

# Management of Preeclampsia

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A 29-year-old African American woman, G1P0, who received no previous prenatal care presented at 28 weeks, 3 days' gestation for a pregnancy-related visit. She had no previous medical problems. Her blood pressure was 128/70 mm Hg with a normal physical examination and good fetal heart beat. Urine dipstick revealed no proteinuria, and her serum creatinine concentration was 0.7 mg/dL. She returned for follow-up 2 weeks later complaining of mild headache. Her blood pressure was 134/70 mm Hg, and urine dipstick revealed trace proteinuria. At 32 weeks' gestation, she presented with a severe headache, her blood pressure was 150/92 mm Hg, and urine dipstick revealed 2+ proteinuria. She was started on labetalol 200 mg twice daily, and a 24-hour urine sample was ordered. The patient was not hospitalized as she was the caregiver for her elderly mother and hospitalization would have imposed great hardship. The 24-hour urine sample revealed 750 mg of proteinuria. She was placed on bedrest, and her blood pressure was controlled at 125/75 mm Hg. One week later, she presented to the clinic feeling poorly. Her blood pressure was 150/80 mm Hg on the labetalol, and urine dipstick revealed 3+ proteinuria, with a spot urine protein:creatinine ratio returning that day at 1.3. As she was at 34 weeks' gestation, she underwent a cesarean section, delivering a healthy baby boy.

**P**reeclampsia is a syndrome characterized by hypertension and proteinuria that occurs during the second and third trimester of pregnancy. It can cause disseminated intravascular coagulation, vasospasm, sodium retention, and seizures; the occurrence of seizures in a preeclamptic woman marks the onset of eclampsia. Preeclampsia is the leading cause of maternal morbidity and mortality worldwide,<sup>1</sup> affecting 5% to 7% of first pregnancies and recurring in 13% to 18% of subsequent pregnancies.<sup>2,3</sup> Although mortality from preeclampsia and eclampsia is highest in underdeveloped countries, the burden of disease and mortality in developed countries is considerable as well. In the United States, almost 20% of pregnancy-related deaths after 20 weeks' gestation are attributed to complications from preeclampsia and eclampsia.<sup>4</sup> Although preeclampsia currently is a significant clinical problem, its impact is likely to increase as conditions that place a woman at risk for preeclampsia, such as diabetes and obesity, continue to become more prevalent.<sup>5</sup> This article reviews the pathophysiology, diagnosis, and management of preeclampsia.

## HYPERTENSION IN PREGNANCY

There are 4 disorders of hypertension in the setting of pregnancy (**Table 1**). *Preeclampsia* is defined as the development of new hypertension after 20 weeks' gestation that is accompanied by new proteinuria. Small

amounts of proteinuria may be present in normal pregnancy, but levels exceeding 300 mg over a 24-hour period is diagnostic of preeclampsia. The diagnosis of preeclampsia may be more difficult in a woman with either preexisting hypertension or proteinuria. In such cases, a dramatic worsening of hypertension or an increase in (or the development of) proteinuria should raise clinical suspicion for preeclampsia. It is prudent to be cautious and to treat these women as if they have preeclampsia.

## RISK FACTORS

Preeclampsia typically affects women with preexisting hypertension but can occur in association with new-onset hypertension in the second half of pregnancy (**Table 2**). Nulliparous women and women with preexisting hypertension, diabetes, obesity, and twin pregnancies are at greatest risk. These comorbidities also increase the risk for early-onset (occurring between 30 and 36 wk) and severe preeclampsia, which are associated with greater rates of adverse neonatal outcomes and excess maternal morbidity during pregnancy.<sup>5</sup> While primigravid women are twice as likely to experience preeclampsia as women who have given

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### TAKE HOME POINTS

- Preeclampsia is defined by the development of new hypertension greater than 140/90 mm Hg and new proteinuria exceeding 300 mg/24 hr after 20 weeks' gestation.
- Preeclampsia is more likely to occur in nulliparas and in patients with preexisting hypertension, diabetes, obesity, and twin gestations.
- Physiologic changes in preeclampsia are different from those in a normal pregnancy: cardiac output increases but peripheral vascular resistance also increases, while glomerular filtration rate and renal plasma flow decrease relative to normal pregnancy.
- The pathophysiology of preeclampsia is related to endothelial dysfunction and abnormal placentation resulting from antagonism of vascular endothelial growth factor and decreased endothelial cell prostacyclins.
- Preeclamptic patients should be managed with careful antihypertensive therapy, usually in the hospital, as well as with magnesium sulfate for seizure prophylaxis and urgent delivery where appropriate.

