Hypertension in Pregnancy

A Comprehensive Update

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Abstract: Hypertensive disorders of pregnancies remain a central public health concern throughout the world, and are a major cause of maternal mortality in the developing world. Although treatment options have not significantly changed in recent years, insight on the pathogenesis of preeclampsia/eclampsia has been remarkable. With improved animal models of preeclampsia and large-scale human trials, we have embarked upon a new era where angiogenic biomarkers based on mechanism of disease can be designed to assist in early diagnosis and treatment. There is also a growing recognition of how elusive the diagnosis of eclampsia can be, especially in the postpartum period. Proper treatment of these patients depends heavily on the correct diagnosis, especially by the emergency physician. Finally, large epidemiologic studies have revealed that preeclampsia, once thought to be a self-limited entity, now appears to portend real damage to the cardiovascular and other organ systems in the long term. This review will present the latest update on our understanding of the various hypertensive disorders of pregnancies and their treatment options.

Key Words: pregnancy, preeclampsia, eclampsia

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Hypertensive disorders represent the most significant complication of pregnancy and affect about 10% of all pregnancies. They contribute greatly to maternal and perinatal mortality throughout the world. In many low income countries, complications from pregnancy and childbirth are the leading cause of death among women of reproductive years.[1] Hypertension during pregnancy carries with it the increased risk of abruptio placentae, disseminated intravascular coagulation, cerebral hemorrhage, hepatic failure, and acute renal failure.

Preeclampsia, in particular, can be devastating and life-threatening for both the mother and the fetus. Overall, 10% to 15% of maternal deaths are associated with preeclampsia and eclampsia. This number is likely to be higher in developing nations, up to 100 times higher in some parts of Africa and Asia (available at: http://www.preeclampsia.org/statistics.asp) as compared with Western nations. Reduction in maternal mortality by 75% has been set as one of the millennium development goals by the United Nations to be achieved by year 2015.[1]

In recent years, there have been important advances regarding the pathophysiology, prevention, and treatment of preeclampsia. There are also new reports of unusual presentations of eclampsia. Studies of long-term outcomes of preeclampsia on different organs are still being unraveled. In this review, we have tried to update the latest information on these findings.

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PHYSIOLOGIC CHANGES IN NORMAL PREGNANCY

Several physiologic adaptations occur during normal pregnancy. There is plasma volume expansion, a fall in mean arterial pressure and systemic vascular resistance, and an increase in cardiac output.[2–4] The fall in blood pressure usually peaks at the beginning of the second trimester, and is a result of several factors, including vascular refractoriness to angiotensin II, increased endothelial prostacyclin, and nitric oxide production.[5–9] If the fall in blood pressure is significant, it may obscure the diagnosis of preexisting mild hypertension, particularly in the pregnant women who do not have blood pressure check-ups before pregnancy. In addition, plasma and red cell volumes increase by 40% and 25%, respectively during pregnancy. These changes begin as early as the fourth week of gestation and peak around the 28th week. The rise in red cell mass is lower compared with the rise in plasma volume which contributes to the physiologic anemia of pregnancy. Despite a 30% to 50% increase in plasma volume at term, there is a decrease in plasma renin activity, an increase in atrial natriuretic peptide levels, and a resultant drop in systemic blood pressure due to a decrease in systemic vascular resistance.

CLASSIFICATION OF HYPERTENSION DURING PREGNANCY

According to the American College of Obstetrics and Gynecology and the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, hypertension during pregnancy has been classified into the following groups:

1. Chronic hypertension.
2. Gestational hypertension.
3. Preeclampsia-eclampsia.
4. Preeclampsia-eclampsia superimposed on chronic hypertension.

Hypertension has been defined as a sustained increase in blood pressure $>140/90$ mm Hg. Multiple studies have shown that up to 73% of primiparous patients have increases in diastolic blood pressure of 15 mm Hg at some point during a normotensive pregnancy without any increase in adverse outcomes.[9] Yet, it is recommended that any pregnant woman with a rise in systolic blood pressure of $\geq$30 mm Hg or a diastolic blood pressure of $\geq$15 mm Hg should be closely monitored.

Chronic Hypertension

Chronic hypertension is defined as a systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mm Hg prior to pregnancy or before 20 weeks of gestation, or hypertension that persists for more than 12 weeks postpartum. Hypertension is classified as mild when blood pressure is in the range of 140 to 159 mm Hg systolic and $<$90 to 99 mm Hg diastolic. Severe hypertension is present with a blood pressure of $\geq$160/100 mm Hg and is especially associated with end-organ damage.

It is estimated that 3% of pregnant women in the United States have chronic hypertension.[10–14] The prevalence of hypertension is strikingly high among black women (44%), as well as older women (up to 12.6% in ages 35–44 years).[15] Hence, the trend of late

life pregnancies (available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5419a5.htm) and increased rates of obesity and type II diabetes mellitus have significantly augmented this diagnosis.[16] The major cause of chronic hypertension is primary or essential hypertension (90%), whereas secondary causes account for the rest (10%). Secondary hypertension may be due to renal diseases such as glomerulonephritis, renal artery stenosis, collagen vascular diseases (lupus, scleroderma), or endocrine disorders (thyrotoxicosis, pheochromocytoma, hyperaldosteronism).[17]

Pathophysiologic Changes in Chronic Hypertension

Unlike normal pregnancy, adaptations in chronic hypertensive pregnant women are characterized by persistently high vascular resistance. Their systemic vascular resistance index and pulse wave velocity remain higher during the whole pregnancy compared with healthy pregnancies.[18,19] Arterial stiffness (as measured by the ratio of stroke index to pulse pressure), however, is less in chronic hypertensives compared with preeclamptic subjects.

