Preeclampsia is a pregnancy-specific form of hypertension that presents a major health problem worldwide. Preeclampsia complicates 5% to 8% of all pregnancies and increases both maternal and neonatal morbidity and mortality.\(^1,2\) The mainstay of therapy for preeclampsia remains clinical recognition through prenatal care and termination of the disease process with delivery. Maternal mortality has been reduced in the United States, but in countries where prenatal care is not adequate, preeclampsia/eclampsia accounts for 40% to 80% of maternal deaths, an estimated 50,000 per year. Many of these deaths may be preventable with prenatal care and evidence-based prophylactic seizure therapy.

Infants of women with preeclampsia have a 5-fold increase in mortality compared with infants of mothers without the disorder. Much of the neonatal mortality is attributable to iatrogenic prematurity. Approximately 10% of preeclampsia occurs before 34 weeks' gestational age, and indicated delivery for preeclampsia is responsible for 15% of preterm US births.\(^3\) In developing countries, perinatal mortality is further increased. Advances in the understanding of preeclampsia are essential to guide preventive and therapeutic strategies to decrease the worldwide impact of this disease.

**Definitions of Hypertensive Disorders in Pregnancy**

Hypertensive disorders of pregnancy antedate pregnancy and are specific to pregnancy. The nonspecific term *pregnancy-induced hypertension* is not recommended. *Gestational hypertension* is defined as only gestational blood pressure elevation, without proteinuria, and complicates approximately 6% of pregnancies.\(^2\) Gestational blood pressure elevation is blood pressure greater than 140 mm Hg (systolic) or 90 mm Hg (diastolic) in a woman who was normotensive before 20 weeks' gestation. This group is a heterogeneous mix of patients: patients with unrecognized chronic hypertension, transient hypertension of pregnancy that will resolve postpartum, and patients developing preeclampsia.\(^4\) Gestational hypertension with minimally elevated blood pressure and without proteinuria is not a reliable indicator of maternal or fetal morbidity or mortality but mandates close attention to mother and fetus.\(^5\)

Preeclampsia is defined as gestational blood pressure elevation with proteinuria\(^4\) and usually occurs after 20 weeks of gestation. Proteinuria is defined as the urinary excretion of 300 mg or greater of protein in a 24-hour period. Because of poor specificity, edema and incremental blood pressure increases are no longer included in the diagnosis of preeclampsia.\(^4\) Nonetheless, it is recommended that pregnant women with an increase in blood pressure that does not achieve 140 mm Hg (systolic) or 90 mm Hg (diastolic) warrant close observation.\(^4\) Likewise, patients who have gestational hypertension without proteinuria but with other evidence of new end-organ involvement should be managed as if they have preeclampsia. *Eclampsia* is the occurrence of seizures that cannot be otherwise explained in a woman with preeclampsia.

*Chronic hypertension* complicates 3% to 5% of all pregnancies and is the presence of increased blood pressure prior to pregnancy, hypertension before 20 weeks' gestational age, or persistent hypertension 12 weeks postpartum.\(^6\) *Chronic hypertension with superimposed preeclampsia* is diagnosed by the presence of increased blood pressure above the patient's baseline, a change in baseline proteinuria, or evidence of end-organ dysfunction. Superimposed preeclampsia occurs in approximately 20% to 25% of women with chronic hypertension.\(^7,8\) The *HELLP* (hemolysis, elevated liver enzymes, and low platelets) syndrome is defined by the presence of all 3 criteria: hemolysis (abnormal peripheral smear, bilirubin \(\geq 1.2\) mg/dL [20.5 µmol/L]), or lactate dehydrogenase \(\geq 600\) IU/L), elevated liver enzymes (aspartate aminotransferase \(\geq 2\) normal), and thrombocytopenia (platelets \(< 100 \times 10^9/µL\)).\(^9\)

**Pathogenesis of Preeclampsia**
Preeclampsia can be considered a 2-stage disease and the linkage of these 2 stages remains the focus of preeclampsia research.\(^10\) The first stage of preeclampsia involves abnormal placentation. Preeclampsia can occur without uterine distension (eg, abdominal pregnancies) and in pregnancies without a fetus (eg, hydatidiform mole) but requires the presence of the placenta.\(^11\) The maternal spiral arteries undergo extensive remodeling in healthy pregnancy secondary to trophoblast invasion. This remodeling is not complete in preeclamptic pregnancies.\(^12,13\) The failure of the spiral arteries to transform to dilated flaccid tubes with a 4-fold increase in diameter, and the fre-
quent finding of atherosis, leads to reduced placental perfusion. It is proposed that the poor placental perfusion is the root cause of preeclampsia.