birth previously, the risk appears to be increased in multiparous women with a new partner, suggesting that exposure to paternal antigens may be protective for future pregnancies.<sup>6</sup>

### PATHOPHYSIOLOGY

#### Physiologic Changes of Normal Pregnancy and Preeclampsia

Several hemodynamic changes occur during pregnancy, including an increase in cardiac output, an expansion of plasma volume, and a decrease in systemic vascular resistance and blood pressure (Table 3). These changes begin during the first trimester (weeks 1–12), peak during the second trimester (weeks 13–26), and remain constant through the third trimester (weeks 27 to delivery). Plasma volume expansion and increased red blood cell mass begin as early as week 4 of pregnancy, peaking between 28 and 34 weeks. This expansion in total body volume is associated with retention of 900 to 1000 mEq of sodium and 6 to 8 L of water, which are distributed among the fetus, amniotic fluid, and extracellular and intracellular spaces. Despite this massive volume expansion, the kidney appears to sense a relative underfilling, and, in response, plasma renin activity increases. Systemic vascular resistance (SVR) is decreased

**Table 1.** Hypertensive Diseases of Pregnancy

Disease State	Definition
Chronic hypertension	Hypertension that existed before pregnancy or is diagnosed before 20 weeks' gestation; can be primary or secondary
Gestational hypertension	Hypertension diagnosed after 20 weeks' gestation with no proteinuria; may or may not resolve by 12 weeks' postpartum
Preeclampsia	Hypertension that developed after 20 weeks' gestation; proteinuria (> 300 mg/24-hr collection) is present
Preeclampsia superimposed on chronic hypertension	Sudden increase in blood pressure after 20 weeks' gestation with development or acute worsening of proteinuria

**Table 2.** Risk Factors for Preeclampsia

Preexisting hypertension	Diabetes
Genetic factors	Paternal-specific antigens
Nulliparity	Fetal factors from donor eggs
Multiple gestation	Black race
Molar pregnancies	Increased testosterone
Older maternal age	Increased blood homocysteine concentration
Obesity	

due to peripheral vasodilatation by a mechanism not fully understood, but it may be attributed to a relative resistance to angiotensin II and norepinephrine.<sup>7</sup> The potent vasodilator prostacyclin has been found to be elevated in pregnancy.<sup>7</sup> This peripheral vasodilatation causes systemic blood pressure to fall to 100/70 mm Hg or lower in spite of the increase in cardiac output, with a nadir reached at 16 to 20 weeks' gestation.

Changes in renal function are among the earliest manifestations of pregnancy. The glomerular filtration rate (GFR) increases by 50% and renal plasma flow increases by 50% to 85% during normal pregnancy, thus causing levels of blood urea nitrogen (BUN) and creatinine to fall. The increase in GFR is caused by renal vasodilatation and is mediated by the ovarian hormone relaxin. GFR has been found to rise by 25% by the fourth week of gestation, peaking by week 9.<sup>8</sup> Normal pregnancy results in an increase in protein excretion due to physiologic impairment of proximal tubular reabsorption of protein, resulting in a mild degree of albuminuria; however, levels of protein should not exceed 300 mg over a 24-hour period.

In preeclampsia, many of the normal physiologic

**Table 3.** Hemodynamic Changes in Pregnancy

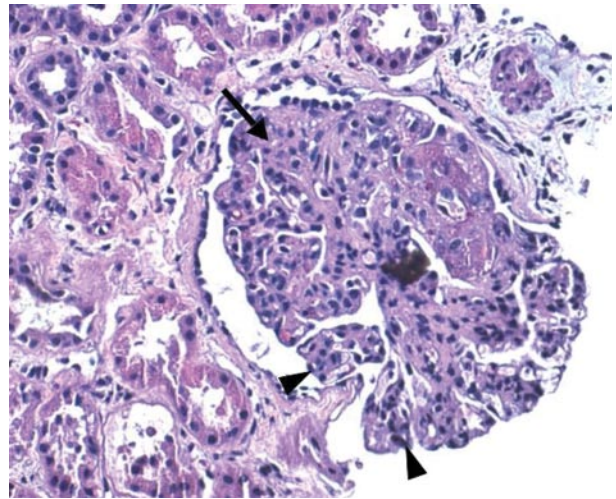
Change	Normal Pregnancy	Preeclampsia
Cardiac output	Increased	No change or decreased
Systemic vascular resistance	Decreased	Increased
Blood pressure	Decreased	Increased
Glomerular filtration rate	Increased	Decreased