Complications of Chronic Hypertension

Chronic hypertension in pregnancy is associated with increased adverse maternal and fetal outcomes such as superimposed preeclampsia, perinatal mortality, abruptio placentae, low birth weight, and intrauterine growth restrictions (IUGR).[17,20] It is estimated that about 10% to 25% of pregnant women with preexisting hypertension develop superimposed preeclampsia. In a large retrospective cohort, women with preexisting hypertension had 2.7 times more risk of severe preeclampsia compared with pregnant women without this diagnosis.[20] This risk is even higher in women with severe uncontrolled preexisting hypertension or other cardiovascular and renal diseases. Diagnosis of superimposed preeclampsia could be obscured in a patient with preexisting proteinuria. However, a sudden 2- to 3-fold increase in proteinuria, acute increase in blood pressure concomitant with involvement of other organ systems (as will be discussed in the preeclampsia section) should alarm the physician of superimposed preeclampsia. Chronic hypertension and proteinuria, regardless of the development of preeclampsia, is associated with about 3-fold increased incidence of premature deliveries ($<$35 weeks of gestation) and infants who are small for gestational age.[17] Incidences of abruptio placentae and perinatal death are higher in women with superimposed preeclampsia as well.[17]

Management of Chronic Hypertension

The optimal blood pressure during pregnancy is still unknown and remains controversial. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) report, there is a linear increase in cardiovascular morbidity from blood pressure levels as low as 115 mm Hg systolic and 75 mm Hg diastolic upwards. This has led the JNC 7 to include a new classification of prehypertension for blood pressures in the range of 120–139/80–89 mm Hg. The goals of treating hypertension are to reduce the cardiovascular morbidities; however, most effects are observed in those who achieve sustained reduction in blood pressure over 10 years.[21] Pregnant women with mild hypertension are different in that the short term benefit of antihypertensive treatment is not as well-defined as the potential adverse outcomes to the fetus.[17,21] There is no convincing evidence that medical treatment of mild hypertension improves maternal outcome in pregnancy. In addition, use of medications in mild hypertension during pregnancy may lead to a fall in mean arterial pressure with the increased risk of restrictive fetal growth, regardless of the type of antihypertensive used.[17,22,23] Thus, the current recommendation is that antihypertensive medications initiated prior to pregnancy should be adjusted for adequate blood pressure control while avoiding those with teratogenic risks. Pregnant women with mild hypertension ($\leq$159/99 mm Hg) and not on medications should be closely observed; medications should not be initiated unless blood pressure persists $\geq$159/99 mm Hg, or end-organ damage occurs.[17,24,25] Intense blood pressure monitoring and antihypertensive treatment in these cases are to diminish the risk of cerebral vascular accidents.

Choices of Medications

The α-adrenergic agonist methyldopa is the drug of choice according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy report, lasted updated in 2000.[11] This recommendation is based on extensive postmarketing surveillance, controlled trials, and 7.5 years of follow-up in neonates.[26] However, its mild antihypertensive effect, along with its sedative properties, often require either the addition of or the substitution of another agent. Labetalol, with combined α-β-adrenergic blockade activity, is another preferred agent with potent results and limited side effects. Extended release metoprolol is also an alternative.[27–31] This is in contrast with other β-blockers, such as propranolol and atenolol, which are not favored in pregnancy. Propranolol, a nonselective β-blocker, has been associated with premature labor, IUGR, and neonatal apnea. The cardioselective β-blocker atenolol was also noted to have significant effects on fetal hemodynamics, possibly resulting in IUGR in the first trimester.[32–35] However, long-term follow-up studies are lacking.

Calcium channel blockers, such as the long-acting nifedipine, is gaining popularity, though there are concerns that it may inhibit labor and have synergistic interaction with magnesium sulfate.[26] Both first trimester and second trimester exposure to nifedipine have revealed no increase in teratogenicity or harm.[11,36] Experience with other calcium channel blockers (amlodipine, diltiazem, verapamil) is limited.[37–39] To date, no major human teratogenicity has been reported for any of the calcium channel blockers.

The use of diuretics in the treatment of hypertensive pregnant women remains controversial. The risk is largely theoretical, as it may potentiate the volume depletion seen in preeclampsia, especially since fetal outcome is worse in women with chronic hypertension who do not have expansion of plasma volume.[40] In addition, both thiazide and loop diuretics may be associated with fetal malformations and can potentially cause electrolyte abnormalities in the fetus.[41,42] However, a meta-analysis of more than 7000 subjects receiving diuretics confirmed that there was no increased incidence of adverse fetal effects, and showed a benefit toward better volume and blood pressure control in the mother.[41] Thus, the current recommendation is that women who are already on diuretics prior to pregnancy may continue these medications, however, if they develop superimposed preeclampsia, they should be discontinued.[43]

Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, and direct renin inhibitors are absolutely contraindicated in pregnancy at any time. Women contemplating pregnancies should be counseled to discontinue these medications prior to conception. First trimester exposure to ACEI may result in a decrease in placental blood flow which can lead to oligohydramnios, IUGR, renal failure, low birth weight, cardiovascular anomalies, polydactyly, hypospadias, and spontaneous abortions. Exposures in the second and third trimesters have resulted in fetal hypocalvaria, renal failure, oligohydramnios, pulmonary hypoplasia, craniofacial, limb, and cardiovascular defects.[44–60] Cooper et al specifically assessed the risk of congenital malformations in women who were exposed to ACEIs in the first trimester of pregnancy and found that there was a significant increased risk of major congenital malformations, mainly in the cardiovascular and central nervous systems. ACEIs are therefore categorically contraindicated in all

TABLE 1. Medication Choices in Chronic Hypertension of Pregnancy

Drug/Class*	Doses	Adverse Events in Pregnancy	Evidence	Comments
Methyldopa (B)	500 mg–3 g in 2 divided doses	Peripheral edema, anxiety, night mares, drowsiness, dry mouth, hypotension, maternal hepatitis, no major fetal adverse events	Large	Large post marketing evidence on safety
Labetalol (C)	200 mg–1200 mg/d in 2–3 divided doses	Persistent fetal bradycardia, hypotension, neonatal hypoglycemia	Large	
Hydrochlorothiazide (C)	12.5 mg–25 mg/d	Fetal malformations, electrolyte abnormalities, volume depletion	Large	
Nifedipine (C)	30 mg–120 mg/d	Hypotension and inhibition of particularly if used in combination with magnesium sulfate	Small	Immediate release nifedipine not recommended
Hydralazine (C)	50 mg–300 mg/d in 2–4 divided doses	Hypotension, neonatal thrombocytopenia	Moderate	
Angiotensin converting enzyme inhibitor (ACEI) (D)	Contraindicated in pregnancy	Oligohydraminos, IUGR, renal failure, low birth weight, cardiovascular anomalies, polydactyly, hypospadias, and spontaneous abortions, fetal hypocalvaria, renal failure, oligohydraminos, pulmonary hypoplasia, craniofacial, limb	Large	
Angiotensin receptor blocker (D)	Contraindicated in pregnancy	Similar to ACEIs	Moderate	
Direct rennin inhibitor (Aliskiren) (D)	Contraindicated in pregnancy	Similar to ACEIs	None	

*Drug rating in pregnancy—see Table 2.

