HYPERTENSIVE DISORDERS OF PREGNANCY

Cullen Archer, MD

Epidemiology

Hypertensive disorders of pregnancy are the third leading cause, after embolism and hemorrhage, of maternal mortality in the United States, accounting for up to 16 % of deaths. [1]Hypertensive disorders of pregnancy occur in 12 to 22% of pregnancies.[2]

Pathophysiology

The cause of preeclampsia is not known. The syndrome is characterized by both maternal and fetal manifestations. The maternal disease is characterized by vasospasm, activation of the coagulation system, and perturbations in many humoral and autocoid systems related to volume and blood pressure control. The pathologic features in this disorder are primarily ischemic in nature and affect the placenta, kidney, liver, and brain.[3] Many consider the placenta as the pathologic focus for all the manifestations of preeclampsia because delivery is the only definitive cure. Early in gestation the spiral arteries (terminal branches of the uterine artery) are transformed from thick-walled, muscular vessels to sac-like flaccid vessels, which eventually accommodate a ten-fold rise in uterine blood flow. There is evidence in women destined to become preeclamptic that trophoblastic invasion of the uterine spiral arteries is incomplete, and the vessels remain thick-walled and muscular.[4]

Classification and Definitions

Chronic Hypertension

Chronic hypertension is defined as hypertension that is present and observable before pregnancy or that is diagnosed before the 20th week of gestation. Hypertension is defined as a blood pressure equal to or greater than 140 mm Hg systolic OR 90 mm Hg diastolic. Hypertension that is diagnosed for the first time in pregnancy that does not resolve postpartum is also defined as chronic hypertension.

Preeclampsia

The pregnancy specific syndrome usually occurs after 20 weeks gestation although may occur earlier with gestational trophoblastic or collagen vascular disease. It is defined by an increase in blood pressure associated with proteinuria. Blood pressure elevation is defined as a blood pressure equal to or greater than 140 mm Hg systolic and/or 90 mm Hg diastolic in a woman who was normotensive prior to 20 weeks gestation. In the past, a rise in blood pressure of 30 mm Hg systolic or 15 mm Hg diastolic was used as a diagnostic criterion even when the absolute values were below 140/90 mm Hg. This definition is no longer included because the only available evidence shows that women in this group are not likely to suffer increased adverse outcomes. According to the Working Group, however, women who demonstrate an elevation of more than 30 mm Hg systolic or more than 15 mm Hg diastolic above baseline "warrant close observation." Proteinuria is defined as a urinary excretion of 0.3 gm total protein in a 24-hour collection. This quantity usually correlates with a concentration of 30 mg/dL (1+ on dipstick) or greater in a random urine determination and no evidence of urinary tract infection.

The following findings increase the certainty of the diagnosis: [5] [6]

- Blood pressure of 160 mm Hg or greater systolic, OR 100 mm Hg of greater diastolic on two occasions at least 6 hours apart while patient is on bedrest.
- Proteinuria of 2.0 gm or more in 24 hours (2+ or 3+ on qualitative urinalysis)
- serum creatinine > 1.2 mg/dL unless previously elevated
- Platelet count < 100,000 cells/mm^3 and/or evidence of microangiopathic hemolytic anemia (elevated LDH)
- Elevated hepatic enzymes (ALT or AST)
- Persistent headache or visual disturbances
- Persistent epigastric pain
- Oliguria (< 500 cc in 24 hours)
- Pulmonary edema
- Fetal growth restriction
- Convulsions (eclampsia)

Edema occurs in too many normal pregnant women to be discriminate and has been abandoned as a marker in these classification schemes.

Superimposed Preeclampsia on Chronic Hypertension

Preeclampsia is more common in women with chronic hypertension and complicates almost 25% of those pregnancies.[7] The diagnosis of superimposed preeclampsia is highly likely with the following findings:[8]

- In women with hypertension and no proteinuria early in pregnancy (< 20 weeks), new-onset proteinuria, defined as the urinary excretion of 0.3 gm protein or greater in a 24-hour collection
- Sudden increase in proteinuria
- Sudden increase in blood pressure in a women who hypertension was previously well controlled
- Thrombocytopenia
- An increase in ALT or ALT to abnormal levels