changes associated with pregnancy are reversed (Table 3). Cardiac output increases as in a normal pregnancy, but peripheral vascular resistance increases, leading to hypertension. In addition, GFR and renal plasma flow decrease by 30% to 40% compared with normal pregnancy.<sup>9</sup> Increased peripheral vascular resistance is caused by greater sympathetic activation in preeclamptic patients compared with normotensive pregnant patients, as measured by sympathetic nerve activity.<sup>10</sup> Greater concentrations of circulating catecholamines have been measured in preeclamptic patients.<sup>11</sup> Also, effective circulating volume appears to be reduced, evidenced by suppressed renin and aldosterone levels and elevated brain natriuretic hormone.<sup>7</sup>

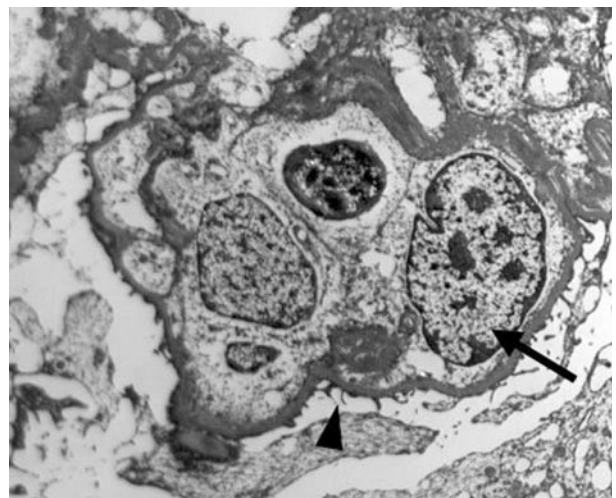
The proteinuria of preeclampsia is attributed to altered glomerular permeability and changes in tubular handling of filtered proteins. These changes in urinary protein handling are associated with a characteristic renal lesion known as glomeruloendotheliosis (Figure 1). Histologically, the glomeruli are enlarged but not hypercellular, and the podocytes appear swollen; fibrin deposition also can be seen. On electron microscopy, there is loss of endothelial fenestrae, although foot processes are relatively preserved (Figure 2). Systemic capillary permeability is also noted to be increased in preeclampsia and is attributed to increased circulating levels of tumor necrosis factor  $\alpha$ .<sup>12</sup> Loss of serum protein from renal losses combined with increased capillary permeability and thus decreased plasma oncotic pressure leads to decreased intravascular volume, increased tissue edema, and hence involvement of multiple other organs.<sup>13,14</sup>

**Molecular Mechanisms**

Endothelial function is markedly abnormal in preeclampsia. Instead of the vasodilatation of normal pregnancy, vascular constriction is observed in preeclampsia, which is probably mediated by alterations in vasoconstrictors (norepinephrine, endothelin, and thromboxane) and in vasodilators (prostacyclin and nitric oxide).<sup>7</sup> Prostacyclin, which is normally increased in pregnancy, is produced in significantly lower