TABLE 2. Drug Rating in Pregnancy

A. Controlled studies show no risk
Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus

B. No evidence of risk in humans
Either animal findings show risk (but human findings do not) or, if no adequate human studies have been done, animal findings are negative

C. Risk cannot be ruled out
Human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk

D. Positive evidence of risk
Investigational or post marketing data show risk to fetus. Nevertheless, potential benefits may outweigh the risk

X. Contraindicated in pregnancy
Studies in animals or humans, or investigational or post marketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient

trimesters.[61] There were also case reports linking angiotensin receptor blockers with similar adverse fetal/maternal outcomes.[62–67] The newest renin inhibitor, aliskiren, was approved in 2007 in the United States for the treatment of hypertension. It is classified by the FDA as pregnancy category C for the first trimester, and category D for the second and third trimesters. Thus, aliskiren should be discontinued immediately upon detection of pregnancy, as it is thought to cause fetal and neonatal injury, such as hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death.[68] In short, it is believed to have similar adverse effects as other blockers of the renin-angiotensin system, though there have been no adverse human fetal/maternal reports thus far.

In accelerated hypertension of pregnancy, the most commonly used drug is hydralazine, which can be given either intravenously (IV) or intramuscularly. Other effective parenteral treatment includes IV labetalol, nicardipine, metoprolol, and methyldopa.[69–72] Because nicardipine is a potent IV calcium channel blocker, careful titration of dose is necessary to prevent maternal hypotension episodes, as up to 20% of women have been reported to develop hypotension.[71,73,74] Oral nifedipine (short release) can also be used as an alternative. In contrast, immediate release sublingual nifedipine is no longer recommended for acute treatment, as it can cause an unsafe drop in blood pressure, causing significant cardiovascular morbidity.[75,76] The use of IV nitroprusside is contraindicated, except as a last resort, due to risk of fetal cyanide toxicity.

With the proper monitoring and treatment of pregnant women with chronic hypertension, it is possible to achieve optimal pregnancy outcomes. In addition to the multiple medications to treat hypertension (Tables 1–3), it must be remembered that lifestyle and dietary changes are necessary as well. However, we are still in need of a large and well-designed study to determine optimal blood pressure control during pregnancy.

Gestational Hypertension

Gestational hypertension applies to women who develop new-onset hypertension after midpregnancy, in the absence of proteinuria. This may include patients who later progress to preeclampsia, but who at the time of diagnosis have not manifested proteinuria. This entity usually affects women near term, though severe forms of hypertension may arise earlier. When this occurs, preeclampsia usually follows shortly. The etiology of gestational hypertension is not clear, though it appears to identify women destined to develop

TABLE 3. Parenteral Medications for Accelerated Hypertension in Pregnancy

Drug/Class*	Dose	Comment
Labetalol (C)	IV bolus: 20 mg IV push over 2 min, may give 40–80 mg at 10-min intervals, up to 300 mg total dose; IV infusion: start with 2 mg/min; titrate to response up to 300 mg total dose	Risk of fetal bradycardia, and hypoglycemia
Hydralazine (C)	IM, IV bolus: initial: 10–20 mg/dose every 4–6 h as needed, may increase to 40 mg/dose; IV infusion: start with 0.5 mg/h; titrate to response up to 10 mg/h	Risk of tachycardia
Nicardipine (C)	IV: initial: 5 mg/h increased by 2.5 mg/h every 15 min to a maximum of 15 mg/h	Hypotension and inhibition of labor especially when combined with magnesium sulfate
Nifedipine (C)	10–30 mg tablets, may repeat dose in 45–60 min	Immediate release/sublingual nifedipine not recommended. Hypotension and inhibition of labor especially when combined with magnesium sulfate
Nitroprusside (C)	IV: initial: 0.3–0.5 μg/kg/min; increase in increments of 0.5 μg/kg/min, titrating to the desired hemodynamic effect, maximum: 10 μg/kg/min	Use >4 h and dose higher than 2 μg/kg/min associated with increased risk of cyanide toxicity. Use only as a last resort

*Refer Table 2.

essential hypertension later in life.[77,78] Blood pressure returns to normal immediately after delivery, but may relapse in subsequent pregnancies. Often times a true diagnosis of gestational hypertension can only be made postpartum, when it is clear that the patient has not developed preeclampsia. And if the patient's hypertension persists, she is deemed to have chronic hypertension.

Late Postpartum Hypertension

Late postpartum hypertension is an unusual entity that describes women with normotensive gestations who develop hypertension several weeks to months after delivery. It is self-limited and resolves by the end of the first postpartum year.[79] Little is known about its pathophysiology, except that it may also predict essential hypertension later in life.

Preeclampsia-Eclampsia

Preeclampsia is exclusively a disease of pregnancy. It is characterized by new onset hypertension and proteinuria, usually after 20 weeks gestation, and is commonly associated with edema, hyperuricemia, and proteinuria. It affects about 5% of all pregnancies, and is about twice as common in first pregnancies as in multigravidas. However, it is common in multigravidas who have new partners, suggesting that prior exposure to paternal antigens may be protective.[80]

The maternal syndrome of preeclampsia is characterized by elevated blood pressure, proteinuria, and possible damage of different organ systems including the liver, kidney, brain, heart, and lungs. The disease spectrum can vary from mild cases with little systemic involvement (mild preeclampsia) to multiorgan failure (severe preeclampsia). In about 30% of the cases, the disease may cause placental insufficiency enough to cause IUGR or fetal death.[81]

When new onset seizures occur in the setting of preeclampsia, it is called *eclampsia*. Eclampsia seizures may occur antepartum, intrapartum, in the immediate puerperium, or late postpartum (48 hours to 1 month later).[79] Surprisingly, it may also occur in women with no history of preeclampsia (up to one-third).