Gestational Hypertension

Gestation hypertension is defined as blood pressure elevation detected for the first time after midpregnancy, without proteinuria. This nonspecific term will include women with preeclampsia who have not yet manifested proteinuria as well as women who will never manifest proteinuria. The final diagnosis is only confirmed postpartum when the blood pressure has returned to normal levels by 12 weeks.[9]

Management of Preeclampsia and Eclampsia

Fetal Evaluation

Any therapy for preeclampsia other than delivery must have as its successful endpoint the reduction of perinatal morbidity and mortality. The cornerstone of obstetric management of preeclampsia is based upon whether the fetus is more likely to survive without significant neonatal complications in utero or in the nursery. Nonstress testing (NST), ultrasound assessment of fetal activity and amniotic fluid volume (biophysical profile [BPP]), and fetal movement counts are the most common fetal surveillance techniques. For all women with preeclampsia, daily fetal movement assessment is a useful screening assessment. More formal testing is indicated if movements are not normal (NST, BPP).[10]

Maternal Evaluation

Antepartum testing has two goals. The first is to recognize preeclampsia early; the second is to observe progression of the condition, both to prevent maternal complications by delivery and to determine whether fetal well-being can be safely monitored with the usual observations. The clinical management of preeclampsia is dictated by overt clinical signs and symptoms. Antepartum hospital management should include daily scrutiny of findings such as headache, visual disturbances, or epigastric pain, weight on admittance and daily thereafter, analysis of proteinuria on admission and every other day, blood pressure readings with an appropriate size cuff in the sitting position every four hours, laboratory evaluation for severe disease, determination of fetal size and amniotic fluid volume.[11] Restricted activity is a usual and reasonable recommendation for women with preeclampsia, although its efficacy is not clearly established. Strict sodium and diuretic therapy appear to have no role in management. Antihypertensive therapy in women with gestational hypertension and preeclampsia does not improve perinatal outcome.

Delivery is the only definitive treatment for preeclampsia and should be considered for all women with this diagnosis at 40 weeks gestation. Delivery at term can be initiated when the cervix is favorable for induction. There is general agreement that severe preeclampsia after 34 weeks gestation should be managed by delivery or prior to that time if there is evidence of maternal or fetal distress.[12] If delivery of a preterm infant less than 34 weeks gestation is anticipated at a Level I or Level II hospital, the mother should be transferred on magnesium sulfate to a tertiary care center with adequate neonatal intensive care facilities.[13] If the fetus is less than 34 weeks gestation, consideration should be made to giving steroids to promote fetal lung maturity. Between 28 and 34 weeks, considerable disagreement exists about the management of severe preeclampsia ranging from immediate delivery to expectant management with delivery for worsening maternal status, fetal compromise, attainment of 34 weeks gestation, labor or rupture of membranes, or vaginal bleeding.[14] [15] When severe preeclampsia develops between 18 and 27 weeks, perinatal mortality was 87% and maternal morbidity was high.[16]

In labor, magnesium sulfate is administered to women with preeclampsia. Magnesium sulfate is loaded intravenously in a dose of 4 grams followed by a continuous maintenance dose at 2 grams per hour. Serum magnesium levels should be measured every 6 hours and adjusted to maintain levels between 4-7 mEq/L (4.8 to 8.4 mg/dL). The use of magnesium sulfate during labor in women with gestational hypertension varies according to clinician. We recommend that if magnesium sulfate is not administered to women with gestational hypertension during labor, continuous reassessment for signs and symptoms of neuroirratibiliy by undertaken.

HELLP Syndrome

The syndrome of hemolysis, elevated liver enzymes, and low platelets develops in approximately 1 of 1000 pregnancies overall and in 10 to 20 percent of women with severe preeclampsia and eclampsia.[17] As many as 15 to 20 percent of patients do not have antecedent hypertension or proteinuria.[18] Patients manifesting this syndrome usually are seen before term (less than 36 weeks' gestation) complaining of malaise (90%), epigastric or right upper-quadrant pain (90%), and nausea or vomiting (50%), and some will have nonspecific viral-syndrome-like symptoms.[19] Laboratory workup should include a complete blood count with peripheral smear, liver profile including AST, total bilirubin, and lactate dehydrogenase (LDH). The diagnosis is established by the presence of :