The second stage of preeclampsia is the transition to the maternal systemic disorder. This syndrome is more than simply hypertension and proteinuria. Once preeclampsia is evident than simply hypertension and proteinuria. This syndrome is more than simply hypertension and proteinuria.14 Once preeclampsia is evident

PATHOGENESIS AND MANAGEMENT OF PREECLAMPSIA

The characteristic abnormal placental implantation of preeclampsia is present in pregnancies complicated by growth restriction and in one third of preterm births without clinically evident preeclampsia. Therefore, multiple maternal factors—genetic, environmental, and behavioral—must interact with the reduced placental perfusion to result in the maternal constellation of signs and symptoms, or syndrome. Many of the maternal factors and associated changes are also associated with cardiovascular disease in later life (increased inflammatory markers, dyslipidemia, insulin resistance, endothelial dysfunction, and oxidative stress).

The link between the pathophysiology of abnormal placentation and the physiology of the maternal syndrome remains unclear. Oxidative stress is an attractive hypothesis but remains as such. Preeclampsia has been a disease of theories that have not stood the test of time, and the effectiveness and safety of antioxidants for prevention of preeclampsia must be evaluated in large clinical trials. The long-term health consequences of preeclampsia for both mother and fetus are also not completely known. Several recent studies indicate that long after a preeclamptic pregnancy women have increased insulin resistance, altered endothelial function, and an atherogenic lipid profile when compared with women who have had healthy pregnancies.

Current Management Strategies

The 2 primary management goals of preeclampsia are recognition of disease and timing of delivery. Prenatal care and blood pressure screening in addition to familiarity with risk factors (Box 1) are important to detect disease. Preeclampsia manifests a spectrum of clinical findings that range from mild disease to more severe disease with signs or symptoms of end-organ involvement (Box 2). Although patients progress through the continuum over time, their rate of progression differs. Maternal and neonatal morbidity and mortality will depend upon multiple factors including the gestational age at delivery, the severity of the disease, and the maternal and fetal condition.

Antepartum Assessment

Essential to the evaluation of the patient with preeclampsia is a thorough maternal and fetal assessment.4 The maternal assessment includes defining the severity of disease and any end-organ involvement and is determined by history, physical examination, and laboratory studies (TABLE). Fetal evaluation includes a nonstress test, which

Box 1. Risk Factors

Obesity
Black race
Chronic hypertension
Diabetes or insulin resistance
Collagen vascular disease
Thrombophilias
Increased circulating testosterone
Multiple gestation
Previous preeclampsia

Box 2. Evidence of End-Organ Involvement

Hematologic
Platelets (<100 x 10^9/L)
Microangiopathic hemolysis (increased lactate dehydrogenase or bilirubin)

Hepatic
Epigastric or right upper quadrant pain
Elevated liver enzymes (aspartate aminotransferase ≥2 x normal)

Neurologic
Cerebral disturbances
Visual disturbances
Persistent headache

Placental
Intrauterine growth retardation
Oligohydramnios
Abnormal Doppler studies of umbilical artery

Pulmonary
Pulmonary edema

Renal
Oliguria (≤500 mL/24 h)
Creatinine level (>1.2 mg/dL [106.1 µmol/L])
is an antepartum noninvasive doppler fetal heart rate test. If delivery is not immediately planned, a detailed ultrasound including measurements of fetal growth, amniotic fluid volume, and a biophysical profile should be obtained. The fetal variables should be interpreted in light of gestational age.