Pathogenesis of Preeclampsia

Defective remodeling of the spiral arteries at the time of trophoblast invasion is the most widely recognized predisposing factor for preeclampsia. Long before the clinical appearance of preeclampsia, immunologically mediated abnormal trophoblastic invasion leads to formation of a placenta in which the uterine spiral arteries fail to undergo the normal thinning out of muscular walls that permit enhanced perfusion of the placenta. As a result, perfusion of intervillous space is impaired, leading to placental hypoxia. Placentas from pregnancies with advanced preeclampsia often have numerous placental infarcts and sclerotic narrowing of the arterioles.[80] Predisposing factors for preeclampsia are pre-existing hypertension, chronic renal disease, obesity, diabetes mellitus, multiple pregnancies, hydatidiform mole, and thrombophilias (factor V Leiden, antiphospholipid syndrome, and antithrombin III deficiency). Also, there is increased sensitivity to the vasopressor effects of angiotensin II, likely resulting from the increased plasma concentrations of angiotensin I/bradykinin B2 receptor heterodimers.[80] In some studies, markers of oxidative stress are elevated.[82]

Genetic factors seem to play a role in the pathogenesis of preeclampsia. Angiotensinogen T235 gene variant and factor V Leiden mutation have been thought to be associated with preeclampsia.[83] Also, the incidence of preeclampsia in pregnancies complicated by trisomy 13 has been shown to be significantly higher than in normal karyotypic pregnancies.[84–88] This is intriguing since the gene for FMS-like tyrosine kinase 1 (Flt-1) is encoded on the long arm of chromosome 13; its splice variant, soluble FMS-like tyrosine kinase 1 (sFlt-1), has been implicated in the pathogenesis of preeclampsia (see later in the text), especially in trisomy 13.[89]

Recently, it has been found that sFlt-1 production is increased in the placenta in preeclamptic women.[90] sFlt-1 is a splice variant of the vascular endothelial growth factor (VEGF) receptor Flt-1. It lacks the transmembrane cytoplasmic domain of the membrane bound receptor Flt-1 and is a potent antagonist to both VEGF and placental growth factor (PlGF), another member of the VEGF family. sFlt-1 binds to these proangiogenic molecules and prevents their interaction with their cell surface VEGF receptors, Flt-1, and KDR.[90] sFlt-1 as a singular pathogenic factor in preeclampsia was demonstrated in a pioneering study by Maynard et al where the authors showed that serum from normotensive pregnant women induced endothelial tube formation, an established in vitro model of angiogenesis, whereas serum from those with preeclampsia inhibited tube formation.[90] When sFlt-1 was added to the serum, tube formation did not occur, but exogenous VEGF and PlGF were able to restore formation. These results suggested that the antiangiogenic properties of serum from preeclamptic patients are due to blockade of VEGF and PlGF by endogenous sFlt-1.[90]

Recent studies have identified another circulating factor, soluble endoglin (sEng) to be a pathogenic factor in preeclampsia.[91,92] sEng is a coreceptor for transforming growth factor-β and an antiangiogenic protein thought to impair transforming growth factor-β1 binding to cell surface receptors and to decrease endothelial

nitric oxide signaling. It is produced by the ischemic placenta in preeclampsia. Circulating sEng levels have been shown to increase beginning 2 to 3 months before the development of preeclampsia, and rose more steeply in women who developed preeclampsia, peaking at the onset of clinical disease.[92] In animal studies, the combination of sEng in combination with sFlt1 amplify the endothelial dysfunction and induce more severe clinical signs of preeclampsia, including the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and cerebral edema that resembles eclampsia.[91] Thus, both circulating sEng and sFlt1 may synergize and contribute to the syndrome of preeclampsia/eclampsia.

Deficiency of catechol-O-methyltransferase (COMT) and 2-methoxyoestradiol (2-ME) is the most recent pathway implicated in preeclampsia.[93] 2-ME, a natural metabolite of estradiol, is generated by COMT in the placenta. It destabilizes microtubules and inhibits hypoxia inducible factor-1α (HIF-1α). A recent study proposed the following working model for the pathogenesis of preeclampsia: disruption of COMT/2-ME, possibly due to variation in the COMT genotype, favors elevated levels of HIF-1α, leading to angiogenic dysfunction and placental insufficiency. HIF-1α elevation and vascular defects may lead to shallow invasion of trophoblasts into the spiral arteries and uterine wall, resulting in vascular defects, hypoxia and inflammation. This study highlights the potential use of 2-ME as both a diagnostic marker for preeclampsia and also as a therapeutic agent.[93]

Multiorgan Pathophysiology and Pathology

Cardiopulmonary

In women with preeclampsia, there is an increase in systemic vascular resistance and a pathologic decrease in the hypervolemia of a normal pregnancy. In other words, plasma volume reduction and hemoconcentration are the hallmarks of this condition, and are proportional to the severity of the disease.[40] Hemodynamic changes have been well-studied by right heart catheterization.[94] Women with severe preeclampsia and eclampsia have hyperdynamic left ventricular function, high normal to elevated systemic vascular resistance, normal or elevated pulmonary capillary wedge pressure, and low central venous pressure. Women with preeclampsia superimposed on chronic hypertension also have elevated systemic vascular resistance, left-sided filling pressures, and increased left ventricular stroke volume indexes. [95]

Acute cardiovascular morbidity in preeclampsia includes the following conditions: pulmonary edema, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) requiring positive pressure mechanical ventilation, myocardial infarction, and cardiopulmonary arrest.

Pulmonary edema is the most common cardiopulmonary complication of preeclampsia. As it is known from the Starling's equation, a decrease in the oncotic pressure, an increase in the hydrostatic pressure, or a change in the capillary permeability will predispose to extravasation of fluid from the intravascular compartment. All of these changes take place in preeclampsia and may be worse after delivery. Factors favoring the development of pulmonary edema are older age, multigravidas, and pre-existing chronic hypertension.[20,96] Prompt diagnosis and treatment are essential as both the maternal and fetal morbidity and mortality are high if left untreated. Medical therapy with furosemide, oxygen, morphine, along with restriction of salt and fluid, should be instituted as needed. Afterload reduction with vasodilators may be necessary.