- preeclampsia
- platelet counts < 100,000 cells/mm^3
- LDH > 600 IU/L or total bilirubin > 1.2 mg/dL
- AST > 70 IU/L
- Microangiopathic hemolytic anemia on peripheral smear

There is general agreement that delivery should be effected for pregnancies greater than or equal to 34 weeks gestation, nonreassuring fetal testing, and presence of severe maternal disease (multiorgan dysfunction, disseminated intravascular coagulopathy, liver infarction, renal failure, or abruption). [20]

Eclampsia

Preeclampsia complicated by generalized tonic-clonic convulsions is termed eclampsia when not attributed to another cause. Until other such causes are excluded, all pregnant women with convulsions should be considered to have eclampsia. The tenets of treatment include control of convulsions using an intravenous (IV) loading dose of magnesium sulfate (4 to 6 gm in 100 cc IV fluid over 15 to 20 minutes), followed by continuous IV infusion of magnesium at 2 gm/hr[21] if renal function is not compromised. An intramuscular (IM) delivery protocol has also been described. Compelling evidence suggest that magnesium sulfate significantly lowers the rate of recurrent convulsions (compared with diazepam and phenytoin) and maternal mortality (compared with phenytoin) in eclamptic women.[22] Serum magnesium levels should be measured at 4 -6 hours and adjusted to maintain levels between 4-7 mEq/L (4.8 to 8.4 mg/dL). Magnesium is discontinued 24 hours after delivery. Acute elevations of blood pressure are treated with oral or IV medications. Magnesium sulfate is not given to treat hypertension. The patient with eclampsia should be delivered in a timely fashion. Fetal bradycardia frequently occurs during an eclamptic seizure; usually, this can be managed by maternal treatment, and cesarean delivery is not necessary. Once the patient is stabilized, the mode of delivery should depend, in part, upon factors such as gestational age, fetal presentation, and the findings on cervical examination.[23]

Treatment of Acute Hypertension

Intermittent IV or oral administration of antihypertensive medication is given when the diastolic pressure is dangerously high. Some clinicians treat at 100 mm Hg to 110 mm Hg. At our institution, we also treat hypertension when the systolic blood pressure is equal to or greater than 160 mm Hg. Hydralazine is the most commonly administered medication, usually given IV but can be administered IM. The maximal effect is at 20 minutes and the duration of action is 6 to 8 hours.[24] At our institution, we start with 5 mg and give escalating doses every 15 minutes, adding an additional 5 mg, until a therapeutic dose is found. The maximum dose is 300 mg in a 24 hour period. Labetolol has also been shown to be effective for the treatment of acute hypertension and can be given as IV bolus injections or as a continuous IV infusion at 1 mg/kg with the appropriate monitoring.[25] However, beta antagonists should be avoided in the setting of acute congestive heart failure and asthma. Labetolol is given as a 20 mg IV bolus followed by 40 mg if not effective within 10 minutes; then, 80 mg every 10 minutes every 10 minutes to a maximum total dose of 220 mg,[26] Oral nifedipine has also been used with success in controlling acute severe hypertension in pregnant women.[27] The immediate release formulation acts rapidly, causing significant reduction is blood pressure within 10 to 20 minutes. It should be noted, however, that the use of nifedipine for this purpose is not approved by the Food and Drug Administration and that fatal and adverse cardiac events have occurred in older patients when nifedipine was used for this purpose. Rarely, sodium nitroprusside has been used after failure of the above agents for acute hypertensive emergency.

