclampsia, our recommendation is to discourage aerobic exercise by pregnant women with hypertension until more data are available. Weight reduction during pregnancy, even for 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 data on pregnant women are sparse, many experts recommend restriction of sodium intake to the same 2.4-g sodium intake recommended for essential hypertension. Women who already maintain 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 deleterious effects on the fetus and the mother. Excessive consumption of alcohol can cause or aggravate maternal hypertension. Tobacco is associated with substantial risks of abruptio placentae and fetal growth restriction.

Treatment of chronic hypertension. Most women with chronic hypertension during pregnancy have stage 1 to 2 hypertension (defined as systolic blood pressure of 140-179 mm Hg or diastolic blood pressure of 90-109 mm Hg) and are at low risk for cardiovascular complications within the short time frame of pregnancy. Among women with stage 1 to 2 preexisting essential hypertension and normal renal function, most pregnancies have good maternal and neonatal outcomes. These women are candidates for nonpharmacologic therapy because to date there is no evidence that pharmacologic treatment results in improved neonatal outcomes.[96, 97] Because blood pressure usually falls during the first half of pregnancy, hypertension may be easier to control with less or even 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, 99] Although it is not generally agreed whether antihypertensive therapy is beneficial or detrimental to pregnancy outcome, several studies offer some clinical guidance. During the past 30 years at least seven studies have compared antihypertensive therapy with either no medication or a placebo among pregnant women with mild chronic hypertension.[100] 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[101] retrospectively evaluated the courses of 298 pregnant women with chronic hypertension whose antihypertensive medications had been discontinued or whose doses were reduced early in pregnancy. Treatment did not decrease the frequency of superimposed preeclampsia, preterm delivery, abruptio placentae, or perinatal death with respect to untreated groups. Much of the 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 obstetric complications.

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

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

On the basis of available data some centers currently manage chronic hypertension during pregnancy by stopping antihypertensive medications under close observation.[101, 103] In patients with hypertension for several years, with evidence of target organ damage, or a regimen of 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 reinstitution of 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, a woman whose blood pressure was well controlled by antihypertensive therapy before pregnancy may continue with the same agents (with the exception of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) during pregnancy.

Antihypertensive drug selection. Although the goal of treatment of chronic hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus, especially with respect 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.[104] One follow-up study of a limited number of infants after 7.5 years showed no long-term adverse effects on development among children exposed to methyldopa in utero.[105] Methyldopa causes somnolence in many individuals. If this agent cannot be tolerated, alternatives such as labetalol are selected on the basis of more limited clinical

experience. If methyldopa is ineffective, alternatives can be substituted on the basis of 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 with adrenergic-blocking drugs including β-blockers and the αβ-blocker labetalol.[106] There is a suggestion that β-blockers prescribed during early pregnancy, specifically atenolol, may be associated with growth restriction.[106-109] On the other hand, none of these agents has been associated with any consistent ill effects; however, long-term follow-up 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.[110] A recent multicenter study that randomly allocated patients to receive slow-release nifedipine or no treatment beginning in the second trimester reported neither benefits nor evidence of harm from nifedipine treatment.[97]

The use of diuretic agents during pregnancy is controversial. The primary concern is theoretic. It is known that preeclampsia is associated with a reduction of plasma volume[111] and that fetal outcome is worse among women with chronic hypertension who do not have expansion of plasma volume.[112] Whether this is a cause-and-effect relationship has not been clearly established. Nonetheless, women who use diuretics from early pregnancy do not have an increase in blood volume to the degree usual in normal pregnancy.[113] Because of the theoretic concerns diuretics are usually not used as first-line drugs. A meta-analysis of nine randomized trials involving >7000 subjects receiving diuretics revealed a decrease in the tendency among the treated women toward development of edema, hypertension, or both[114] and confirmed no increased incidence of adverse fetal effects. If diuretics are indicated, they are safe and efficacious agents that can markedly potentiate the response to other antihypertensive agents and are not contraindicated in pregnancy except in settings in which uteroplacental perfusion is already reduced (preeclampsia and intrauterine growth restriction). Although data concerning the use of diuretics by pregnant women with essential hypertension are sparse, this working group has concluded that gestation does not preclude use of diuretic drugs to reduce or control blood pressure in women with hypertension predating conception or manifesting before midpregnancy.

Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy because of associations with fetal growth restriction, oligohydramnios, neonatal renal failure, and neonatal death.[115-118] Although no data are available regarding 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 therefore 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 during the first trimester described a fetal loss rate of 50% and significant maternal mortality.[119] Most of the poor outcomes were in pregnancies complicated by superimposed preeclampsia.[119] Antihypertensive therapy is indicated for maternal benefit, but it 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 concentration <1.4 mg/dL) fetal survival is moderately reduced, and the underlying disease does not generally worsen.[120] Women with renal diseases that tend to progress should be encouraged to complete childbearing while renal function remains well preserved. The presence of hypertension before conception or early in pregnancy increases the incidences of maternal and fetal complications, with a 10-fold higher relative risk of fetal loss.[92, 121]

Moderate or severe renal insufficiency may accelerate during pregnancy and jeopardize fetal survival.[90, 91, 120, 121] Hypertension occurs in more than half of such pregnancies.[122] A decrease in birth weight correlates directly with rising maternal serum creatinine concentration.[91] 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 is commonly increased among women with glomerular disease during pregnancy. Long-term dialysis during pregnancy is associated with significant maternal morbidity, and conception should be discouraged. Infant survival rates are higher among women with dialysis regimens started after conception (74%-80%) than among women who conceived while receiving maintenance dialysis therapy (40%-50%),[123, 124] presumably because the former are women with greater residual renal function. Infant survival may improve with greater duration of dialysis each week. Although low birth weight and preterm delivery are the rule, the 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, because this distributes to total body water and is not influenced by renal function. Then magnesium sulfate should be administered at a 1-g/h maintenance rate, with therapy guided by hourly to 2-hourly determination of magnesium levels until a steady state is reached. Phenytoin may be considered as an alternative (see the Anticonvulsant Therapy section).

Renal transplant. 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 concentration of ≤2.0 mg/dL.[122, 125] Although pregnancies may be complicated, 92% of infants survive in those pregnancies that go beyond the first trimester. From the National Transplantation Pregnancy Registry, among 115 renal transplant recipients who received cyclosporine, high risks to the neonate were reported in settings of maternal hypertension and serum creatinine levels >1.5 mg/dL. Rates of prematurity approached 55%; thus all pregnancies in transplant recipients are considered high risk.[126]

Treatment of hypertension that persists postpartum. Women with chronic hypertension may acquire encephalopathy, heart failure and pulmonary edema, and renal failure during the postpartum period. Risk factors include underlying cardiac disease, chronic renal disease, superimposed preeclampsia in the second trimester, abruptio placentae complicated by disseminated intravascular coagulation, and requirement for multiple antihypertensive agents.[127, 128] 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.[35] 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.

Treatment of hypertension during lactation. Breast-feeding should be encouraged and can be done safely, with certain limits on antihypertensive drug choices. In the case of mothers with mild hypertension who wish to breast-feed 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 who are taking a single antihypertensive agent, the clinician may consider reducing the dosage and 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 neonate.[129] Further, there are no data concerning long-term effects of these drugs on infants exposed through breast-feeding. The reader is referred to the text by Briggs et al[130] and the recommendations of the Committee on Drugs of the American Academy of Pediatrics.[131] 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.[132] No short-term adverse effects have been reported from exposure to methyldopa or hydralazine. Although the Committee on Drugs considers atenolol compatible with breast-feeding, this β-blocker, as well as metoprolol and nadolol, appears to be concentrated in breast milk. This property is not shared by propranolol and labetalol; for that reason these agents have been recommended if a β-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. In light of the scarcity of data, breast-fed infants of mothers receiving 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, fetal growth restriction, or both. A plan of antepartum fetal assessment is directed by these findings. Efforts should therefore be directed toward the early detection of superimposed preeclampsia and fetal growth restriction. If these conditions are excluded, then extensive fetal antepartum testing is less essential.