ARDS is characterized by the acute onset of hypoxemia and increased alveolar capillary permeability. Preeclampsia complicated by the HELLP syndrome or pulmonary edema can progress to ARDS. Maternal mortality is a startling 25% to 50% with this condition.[97] Since ARDS is uncommon in pregnancy, there is limited data on its management. Treatment is extrapolated from studies in the general population. Respiratory support is the main therapeutic option. Mode of delivery in women with ARDS remains controversial. Therefore, standard obstetric indications for cesarean delivery are used.[98]

Myocardial infarction occurs in $<1\%$ of pregnancies. Hannaford et al found that in the Royal College of General Practitioners' Study,[99] women with a history of preeclampsia had a significantly higher risk of acute myocardial infarction. Coronary spasm may play a role in the absence of risk factors for ischemic heart disease. There were earlier data that women with preeclampsia have elevated cardiac troponin I levels[99a] though this finding has not been reproduced in more recent studies.[99b,99c] It is unclear if earlier elevations in troponin levels were due to undiagnosed ischemic events.

Peripartum cardiomyopathy is an uncommon complication of preeclampsia, although a history of preeclampsia has been reported in up to 70% of women who develop peripartum cardiomyopathy. In a review of 123 charts, Elkayam et al had found hypertension/preeclampsia to be an associated condition in 43% of cases,[100] whereas Witlin et al found a correlation in 68% of their cases.[101]

Renal

Glomerular filtration rate and renal plasma flow are uniformly decreased in preeclampsia. Blood urea nitrogen and serum creatinine usually remain in the nonpregnant normal range. Simultaneous measurements of glomerular filtration rate and renal blood flow indicate that the filtration fraction is lower during preeclampsia than in normal women during the last trimester of pregnancy.[102,103] The urinary sediment is usually bland, however few leukocytes, erythrocytes, or cellular casts can be seen. When proteinuria is heavy, hyaline casts may be found. Glomerular damage resulting in significant proteinuria is an important feature of preeclampsia. Proteinuria in preeclampsia is nonselective. High molecular weight proteins like albumin, along with tubular proteins, are lost in the urine.[103,104]

There is decreased clearance of uric acid during preeclampsia. The degree of serum uric acid elevation correlates with the severity of proteinuria, renal pathologic changes, and fetal demise.[80] Also, preeclamptic pregnancies are characterized by reductions in the fractional excretion of calcium and pronounced hypocalciuria along with reduced plasma levels of dihydroxyvitamin D[105,106] and increased parathyroid hormone levels.[107]

In terms of pathology, preeclampsia is associated with glomerular endotheliosis in the kidney. On light microscopy, the glomerular capillary lumens are narrowed and appear bloodless, and the glomeruli are enlarged. The endotheliosis of preeclampsia is usually not accompanied by prominent capillary thrombi. On immunofluorescence, there are no immune deposits in the glomeruli and the serum complement levels are normal. Deposition of fibrinogen derivatives may sometimes be seen. Electron microscopy shows relative preservation of the foot processes of the podocytes, but there is loss of endothelial fenestrae, and endothelial cells become swollen and separated from the basement membrane by electron-lucent material.[102] Focal segmental glomerulosclerosis accompanies the generalized glomerular endotheliosis of preeclampsia in up to 50% of cases.[80] The specificity of endotheliosis to diagnose preeclampsia has been called into question by an important study that demonstrated that even women with nonproteinuric gestational hypertension as well as normal pregnant women exhibited endotheliosis, albeit milder forms.[108] This suggests that endotheliosis is a spectrum seen in pregnancy, with severe forms corresponding to preeclampsia. The glomerular changes usually disappear within 8 weeks of delivery, which is the same time when the hypertension and proteinuria resolve.

Central Nervous System

Central nervous system complications in preeclampsia are most commonly due to cerebral hemorrhage, brain edema, thrombotic microangiopathy, and cerebral vasoconstriction. This results in the sudden development of seizures (eclampsia), along with headache, blurred vision, scotoma, and cortical blindness. Most pathologic descriptions were obtained by Sheehan and Lynch from their necropsy studies, which revealed gross cerebral hemorrhage and varying degrees of petechiae, along with thrombi within the microvessels.[109] The precise etiology of the seizures is not clear, although angiogenic factors such as sFlt-1 and sEng (as described in Pathogenesis) may play a role. The seizures are usually grand mal, and are associated with a worse prognosis if they occur earlier than 32 weeks of gestation. Unfortunately, it is difficult to predict the risk the seizures as there appears to be no correlation between the magnitudes of blood pressure increase or the degree of proteinuria.[110] Surprisingly, the incidence of late postpartum eclampsia is increasing despite an overall decrease in incidence of eclampsia. Reports of eclampsia have been described for patients returning as late as 24 days post delivery.[111] The correct diagnosis of eclampsia is crucial as the management differs from other etiologies of seizures. Thus, either a recent or remote history of childbirth is an important part of a patient's history when evaluating new-onset seizures in a woman of reproductive age.

Hepatic/Coagulation System

The coagulation system is activated in preeclampsia, starting with mild thrombocytopenia, to the more life-threatening HELLP syndrome, characterized by hemolysis, elevated liver enzymes and low platelets. This coagulopathy appears due to widespread endothelial dysfunction, with increased fibronectin and platelet aggregation, as well as shortened platelet survival and depressed antithrombin III levels.[112] The liver injury in preeclampsia is related to the vasospasm and precipitation of fibrin; it ranges from mild elevation in hepatic enzymes to significant increases in aspartate aminotransferase and lactic dehydrogenase, the latter >1000 IU/dL.[113] Gross hepatic changes, as described by Sheehan and Lynch, detailed occasional petechiae to areas of infarction, subcapsular hematomas, and rarely liver rupture results in death.[109]

EARLY RECOGNITION OF PREECLAMPSIA

Research is ongoing to identify unique screening tests that would predict the risk of developing preeclampsia before the classic symptoms appear. Many studies have been done to verify significant changes in angiogenic factors like PlGF, sFlt-1, or sEng before the onset of preeclampsia.[92,114–125] Changes in the serum PlGF are seen by the first trimester, whereas differences in sFlt-1 and sEng are seen in the second trimester. Urinary PlGF is also significantly decreased in the second trimester as compared with normotensive controls.[126] In addition, an abnormal uterine artery Doppler velocimetry in the first and second trimesters has been proposed as a good screening test to predict preeclampsia.[127–129] Combining the 3 biomarkers into a single angiogenic index[92,115] or with uterine artery Doppler[128–130] may be more predictive than any single marker alone. Whether the angiogenic biomarkers are sensitive and specific enough for widespread clinical use remains to be studied. This question will likely be answered by the ambitious World Health Organization's prospective cohort study of more than 12,000 women, involving developing nations on 4 continents in the use of angiogenic biomarkers for preeclampsia screening (available at: http://www.crep.com.ar/plgf/).