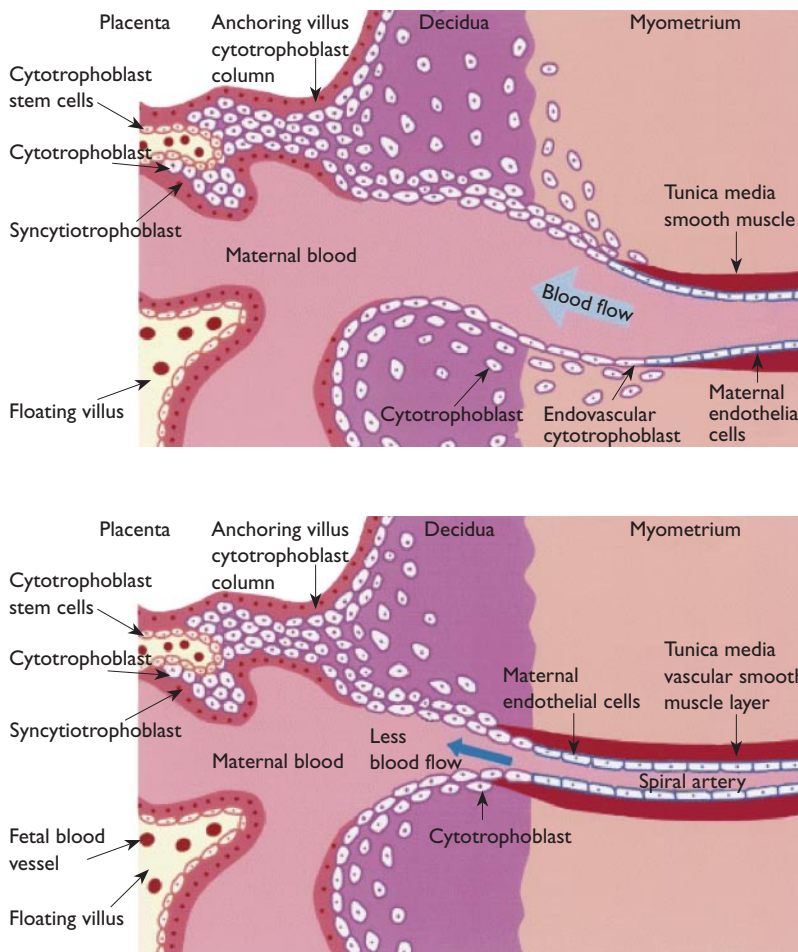
**Figure 1.** Kidney specimen from a preeclamptic patient showing enlarged swollen glomerulus (arrow) that is normocellular with swollen capillary endothelial cells (arrowheads; hematoxylin and eosin stain; 40× magnification).



**Figure 2.** Electron microscopy of a glomerulus from a preeclamptic patient showing markedly swollen and occluding endothelial cells (arrow) with preserved podocyte foot processes (arrowhead).

amounts in preeclampsia, even in the preclinical state.<sup>15</sup> This leads to an early increase in the vasoconstrictor-to-vasodilator ratio and to endothelial dysfunction and preferential vasoconstriction.

Endothelial dysfunction is also apparent in the abnormal placentation that is thought to precipitate the development of clinical preeclampsia. Uterine vascular resistance is increased in preeclamptic patients, with subsequent diminished placental blood flow.<sup>7</sup> The



**Figure 3.** Diagram of abnormalities of cytotrophoblast invasion leading to shallow invasion of spiral arteries during placental development and subsequent placental ischemia. (Adapted by permission from Macmillan Publishers Ltd. Karumanchi SA, Maynard SE, Stillman IE, et al. Preeclampsia: a renal perspective. *Kidney Int* 2005; 67:2107.)

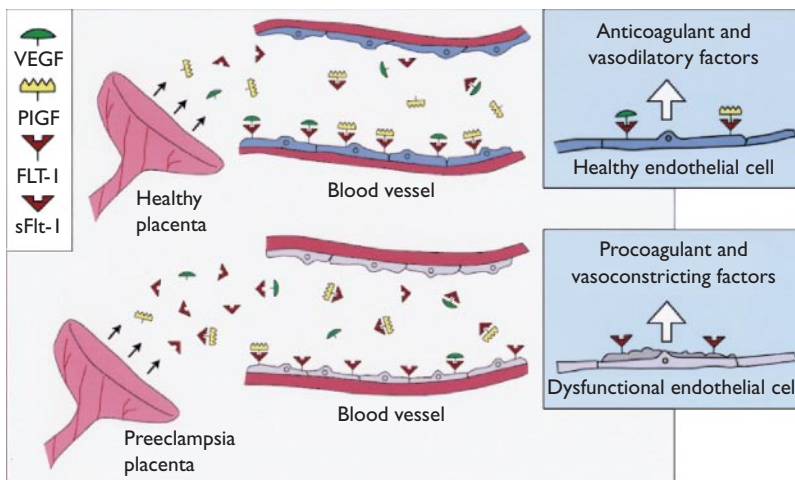
failure of abnormal cytotrophoblasts to adopt an invasive endothelial phenotype causes spiral arteries to invade only shallowly, leading to further placental ischemia (**Figure 3**).<sup>7</sup> Although placental ischemia produces hypertension, proteinuria, and glomerular endotheliosis in animal models, ischemia alone is not sufficient to produce preeclampsia, as the maternal response to placental ischemia varies.<sup>16</sup> Therefore, it was suspected that a circulating factor from the placenta caused the systemic endothelial cell dysfunction that exists in clinical preeclampsia. One such circulating factor is placental soluble fms-like tyrosine kinase-1 (sFlt-1), which is upregulated in preeclampsia.<sup>17</sup> sFlt-1 antagonizes vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), blocking induction of nitric oxide and vasodilatory prostacyclins in endothelial cells (**Figure 4**).<sup>7</sup> A rise in sFlt-1 levels and a corresponding drop in VEGF and PlGF levels have been measured 5 to 6 weeks before clinical preeclampsia and have been established as predictors of the subsequent development of preeclampsia.<sup>18</sup>