---

[1] Centers for Disease Control and Prevention. Pregnancy-Related Mortality Surveillance, United States, 1991-1999. MMWR *Morb Mort Wkly Rep* 2003; 52 (SS02): 1-8.
[2] ACOG Committee on Practice Bulletins. Diagnosis and Management of Preeclampsia and Eclampsia. ACOG Practice Bulletin 33 January 2002.
[3] National High Blood Pressure Education Program of NHLBI. Working Group Report on High Blood Pressure in Pregnancy. *NIH Publication 00-3029*. 2000; 6-10.
[4] Zhou Y, Damsky CH, Chiu K, Roberts JM, Fisher SJ. Preeclampsia is associated with abnormal expression of adhesion molecules by invasive cytotrophoblasts. *J Clin Invest* 1993; 91: 950-60.
[5] Hypertensive Disorders in Pregnancy, *In*: Williams Obstetrics, 22nd ed. Eds. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap L, Wenstrom KD. McGraw-Hill, New York 2005; 761-808.
[6] ACOG Committee on Practice Bulletins. Diagnosis and Management of Preeclampsia and Eclampsia. ACOG Practice Bulletin 33 January 2002.
[7] Sibai BM, Lindheimer MD, Hauth J, Caritis S, VanDorsten P, Klebanoff M, MacPherson C, Landon M, Miodovnik M, Paul R, Meis P, Dombrowski M. Risk factors for preeclampsia, abruption placentae, and adverse neonatal outcomes among women with chronic hypertension. *N Eng J Med* 1998; 339: 667-71.
[8] National High Blood Pressure Education Program of NHLBI. Working Group Report on High Blood Pressure in Pregnancy. *NIH Publication 00-3029*. 2000; 6-10.
[9] Hypertensive Disorders in Pregnancy, *In*: Williams Obstetrics, 22nd ed. Eds. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap L, Wenstrom KD. McGraw-Hill, New York 2005; 761-808.
[10] National High Blood Pressure Education Program of NHLBI. Working Group Report on High Blood Pressure in Pregnancy. *NIH Publication 00-3029*. 2000; 16-22.
[11] Hypertensive Disorders in Pregnancy, *In*: Williams Obstetrics, 22nd ed. Eds. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap L, Wenstrom KD. McGraw-Hill, New York 2005; 761-808.
[12] Schiff E, Friedman S, Sibai BM. Conservative management of severe preeclampsia remote from term. *Obstet Gynecol* 1994; 84: 626.
[13] Sibai BM. Hypertension *In*: Obstetrics: Normal and Problem Pregnancies. Eds. Gabbe SG, Niebyi JR, Simpson JL. Churchill Livingstone, Philadelphia, Pennsylvania 2002; 945-1004.
[14] Odendaal HJ, Pattinson RC, Bam R. Aggressive or expectant management of patient with severe preeclampsia between 28-34 weeks' gestation: a randomized controlled trial. *Obstet Gynecol* 1990; 76: 1070.
[15] Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: a randomized controlled trial. *Am J Obstet Gynecol* 1994; 171: 818.
[16] Sibai BM, Taslimi M, Abdella TN. Maternal and perinatal outcome of conservative management of severe preeclampsia in midtrimester. *Am J Obstet Gynecol* 1996; 174: 452.
[17] Sibai BM; Ramadan MK; Usta I; Salama M; Mercer BM; Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* 1993 Oct;169(4):1000-6.
[18] Reubinoff BE; Schenker JG. HELLP syndrome--a syndrome of hemolysis, elevated liver enzymes and low platelet count--complicating preeclampsia-eclampsia. *Int J Gynaecol Obstet* 1991 Oct;36(2):95-102.
[19] Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? *Am J Obstet Gynecol* 1990 Feb;162(2):311-6.
[20] Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol* 2004 May;103(5 Pt 1):981-91.
[21] Hypertensive Disorders in Pregnancy, *In*: Williams Obstetrics, 22nd ed. Eds. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap L, Wenstrom KD. McGraw-Hill, New York 2005; 761-808.
[22] Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; 345: 1455-63.
[23] ACOG Committee on Practice Bulletins. Diagnosis and Management of Preeclampsia and Eclampsia. ACOG Practice Bulletin 33 January 2002.
[24] Paterson-Brown S, Robson SC, Redfern N, Walkinshaw SA, De Swiet M. Hydralazine boluses for the treatment of severe hypertension in pre-eclampsia. *Br J Obstet Gynecol* 1994; 101: 409-13.
[25] Mabie WC, Gonzalez AR, Sibai BM, Amon E. A comparative trial of Labetolol and Hydralazine in the acute management of severe hypertension complicating pregnancy. *Obstet Gynecol* 1987; 70: 328-33.
[26] Working report of the National High Blood Pressure Education Program of NHLBI. Working Group Report on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; 183: S1-S22.
[27] Scardo JA, Vermillion ST, Hogg BB, Newman RB. Hemodynamic effects of oral nifedipine in preeclamptic hypertensive emergencies. *Am J Obstet Gynecol* 1996; 175: 336-8.