An initial ultrasonographic 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 (eg, because of maternal obesity or multiple examiners), ultrasonographic assessment should be performed at 28 to 32 weeks' gestation and monthly until term. If there is evidence of growth restriction, fetal well-being should be assessed by nonstress testing (NST) or biophysical profile (BPP) as usual for a 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 has normal growth 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 in 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 nulliparous women. 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. This opinion is based on the results of eight large trials in different populations around the world. Overall these trials, which included >27,000 pregnant women, demonstrated minimal to no reduction in the incidence of preeclampsia with low-dose aspirin therapy.[89, 135-142]

An important study on low-dose aspirin prophylaxis among 2539 women at higher risk for preeclampsia was published recently by the National Institutes of Health.[89] Included were four subgroups of women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestation, or preeclampsia in a previous pregnancy. The incidences of preeclampsia, perinatal death, preterm delivery, and fetal growth restriction were 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 to indicate that dietary supplementation with calcium will prevent preeclampsia among low-risk women in the United States. Certainly a diet that provides 1000 mg elemental calcium daily is recommended for general health.[143] Whether a diet enriched with calcium beyond this amount may have benefit remains unproven.

In a large National Institutes of Health trial with 4589 healthy nulliparous women randomly assigned at 13 to 21 weeks' gestation to receive 2 g elemental calcium daily or placebo, calcium supplementation neither reduced the incidence or severity of preeclampsia nor delayed its onset.[144] 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.[145, 146] Still, randomized trials of calcium supplementation in nulliparous women considered at high risk have demonstrated significant reductions in the incidence of preeclampsia.[147-151]

Other dietary supplements. Prophylactic magnesium supplementation has not been shown to be beneficial in preventing preeclampsia.[152, 153] Three randomized trials of fish oil supplementation for women at high risk for preeclampsia revealed no reduction in the incidence of preeclampsia.[154-156] A recent study showing the benefits of vitamins C and E to prevent preeclampsia was encouraging but needs further confirmation.[157, 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 were considered, delivery would be appropriate of all women with preeclampsia, regardless of the severity of preeclampsia or duration of gestation. Conversely, delivery induction is not indicated for a preterm fetus with no evidence of fetal compromise if the mother has mild disease. There are two important corollaries to 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 is palliation of the maternal condition to allow fetal maturation and cervical ripening.

Nonpharmacologic management

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

NST, ultrasonographic assessment of fetal activity and amniotic fluid volume (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 tool. 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 is dictated by the clinical condition. Although weekly to biweekly assessment usually suffices, daily testing is appro-

Table II. 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.
• NST should be performed at diagnosis. If NST is nonreactive, perform BPP. If BPP value is 8 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 8, repeat weekly. Testing should be repeated immediately if there is abrupt change in maternal condition.
• If estimated fetal weight according to ultrasonography 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.

priate for women with severe preeclampsia that is being managed expectantly (Table II).

If potential fetal compromise is indicated by fetal surveillance, then decision making for delivery requires judgment heavily influenced 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. These signs are at most an indication for closer monitoring of blood pressure and urinary protein. Early recognition of impending preeclampsia is based primarily on blood pressure increases during the late second and early third trimesters. Once blood pressure starts to rise (which may be the first sign of developing preeclampsia), a repeated examination within 1 to 3 days is recommended. In selected patients blood pressure and urinary protein excretion 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 (Table I). 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.

Hospitalization is often initially recommended for women with new-onset preeclampsia. After maternal and fetal conditions are serially assessed, subsequent management may be continued in the 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.[159] These complications are rare among women who comply with treatment and 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[160-164] and randomized[165-167] studies 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.[159] 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 such cases is determined day by day. These women should receive intensive maternal and fetal surveillance, usually at a tertiary care facility.[168-170] Laboratory studies are performed at frequent intervals and include serial determinations of platelet count, serum liver enzyme levels, renal function, and urinary protein excretion. Assiduous attention is paid to 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 evidence to suggest that any therapy alters the underlying pathophysiology of preeclampsia. Therapeutic efforts may be palliative, slow progression of the disorder, and permit continuation of pregnancy, but they 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, several randomized trials suggest that antihypertensive therapy for women with gestational hypertension or preeclampsia does not improve perinatal outcomes.[97, 100, 171]

INDICATIONS FOR DELIVERY. Delivery is the only definitive

treatment for preeclampsia, and some suggested indications are listed in Table III. 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 for 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 of women with severe preeclampsia is possible for a select group of women with gestational age between 23 and 32 weeks' gestation. In some cases preeclampsia improves after hospitalization and treatment with magnesium sulfate and antihypertensive agents administered acutely.[96, 169, 170] 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.[172] Delivery of these preterm pregnancies is indicated by worsening maternal symptoms, laboratory evidence of end-organ dysfunction, or deterioration of the fetal condition.