Placental protein-13 (PP-13), which is a placenta-specific protein involved in normal implantation and placental vascular development, has also emerged as an early biomarker for preeclampsia. Maternal serum level of PP-13 in the first trimester has been found to be significantly lower in women who develop preeclampsia later in their pregnancy. Several studies have suggested that first trimester PP-13 levels in the maternal serum have excellent prediction for preeclampsia.[131] Also, combining first trimester PP-13 with uterine artery Doppler may further improve prediction of preeclampsia.[132]

THE PODOCYTE AND PREECLAMPSIA

Despite earlier reports that the podocyte is preserved in preeclampsia, there is increasing evidence that it is affected. The podocyte is a specialized visceral epithelial cell which lines the glomerular basement membrane in the glomerulus. It helps to restrict protein loss with its complex slit-diaphragm. Together with the glomerular basement membrane and the fenestrated endothelium, they form the glomerular filtration barrier. A landmark animal study by Eremina et al showed that when one allele of VEGF is deleted specifically in the podocyte, kidneys develop typical pathologic features of preeclampsia.[133] Furthermore, a small study of autopsy material demonstrated downregulation the podocyte-specific proteins nephrin and synaptopodin in women with severe preeclampsia.[134] Clinically, urinary podocytes (podocyturia) were found in increased numbers in patients with preeclampsia, signifying a shedding process.[135] Our group also studied the expression of the podocyte-specific proteins synaptopodin and podocin by immunofluoresence on renal biopsies of 20 patients with preeclampsia within 4 weeks of delivery. In contrast to the autopsy study, we discovered that in patients with severe endotheliosis, synaptopodin expression was either unchanged or only slightly decreased, whereas podocin expression was uniformly downregulated (unpublished data). In contrast, patients with mild endotheliosis had preserved synaptopodin and podocin expression. We conclude that podocyte-specific proteins are only affected in severe preeclampsia. In addition, we studied the use of podocyturia as a diagnostic marker for preeclampsia in 56 women with high-risk pregnancies, including 28 with preeclampsia and other conditions such as hypertension (gestational or chronic), diabetes (gestational or chronic), and found that the sensitivity and specificity of podocyturia were 39% and 79%, respectively (unpublished data). Thus, we conclude that podocyturia may be a useful, although not a specific clinical tool in evaluating preeclampsia. However, we feel that this study will need to be validated in larger cohorts.

PREVENTION OF PREECLAMPSIA

Throughout the last few decades, both large and small clinical trials have attempted to uncover a medication that could avert preeclampsia (Table 4). However, effective primary prevention proves to be extremely difficult when the pathogenesis is unclear.

Diuretics

Investigators believed early on that sodium retention was the cause of edema and hypertension in preeclampsia, and therefore attempts were made to prophylactically administer diuretics.[136] Now it is known that the plasma volume is lower in preeclampsia than in the normal state and there is a tendency towards hemoconcentration. Thus, diuretics can exacerbate the hypovolemia, which in turn will stimulate the renin-angiotensin system and aggravate hypertension. Thus, diuretics are no longer recommended.

Calcium Supplementation

Early reports of hypocalciuria, increased sensitivity to angiotensin II, and reduced levels of dihydroxyvitamin D[105] in women with preeclampsia led to several trials using calcium supplementation. Previous results were mixed, mostly as a result of different methodologies and populations.[137] A large placebo-controlled, double-blinded trial sponsored by the WHO in 2006 randomized 8325

TABLE 4. Preventive Measures in Preeclampsia

Medications	Benefit	Comment
Diuretics	None	Can aggravate hypertension by worsening hypovolemia and stimulating the renin-angiotensin system
Calcium supplementation	Small	Some benefit in women with very low daily calcium intake
Aspirin	Small to moderate	The numbers needed to treat to avoid adverse events is large
Vitamin C and E supplementation	None	No significant decrease in the rate of preeclampsia or adverse neonatal outcomes; may increase the rate of low birth-weight babies

women before gestational week 20 to either take 1.5 g calcium/d or placebo throughout pregnancy.[138] Although calcium supplementation did not prevent preeclampsia, complications of preeclampsia (severity, fetal mortality, and maternal morbidity) were reduced. These results differ from the earlier Calcium for Preeclampsia Prevention Study where it was shown that 2 g calcium/d did not have significant impact on the incidence of preeclampsia nor its secondary outcomes.[139] The difference may be that the WHO study focused on women with low calcium intake (calcium $<$600 mg/d), whereas the Calcium for Preeclampsia Prevention study enrolled patients who had an average calcium intake of $>$1000 mg/d. A more recent randomized trial of 524 healthy primigravidas with low daily calcium intake (mean calcium 313 mg/d) demonstrated a significant lower incidence of both preeclampsia and preterm delivery in the calcium group.[140] These results suggest that there may be some benefit in the use of calcium in women with very low daily calcium intake.