## DIAGNOSIS

### Clinical Features

Preeclampsia is diagnosed clinically and is defined by the presence of elevated blood pressure and proteinuria. Hypertension in pregnancy is defined by 2 blood pressure readings of greater than 140/90 mm Hg separated by at least 4 hours. Proteinuria (300 mg/24 hr) often exists despite normal serum BUN and creatinine concentrations. Even in the absence of proteinuria or oliguria, preeclampsia should be considered when gestational hypertension is present along with neurologic or abdominal symptoms.

Many patients with preeclampsia have multiorgan involvement. Systemic involvement leads to abdominal pain, headache, seizure, oliguria, and shortness of breath. Right upper quadrant and epigastric abdominal pain occurs as a result of liver edema and subcapsular hematoma or hemorrhage. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) sometimes accompanies liver dysfunction and is a marker of severity in preeclampsia. HELLP



**Figure 4.** Diagram showing mechanism of endothelial dysfunction caused by placental soluble fms-like tyrosine kinase-1 (sFlt-1)—antagonism of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). sFlt-1 = fms-like tyrosine kinase-1. (Adapted by permission from Macmillan Publishers Ltd. Karumanchi SA, Maynard SE, Stillman IE, et al. Preeclampsia: a renal perspective. *Kidney Int* 2005;67:2107.)

can also lead to a coagulopathy that causes bleeding from mucosal membranes and leads to death in 2% to 24% of cases.<sup>4,19</sup>

Neurologic findings are the result of cerebral edema, usually described as the reversible posterior leukoencephalopathy syndrome (RPLS), which is associated with headache, vomiting, confusion, visual abnormalities, and seizures. Renal involvement can eventually include renal failure; it is usually caused by acute tubular necrosis from hemorrhage or sepsis and improves after resolution of preeclampsia. Shortness of breath can be the result of pulmonary edema resulting from capillary leak. While pulmonary edema is a serious complication of preeclampsia, the most common cause of death in preeclampsia and eclampsia is cerebrovascular hemorrhage, occurring in up to 50% to 65% of cases.<sup>4,19</sup>

### Laboratory Findings

In the setting of normal pregnancy, an expansion of maternal blood volume and an increased GFR lead to a slight decrease in serum levels of platelets and to a relative anemia. Serum concentrations of uric acid, BUN, and creatinine are decreased as well. A “normal” creatinine level in pregnancy (which must be viewed with caution as it may still represent a relatively abnormal GFR) is typically less than 0.6 mg/dL. In preeclampsia, the platelet level drops even further due to increased consumption and intravascular destruction. The hemoglobin concentration may increase due to the fall in intravascular blood volume found in preeclampsia, and this may predispose the developing fetus to intrauterine growth restriction.<sup>20</sup> Uric acid levels increase in preeclampsia due to reduced renal clearance and increased production from tissue ischemia and oxidative stress.<sup>21</sup> This finding predicts a

poorer outcome because uric acid potentiates vascular damage in preeclampsia.<sup>8</sup> Serum creatinine concentration is often elevated over baseline values.