ROUTE OF DELIVERY. Vaginal delivery is preferable to cesarean delivery for women with preeclampsia, because it avoids addition of the stress of surgery to the 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 has been made. In gestation remote from term in which delivery is indicated and with fetal and maternal conditions stable enough to permit pregnancy to be prolonged 48 hours, glucocorticoids can be safely administered to accelerate fetal pulmonary maturity (Table III).

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, cesarean delivery should be considered, and it is also performed for other usual obstetric indications.

Neuraxial (epidural, spinal, and combined spinal-epidural) techniques offer many advantages for labor analgesia and can be safely administered to the parturient with preeclampsia. 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 for women with severe preeclampsia. A recent analysis, however, suggests that spinal anesthesia can be safely used in the patient with severe preeclampsia undergoing cesarean delivery, because the magnitude of declines in maternal blood pressure after spinal and epidural anesthesia appear to be similar.[173] 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 randomly assigned to receive epidural, combined spinal-epidural, or general anesthesia, all three regimens appeared equally safe.[174] 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 patient with preeclampsia 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 does regional anesthesia,[175] the risk of a failed intubation must be weighed against the risk of transient hypotension when deciding between general and regional anesthesia for cesarean delivery for the patient with severe preeclampsia-eclampsia. Although neuraxial techniques have become the preferred method to provide labor analgesia or anesthesia for cesarean delivery among 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.

Table III. Indications for delivery in preeclampsia

Maternal	*Fetal*
Gestational age ≥38 wk*	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 on gestational age.

Anticonvulsant therapy. Anticonvulsant therapy is usually indicated, either to prevent recurrent convulsions in women with eclampsia or to prevent initial convulsions in women with preeclampsia. There is universal agreement that women with eclampsia should receive anticonvulsant therapy.[176] In several randomized studies parenteral magnesium sulfate reduced the frequency of eclampsia more

Table IV. Treatment of acute severe hypertension* in preeclampsia

Drug†	*Recommendations*
Hydralazine	Start with 5 mg intravenously or 10 mg intramuscularly. If blood pressure is not controlled, repeat at 20-min intervals (5 to 10 mg, depending on response). Once blood pressure control has been achieved, repeat as needed (usually about 3 h). If no success with total of 20 mg intravenously or 30 mg intramuscularly, consider another drug.
Labetalol	Start with 20 mg intravenously as a bolus; if effect is suboptimal, then give 40 mg 10 min later and 80 mg every 10 min for 2 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 min if necessary. See precautions in Treatment of Acute Hypertension section. Short-acting nifedipine is not approved by US Food and Drug Administration for management of hypertension.
Sodium nitroprusside	Use in rare cases of hypertension not responding to drugs listed here, clinical findings of hypertensive encephalopathy, or both. 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 >4 h.

*Blood pressure ≥160 mm Hg systolic, ≥105 mm Hg diastolic, or both, if sustained.
†For side effects see *Physicians Desk Reference,* 53rd ed. *Caution:* Sudden and severe hypotension can result from 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 normal range (see Treatment of Acute Hypertension section). *Clinical note:* In managing hypertensive emergencies the intravenous route is safer than oral or intramuscular administration, because it is easier to combat inadvertent hypotension by stopping an intravenous injection or infusion than it is to stop intestinal or intramuscular absorption of an orally or intramuscularly administered drug.

effectively than did phenytoin for a mixed group of women with gestational hypertension and with preeclampsia.[177, 178] Parenteral magnesium sulfate is given during labor, delivery, and for variable durations post partum. There is no clear agreement concerning the prophylactic administration of magnesium sulfate to women with preeclampsia.[179] In two large randomized trials parenteral magnesium sulfate reduced the frequency of eclampsia among women with either pregnancy-induced hypertension or severe preeclampsia.[179, 180] Although parenteral magnesium sulfate should be given peripartum to women with severe preeclampsia, its benefits for women 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 among 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 the management of women with severe preeclampsia-eclampsia. Invasive techniques have been used to monitor fluid therapy during plasma volume expansion;[181] in management of women with pulmonary edema, persistent oliguria unresponsive to fluid challenge, and intractable severe hypertension; and for some patients receiving epidural anesthesia.[182] There is no published evidence that the use of invasive hemodynamic monitoring is indicated for these purposes.