Aspirin

Since preeclampsia is associated with vasospasm and activation of the coagulation-hemostasis systems, low dose aspirin is thought to be beneficial. It inhibits biosynthesis of platelet thromboxane A2 with little effect on vascular prostacyclin production, thus decreasing the vasospasm and coagulation abnormalities. In the 1980s and 1990s, some trials with aspirin showed significant reductions in the incidence of gestational hypertension and preeclampsia.[141] However, given the limited size of these trials, no definitive conclusions could be drawn. Later, several multicenter studies also failed to demonstrate any significant benefits. A randomized, placebo-controlled multicenter prospective study performed in 1994, the Collaborative Low dose Aspirin Study in Pregnancy study, did not support the routine prophylactic or therapeutic administration of aspirin to all women at risk for preeclampsia or fetal growth retardation.[142] But it did show some benefit in a subgroup of women at risk for early-onset, severe preeclampsia. However, other studies conducted around the same time failed to validate these positive outcomes in high-risk pregnancies.[143,144] Recently, the Perinatal Antiplatelet Review of International Studies Collaborate Group completed a meta-analysis of the effectiveness and safety of antiplatelet agents (predominantly aspirin) for the prevention of preeclampsia.[145] Thirty-one randomized trials involving 32,217 women were included in this review. The data suggest that antiplatelet agents, specifically aspirin, have small to moderate benefits in primary prevention, though the number of patients needed to treat is large.[145]

Given the high prevalence of placental thrombotic lesions in patients with severe preeclampsia, it has also been hypothesized that antithrombotic prophylaxis could improve pregnancy outcome in women at risk for a recurrence of disease. Only observational studies have been reported. One study assessed the effects of prophylaxis with low-molecular weight heparin and low-dose aspirin on pregnancy outcome in women with a history of severe preterm preeclampsia and low birth weight infants.[146] The incidence of recurrent preeclampsia in the patients treated with low-dose aspirin was significantly higher (30%) than that in patients treated with low-dose aspirin plus heparin (3%).[146] Furthermore, patients treated with low-dose aspirin plus heparin also had a statistically greater gestational age at delivery, higher birth weight and percentile compared with low-dose aspirin group.[146] However, there is a need for randomized controlled trials in larger groups to validate these results.

Vitamin C and E Supplementation

One of the causes of maternal endothelial cell dysfunction may be poor placental perfusion initiating the release of factors to induce oxidative stress. In the past, a single-center randomized trial investigated the use of vitamins C and E to prevent preeclampsia in high-risk women and found that preeclampsia was significantly lower in this group.[147,148] But recent randomized trials and a Cochrane review did not show any significant difference in the rates of preeclampsia or adverse neonatal outcomes in treatment compared with placebo groups.[149–151] Furthermore, a multicenter study involving 2400 patients even showed an increased rate of low birth-weight babies.[152] At this time, we do not recommend the use of vitamin C and E in preeclampsia prevention.

MANAGEMENT OF PREECLAMPSIA

Delivery

The most reliable treatment of preeclampsia is delivery. Removal of placenta usually produces prompt improvement, though in a few cases, symptoms may persist for several days after delivery. The decision to deliver involves balancing the risks of worsening preeclampsia against those of prematurity. Delivery is warranted for women who develop severe preeclampsia after 34 weeks of gestation. In any woman between 32 to 34 weeks of gestation with severe preeclampsia, prompt delivery should be considered, especially if conservative management has failed. Women under 28 weeks of gestation who develop severe preeclampsia can be managed conservatively if the mother and fetus are closely monitored in a tertiary perinatal center.[136]

Women who have mild preeclampsia should also be closely monitored for signs of rapid deterioration. If signs, like headache, epigastric pain, visual changes, or abnormal laboratory results are present, then the patient should be admitted to the hospital. When the blood pressure elevation is mild, with normal laboratory results and favorable fetal evaluation, management is conservative. Patients can be treated on an outpatient or inpatient basis, depending upon the compliance of the patient. Patients who are to maintain on bed rest and can return for fetal nonstress testing and growth assessment can be managed as outpatients. Otherwise, they should be admitted to the hospital. The goals of treatment are to prevent seizures, lower blood pressure to avoid maternal end-organ damage, while aiming for as much fetal maturity as possible, and to expedite delivery when this

cannot be achieved.[153] The results of a recent trial suggested that maternal outcomes are improved with induction of labor beyond 37 weeks of pregnancy in patients with gestational hypertension and diastolic blood pressure >95 mm Hg, and in patients with mild preeclampsia.[154]

When eclampsia occurs at any time during gestation, termination of the pregnancy is indicated, irrespective of the stage of the pregnancy, as the risk to the mother is too great.[79] Treatment with magnesium sulfate may also be appropriate (as described in magnesium sulfate later in the text).

Antihypertensive Medications

As mentioned before, the optimal level of blood pressure control in pregnancies complicated by hypertension is unknown.[155,156] Less than tight control may decrease the risk of small for gestational age infant, but may increase the risk of respiratory distress syndrome of the newborn, severe hypertension in the mother, and antenatal hospitalization.[155,156]

The primary goal of hypertension treatment in patients remote from term is to prolong the pregnancy. There have been no compelling studies that demonstrated improved clinical outcome with treatment of mild preeclampsia and antihypertensive drugs. In fact, studies that have used labetalol to treat women with mild gestational hypertension or preeclampsia have shown no improvement in perinatal outcome, with an increased incidence of infants who were small for gestational age.[22,96,157] Nonetheless, the risk:benefit ratio for drug treatment in women with mild preeclampsia is unclear. Presently, there is no uniform recommendation to administer antihypertensive medications to patients with mild preeclampsia.

The treatment goal for women with severe hypertension is to lower the blood pressure to prevent cerebral hemorrhage. Although traditional recommendations are based on diastolic blood pressure, a retrospective review of 28 women with severe preeclampsia who had a cerebrovascular accident showed that >90% had systolic blood pressures >160 mm Hg, but only 12.5% had diastolic blood pressures >110 mm Hg.[158] Recommendations are that antihypertensive therapy should be given for a systolic blood pressure >160 mm Hg or diastolic >110 mm Hg, to achieve a systolic measurement of 140 to 155 mm Hg and/or a diastolic measurement of 90 to 105 mm Hg.[159]

As in the management of accelerated hypertension of pregnancy, IV labetalol and hydralazine are the most commonly used agents for the acute management of severe preeclampsia.[70] A Cochrane review showed no evidence that any one IV agent is superior to another in terms of effectiveness.[70] For women with severe preeclampsia undergoing expectant management remote from term, oral labetalol and nifedipine are acceptable.[159]

Magnesium Sulfate

Magnesium sulfate is used to prevent seizures in women with preeclampsia.[160–162] Its efficacy has been demonstrated in randomized clinical trials when leading neurologists felt that traditional antiepileptics (phenytoin, diazepam) would better control seizures. These trials proved that parenteral magnesium sulfate is superior to both phenytoin and diazepam in preventing the initial and recurrent seizures, and in lowering maternal mortality.[163] However, the use of magnesium sulfate is still controversial in women with mild preeclampsia because the incidence of seizures in this population is very low. A large prospective trial involving more than 10,000 patients demonstrated that the prophylactic use of magnesium sulfate decreased the overall risk of eclampsia.[160] However, due to the large numbers needed to treat, some investigators feel that it should be administered only when the condition is "severe." However, we and others[164,165] feel that since the severity of preeclampsia may be unpredictable, the benefits of treatment outweigh the risks. Magnesium sulfate has the additional benefit of reducing the incidence of placental abruption.[165]