### MANAGEMENT

Because the progression from preeclampsia to eclampsia can be deadly for both mother and fetus, prevention of eclampsia is one of the primary goals in the management of preeclampsia. Progression to eclampsia can sometimes be prevented by close in-hospital or outpatient monitoring, antihypertensive therapy, and prophylactic intravenous magnesium sulfate during labor and the postpartum period, but these therapies and the incidence of progression to eclampsia have not been studied in controlled trials.<sup>22</sup> Importantly, many cases of eclampsia are associated with abrupt-onset seizures despite prophylactic magnesium sulfate or with onset of seizures more than 48 hours postpartum. These patients may or may not have had both hypertension and proteinuria in the week preceding their first seizure, suggesting that it is important to consider all women with either hypertension or proteinuria as being at risk for eclampsia. Among women with preeclampsia, predictors of eclampsia include severe headaches (especially occipital headaches), brisk reflexes (3+), papilledema, and/or visual disturbances. Prophylaxis with magnesium sulfate should be administered to patients with severe preeclampsia (**Table 4**). Typical dosing of magnesium sulfate is a loading dose of 6 g over 15 to 20 minutes, followed by a maintenance dose of 2 g/hr by continuous infusion.<sup>20</sup>

Management is directed by severity and gestational age. Indications for possible hospitalization are listed in **Table 5**. Once hospitalized, patients are evaluated and the decision is made for either conservative

**Table 4.** Features of Severe Preeclampsia

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Severe preeclampsia is the presence of proteinuria plus 1 of the following:

Maternal symptoms: severe nausea and vomiting, frontal or occipital headache, visual disturbance, persistent epigastric or right upper quadrant pain, chest pain, dyspnea

Maternal signs: diastolic blood pressure  $\geq 110$  mm Hg, systolic blood pressure  $\geq 160$  mm Hg, urine output  $< 500$  mL/day, pulmonary edema, and/or suspected placental abruption

Maternal laboratory findings: platelets  $< 100 \times 10^9/L$ , elevated ALT or AST, heavy proteinuria  $> 5$  g/day, elevated lactate dehydrogenase, peripheral smear with schistocytes (hemolysis)

Fetal assessment: intrauterine growth restriction, oligohydramnios, placental abruption, absent or reversed end diastolic flow on umbilical artery Doppler

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ALT = alanine aminotransferase; AST = aspartate aminotransferase.

management or immediate delivery. Conservative management consists of bed rest and close surveillance of mother and fetus (including biweekly non-stress test and ultrasound monitoring). This strategy is appropriate if blood pressure is stable and well-controlled on less than maximal doses of 2 oral antihypertensive agents, proteinuria is less than 2+ on dipstick, platelet levels are greater than  $100 \times 10^9/L$ , and the fetus is of mature gestational age ( $\geq 34$  wk). If gestational age is less than 34 weeks, maternal risks should be weighed carefully against fetal viability, and in severe cases, pregnancy termination should be considered. Steroids should be administered to accelerate fetal lung maturation at gestational ages less than 34 weeks while patients are being either managed conservatively or prepped for delivery.<sup>23</sup> Delivery, either vaginally or by cesarean section, is indicated when the mother's condition deteriorates or when fetal compromise is noted. Urgent delivery is performed when convulsions occur.

Antihypertensive therapy is urgently indicated when systolic blood pressures reach 160 mm Hg or diastolic blood pressures reach 105 mm Hg. Controlling hypertension acutely is important to prevent cerebral vascular accidents, but reduction in blood pressure should be accomplished slowly in order not to jeopardize uteroplacental blood flow, with no more than a 25% reduction in 1 hour. Generally, 5 to 10 mg doses of hydralazine or labetalol can be administered every 15 minutes until a systolic blood pressure between 140 and 160 mm Hg and a diastolic blood pressure between 90 and 110 mm Hg is achieved.<sup>20</sup> Pharmacologic treatment decisions should be made based on an individual patient's history and physical examination. Methyldopa, calcium channel blockers, and labetalol are widely used and appear to be

**Table 5.** Indications for Hospitalization

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Systolic blood pressure  $\geq 140$  mm Hg and/or diastolic blood pressure  $\geq 90$  mm Hg

$\geq 1+$  proteinuria on dipstick

$> 30$  mg of protein per mmol of creatinine

Hyperuricemia

Platelet count  $\leq 100 \times 10^9/L$

Abnormal liver function tests

Ultrasound evidence of oligohydramnios

Inadequate fetal growth

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safe (**Table 6**).  $\beta$ -Blockers may be associated with an increased risk of small-for-gestational-age infants and fetal bradycardia.<sup>24</sup> Hydralazine, which had been extensively used in the past for severe hypertension in pregnancy, is associated with more maternal hypotension, cesarean sections, placental abruption, maternal oliguria, and lower Apgar scores and is no longer considered a proven first-line treatment for severe hypertension in pregnancy, although it is still commonly used.<sup>25</sup> Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers should be avoided due to their teratogenic effects. There is a lack of randomized, controlled studies large enough to determine a preferred antihypertensive agent, and first-choice agents have been determined by clinical experience.<sup>26</sup> Intravenous agents are generally preferred in the acute setting with severe disease, but most patients can be managed with oral agents.