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 blood pressure is only mildly elevated. Some experts suggest treatment for persistent diastolic blood pressure ≥105 mm Hg. Others advise withholding treatment until diastolic blood pressure reaches 110 mm Hg.[103] For adolescents whose diastolic pressures were recently <75 mm Hg, treatment of persistent diastolic blood pressures of ≥100 mm Hg 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 during pregnancy, and their routes of administration, are summarized in Table IV. Details of their pharmacology and safety are discussed elsewhere.[183]

The most commonly used drug is hydralazine, either intravenously or intramuscularly administered, which, if given cautiously, is successful in most instances. It has been shown to be effective against preeclamptic hypertension.[184, 185] 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 that intermittent bolus injections are more sensible. A 5-mg bolus is given intravenously during 1 to 2 minutes. After 20 minutes subsequent doses are dictated by the initial response. Once the desired effect has been obtained, the drug is repeated as necessary (frequently in several hours).[185] Parenteral labetalol has been shown to be effective for the treatment of acute severe hypertension during pregnancy.[106, 184] The drug may be administered in intravenous bolus injections of 20 mg or 40 mg or as a 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 for a limited number of women with acute severe hypertension during pregnancy.[186] Details of these reports are summarized elsewhere.[100] Nifedipine acts rapidly, causing significant reduction in arterial blood pressure within 10 to 20 minutes of oral administration. Although it has favorable hemodynamic effects,[186] physicians should be advised that rapidly acting nifedipine (in capsules containing the liquid form) has never been approved by the US Food and Drug Administration for the treatment of hypertension or hypertensive emergencies. "The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure"[2] recommended that nifedipine not be used for this purpose, because the drug has been associated with fatal and nonfatal untoward cardiovascular events, especially among older patients.[187] Of the 16 case reports reviewed by Grossman et al,[187, 188] 1 was that of a 37-year-old pregnant woman whose blood pressure was reduced from 150/118 mm Hg to 90/55 mm Hg, precipitating the need for caesarean delivery because of fetal distress. Care should be exercised when using nifedipine or any calcium antagonist in association with magnesium sulfate.[189-191]

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

Postpartum counseling and follow-up

The woman in whom hypertension develops during pregnancy should be carefully reevaluated during the immediate postpartum months and also should be counseled with respect to future gestations and remote cardiovascular risks. Any laboratory test abnormality or physical finding that has not returned to normal before postdelivery discharge should be reassessed at postpartum follow-up. 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; if abnormalities persist, however, the patient should be reexamined 6 weeks later, when any persisting pathologic conditions will probably be chronic.

Counseling for future pregnancies. Women who have had preeclampsia are more susceptible to hypertensive complications in subsequent pregnancies. Risk is best established for nulliparous women with a history of preeclampsia, with 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%.[192, 193] Preeclampsia reappearance rates may also be population specific. For example, among white women with well-defined disease after gestational week 36 recurrence is barely 10%,[194] whereas it may be substantially greater among black patients.[192] The recurrence rate among women with one episode of HELLP syndrome is almost 5%.[195]

Recurrence rates are higher among multiparous women with preeclampsia than among nulliparous women with preeclampsia.[196] Risk is also increased among multiparous women who conceive with a new father, even when the first pregnancy was normotensive; the incidence is intermediate between that of primiparous women and monogamous multiparous women who have not had a preeclamptic pregnancy.[196]

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.[197-200] Therefore patients with a history of early-onset severe preeclampsia should be evaluated for evidence of previously existing thromboembolic diseases. If they have such a history, they should be tested for the previously described abnormalities, which when present jeopardize not only future pregnancies but a patient's general health.