Following diagnosis and assessment, there are 2 management options, delivery or expectant management. The decision will incorporate maternal stability, fetal well-being, gestational age, and supportive services for both the mother and neonate. Delivery should be considered for patients at term, patients at term or preterm who have end-organ involvement, patients in labor or who have had premature rupture of membranes, or rapid disease progression. Delivery is indicated at any gestational age with nonreassuring fetal assessment, severe maternal symptoms, or hemodynamic instability. An especially important maternal indication for delivery is the presence of hepatic subcapsular hematoma, because of the risk of hepatic rupture. This is indicated by increased liver size (on physical examination or ultrasound) associated with abdominal tenderness and elevated liver enzymes. Once fetal lung maturity is reached, delivery should always be considered in women with preeclampsia who have severe blood pressure elevation, end-organ involvement, or fetuses with intrauterine growth retardation.

Expectant management may be appropriate in preterm patients with mild disease or in more severe disease to obtain benefit for the preterm fetus by maternal administration of corticosteroids. Any delay in delivery, however, is always accompanied by the possibility of unavoidable maternal and fetal morbidity. Expectant management schemes for early disease have been proposed by several investigators. Any patient considered a candidate for expectant management should initially be observed closely to ensure that the disorder is not rapidly progressive; for many patients, this requires hospitalization. The decision to continue expectant management is dynamic, and maternal and fetal assessment must be continuous with physical examinations, blood pressure monitoring, laboratory evaluations, and fetal testing with frequency of these evaluations guided by severity. Consultation with those experienced in caring for these patients, such as specialists in maternal-fetal medicine, and hospitalization at a tertiary center should be considered when expectant management is chosen.

**Intrapartum Management**

The route of delivery must be individualized. Although vaginal delivery avoids the additional stress of surgery, the option of induction of labor depends on maternal and fetal stability and availability of support services. Although delivery ultimately cures preeclampsia, this resolution is not immediate; time saved by cesarean delivery must be weighed against the increased maternal risk of operative delivery vs vaginal delivery.

Intrapartum treatment for seizure prophylaxis, hypertension, and fluid imbalance is essential. There is general agreement for the use of seizure prophylaxis in the patient with eclampsia and the patient with more severe disease. Evidence supports the use of parenteral magnesium sulfate. Magnesium is more effective than diphenylhydantoin or diazepam to prevent recurrent seizures and it reduces maternal mortality. Diastolic blood pressures persistently greater than 105 mm Hg to 110 mm Hg should be treated with antihypertensive agents. Hydralazine and labetalol are frequently the agents of choice. Fluid management of patients with preeclampsia is usually done clinically with controlled infusion rates and attention to urine output and physical examination. Patients who are volume depleted should receive careful rehydration with an isotonic balanced salt solution, guided by clinical parameters. Central venous pressure monitoring may be helpful in some patients with persistent oliguria, pulmonary edema, or other complicating medical conditions.

**Postpartum Care**

Although delivery is the definitive cure for preeclampsia, the disease process does not immediately reverse. Patients with preeclampsia should be closely monitored in the postpartum period. Seizure prophylaxis should be continued postpartum during the resolution phase (12-48 hours) and fluid status should be monitored closely. Women with preeclampsia may require an oral antihypertensive agent for persistent hypertension (>160/100 mm Hg). Following hospital discharge, frequent blood pressure monitoring is required; blood pressures usually normalize by 6 weeks postpartum. Women with hypertension beyond 12 weeks postpartum may require long-term treatment.

Women with preeclampsia should be counseled regarding their risk of hypertensive complications in future preg-
nancies. Risk of recurrence is related to gestational age at onset, race, fetal parity, and other medical complications but is approximately 20%. Women with early-onset preeclampsia should also be counseled regarding the association with thrombophilias. Testing strategies for these women include antiphospholipid antibodies, homocysteine concentrations, protein S concentrations, and protein C concentrations.

Conclusion

Preeclampsia is a syndrome that affects women and their infants worldwide. The current definitive therapy, delivery, with its potential for iatrogenic prematurity, is the same now as a hundred years ago. The most appropriate therapy (magnesium sulfate) for eclampsia, one of the major causes of mortality in third-world countries, is established but not widely incorporated into clinical health care. Definitive preventive therapy for preeclampsia is not yet available, but well-supported hypotheses will soon justify clinical trials. The relationship of preeclampsia to cardiovascular disease later in life for mother and infant awaits resolution. Nonetheless, the dramatic increase in our understanding of the pathogenesis of preeclampsia in the last decade warrants optimism that a solution may be at hand.

REFERENCES