With greater understanding of the molecular mechanisms underlying preeclampsia, it is possible to imagine future alternative treatment strategies. For example, blocking elevated production of sFlt-1 may prove beneficial.<sup>7</sup> Pharmacologic methods for restoring PIGF and VEGF balance also could modify the course of preeclampsia. Finally, administration of relaxin would be expected to improve renal plasma flow and GFR in women with preeclampsia as well as reduce SVR and improve maternal organ perfusion. However, better understanding of the role of relaxin in renal vasodilatation in the face of the endothelial dysfunction of preeclampsia is required before implementation of this potential strategy.

## PREVENTION

Most of the strategies that have been proposed for the prevention of preeclampsia have had disappointing results.<sup>27</sup> Antiplatelet therapy with aspirin has been proposed as a strategy for preventing preeclampsia by altering the prostacyclin-thromboxane balance; some studies

**Table 6.** Antihypertensive Therapy for Hypertension Disorders in Pregnancy

Agent	Initial Dosage	Side Effects
<b>Severe pregnancy hypertension</b>		
Nicardipine	5 mg IV/hr	Peripheral edema, dizziness, headache
Labetalol	20 mg IV or 200 mg orally (max dose 300 mg IV)	Vomiting, dizziness, scalp tingling
<b>Nonsevere pregnancy hypertension</b>		
Methyldopa	250 mg orally twice daily	Diarrhea, nausea, myalgia
Labetalol	100 mg orally twice daily	Vomiting, dizziness, scalp tingling
Nifedipine XL	30 mg orally daily	Headache, dizziness, flushing, nausea

IV = intravenously.

of aspirin have found a moderate benefit in reducing the incidence of preeclampsia, although other studies have found no protective effect.<sup>28</sup> In 2 prospective, randomized trials involving more than 4000 women, treatment with antioxidant vitamins and calcium supplementation did not improve the incidence of preeclampsia and, in fact, potential adverse effects (increased low birth weight, late stillbirth, and severity and timing of preeclampsia and neonatal acidosis) were increased.<sup>29</sup> Similar inconclusive findings have been reported for magnesium supplementation and fish oil supplementation.<sup>30,31</sup> Finally, in spite of the fact that women with preexisting chronic hypertension are at significantly higher risk of preeclampsia as compared with normotensive women, use of the antihypertensives methyldopa, labetalol, and atenolol to control superimposed preeclampsia has not been found to be effective as preventive treatment.<sup>27</sup>

### LONG-TERM SEQUELAE

Preeclamptic women are at increased risk for dyslipidemias and insulin resistance.<sup>32</sup> Also, chronic salt-sensitive hypertension from renal injury incurred during preeclampsia has been described.<sup>33</sup> Although these conditions often coexist with preeclampsia, an increased cardiovascular mortality attributed to increased rates of coronary heart disease and stroke has been noted.<sup>34,35</sup> Women who have had preeclampsia should be considered to have a risk factor for coronary artery disease. A decreased long-term incidence of breast cancer has been noted in case-control and cohort studies, possibly due to a persistent anti-angiogenic state.<sup>7,36</sup> This has not been proven but has important implications for further elucidating the mechanisms behind preeclampsia and carcinogenesis.

### CONCLUSION

New understanding of the molecular basis for preeclampsia promises to lead to improved therapies and interventions. In the meantime, the need

for effective prevention and treatment strategies for preeclampsia is critical. Appropriate management begins with identification of risk factors for preeclampsia in expectant patients, including preexisting hypertension, diabetes, obesity, and twin gestations. Patients without such factors should be monitored for new-onset proteinuria (> 300 mg/24 hr) and hypertension. Clinical vigilance and treatment may lead to improved outcomes while molecular therapies are in development. **HP**

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