PREECLAMPSIA AND LONG-TERM OUTCOMES

Cardiovascular/Stroke

Numerous epidemiologic studies have demonstrated that after a pregnancy with preeclampsia, a woman has a higher risk of cardiovascular consequences. Preeclampsia, especially if complicated by the HELLP syndrome, predisposes to the development of hypertension related consequences in future pregnancies.[113] This may be due to either a common pathophysiologic process or subclinical vascular damage. A meta-analysis found a relative risk (RR) of 3.70 in developing future hypertension in women with a history of preeclampsia.[166] In those with pregnancy-induced hypertension without proteinuria, the RR of hypertension later in life was lower at 3.39. The risk of fatal as well as nonfatal ischemic heart disease events in women with preeclampsia was twice as likely.[166] Furthermore, higher risks of future cardiac events in both primiparous women with preeclampsia as well as those with preeclampsia in any pregnancy have been described.[99,167] Timing of preeclampsia is important since preeclampsia before 37 weeks was associated with an 8-fold increase of ischemic heart disease for women compared with those with normotensive pregnancies after this period.[168] The risk of developing ischemic heart disease is also affected by the severity of disease[169]; patients with blood pressures >160/110 mm Hg and the presence of proteinuria had a RR of 3.65 of ischemic heart disease later in life as compared with those with mild preeclampsia.

Very early onset severe preeclampsia (before 24 weeks) appears to behave very differently than late-onset (after 24 weeks) preeclampsia. The former has a high maternal and perinatal morbidity and a 50% chance of recurrence of preeclampsia in subsequent pregnancies.[170] They also exhibit more chronic hypertension and increased microalbuminuria, but no difference in the incidence of insulin insensitivity or other features of the metabolic syndrome. As microalbuminuria is known to be a strong predictor of ischemic heart disease in hypertensive individuals in the general population, this group is at an even higher risk of developing cardiovascular outcomes.[171] These data suggest a different pathogenesis for early versus late onset preeclampsia, with a hypertension related vascular etiology in those with early onset disease. Biochemical markers to differentiate the 2 types of preeclampsia are currently lacking.

The risks of fatal as well as nonfatal stroke after preeclampsia have been studied.[99,166,172,173] There appears to be a higher risk of fatal compared with nonfatal strokes after preeclampsia, with an overall increase in women with earlier onset of preeclampsia (<37 weeks) (RR of 5.0).[166]

In summary, women with preeclampsia have a 4-fold increased risk of hypertension and a 2-fold increased risk of ischemic heart disease and stroke. The exact mechanism needs to be understood. However, there seems to be enough accumulating evidence to show that a history of preeclampsia should be part of an initial evaluation for ischemic heart disease in women.

Renal

There is also emerging evidence that preeclampsia is associated with developing renal disease later in life. Despite glomerular injury during the period of preeclampsia, it was previously thought that preeclampsia did not have adverse effects on the kidney in the long-term. An earlier study that followed patients who experienced the HELLP syndrome for 5 or more years revealed significantly higher diastolic and systolic blood pressures but no difference in creatinine clearance or urinary microalbumin/creatinine ratio.[174] Similarly, women with preeclampsia and pregnancy-induced hyper-

tension who were studied for 10 years were found to have an increased risk of development of chronic hypertension, but unaffected serum urea and creatinine levels.[175] However, more recent studies demonstrated that there are renal consequences. The Medical Birth Registry of Norway database of all childbirths in Norway since 1967 revealed that women with preeclampsia who delivered low birth weight offspring have a substantially increased risk of later having a kidney biopsy.[176] Furthermore, a history of preeclampsia is associated with a high occurrence of microalbuminuria and hypertension, both of which may be predictive of future renal disease.[177–179] Interestingly, a significant number of women with preeclampsia who were later biopsied exhibited focal segmental glomerulosclerosis, whereas none of the women without preeclampsia had this finding.[180] This suggests that focal segmental glomerulosclerosis may be a specific nephropathy in the aftermath of preeclampsia. Most surprisingly, a recent report by Vikse et al showed that preeclampsia during the first pregnancy is associated with a RR of 4.7 of developing end-stage renal disease.[181] Women who develop preeclampsia during their second on third pregnancies increased their RR to15.5. The authors conclude that preeclampsia is a marker for an increased risk of subsequent end-stage renal disease. Of course all of the above-mentioned findings may be confounded by the fact that women with preeclampsia had undiagnosed renal disease before their pregnancies. In fact, a small Japanese study showed that when antepartum clinical and postpartum data were available, 19 of 86 women, or 22.1%, exhibited underlying renal disease.[182] Nevertheless, we conclude that there is mounting evidence that preeclampsia leads to risk factors for chronic kidney disease and perhaps the development of end-stage renal disease; however, the absolute risk remains small.

Death

Women with a history of preeclampsia appear to have a higher risk of death; the exact risk depends on the cause of death and the particular study.[172,173,183] However, it is clear that the majority of deaths are due to cardiovascular events and strokes. For example, the risk of death from cardiovascular causes was increased by 8.1-fold,[172] whereas the adjusted incident rate ratio for death from strokes was 3.59.[173] Generally, the excess risk in mortality is manifest only after 20 years.[183] This observation points to the need to vigilantly monitor women with a history of preeclampsia after delivery for the development of hypertension and other cardiovascular risk factors.

CONCLUSIONS

It is an exciting era for the study of hypertension in pregnancy and preeclampsia. Of course, with every new discovery, more questions arise. However, we may have finally found a set of angiogenic factors that are not only pathogenic but also predictive of preeclampsia. This is especially important at a time when there is increasing evidence of preeclampsia's devastating impact on the mother's long-term health. Though new treatment options for preeclampsia will be slow to come, we are hopeful that these newly discovered angiogenic factors may be targeted for rational drug design.

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