Remote cardiovascular prognosis

Preeclampsia-eclampsia. The remote prognosis of women with preeclampsia or eclampsia is best summarized as follows: The more certain that the diagnosis is preeclampsia alone (eg, 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 among nulliparous women with preeclampsia or eclampsia manifesting hypertension in subsequent gestations, multiparous in whom the disorder develops, and women of any parity with severe early-onset disease. 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 multiparous woman, 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.[89, 192-194, 201]

In summary, it is reasonable to counsel patients as follows: If preeclampsia occurred late in an initial gestation, there is no evidence for remote cardiovascular risk, but subsequent pregnancies will help define the 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 with 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 outcomes. 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 this process, however, many women receiving the clinical diagnosis will not in reality have true preeclampsia. The use of the label of preeclampsia according to 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 on preeclampsia. Specifically, case patients should be documented to be normotensive before pregnancy or 12 weeks after pregnancy.

Studies of nulliparous women are important to distinguish unique pathologic features of preeclampsia from other preexisting or future pathophysiologic conditions, which are often present in multiparous women who appear to acquire the disorder. There are situations in which studies of multiparous women are useful, mainly studies designed to understand factors that predispose toward preeclampsia and 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 or specifically accompany the preeclampsia 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, however, and none are likely until we understand the pathogenesis of the syndrome more completely. In the absence of 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 threshold values of blood pressure or change in pressure, and the magnitude of overlap with the different criteria, must be developed. Ideally receiver operating characteristic curves should be defined for both absolute blood pressures and changes with respect to baseline, so that the most appropriate criterion values can be chosen and the need for revising current definitions can be 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 values of other signs and symptoms in the diagnosis of preeclampsia when proteinuria is absent (eg, platelet count, liver function, abdominal and neurologic symptoms, and markers of endothelial activation[58]). Such data may help to improve both the clinical and research diagnoses of preeclampsia.

A substantial subset of the desired data, at least with respect to blood pressures if not other tests, may be obtained by reanalyzing the original data sets of the large prospective trials of aspirin or calcium supplementation for preeclampsia prophylaxis. This 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 during 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 follow-up. In light of both their importance and costs, such trials can rarely rely on industry funding; they require governmental 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 pathophysiologic features. This approach has increased our understanding of other complex syndromes (eg, type 1 and type 2 diabetes). Criteria for determination of subsets could include gestational age at delivery and association with intrauterine growth restriction, as well as research into the genetic predisposition toward preeclampsia, including both population genetics and biochemical markers for women at risk for preeclampsia. Such studies should discriminate women at risk for adverse maternal and fetal outcomes as a result of preeclampsia.

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Appendix

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National High Blood Pressure Education Program Coordinating Committee Member Organizations

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American Academy of Family Physicians
American Academy of Insurance Medicine
American Academy of Neurology
American Academy of Ophthalmology
American Academy of Physician Assistants
American Association of Occupational Health Nurses
American College of Cardiology
American College of Chest Physicians
American College of Occupational and Environmental Medicine
American College of Physicians
American College of Preventive Medicine
American Dental Association
American Diabetes Association
American Dietetic Association
American Heart Association
American Hospital Association
American Medical Association
American Nurses Association
American Optometric Association
American Osteopathic Association
American Pharmaceutical Association
American Podiatric Medical Association
American Public Health Association
American Red Cross
American Society of Health-System Pharmacists
American Society of Hypertension
Association of Black Cardiologists
Citizens for Public Action on High Blood Pressure and Cholesterol, Inc
Council on Geriatric Cardiology
International Society on Hypertension in Blacks
National Black Nurses Association, Inc
National Heart, Lung, and Blood Institute Ad Hoc Committee on Minority Populations
National Hypertension Association, Inc
National Kidney Foundation, Inc
National Medical Association
National Optometric Association
National Stroke Association
Society for Nutrition Education

Federal agencies

Agency for Health Care Policy and Research
Department of Veterans Affairs
Health Care Financing Administration
Health Resources and Services Administration
National Center for Health Statistics, Centers for Disease Control and Prevention
National Heart, Lung, and Blood Institute
National Institute of Diabetes and Digestive and Kidney Diseases