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Hypertensive disorders of pregnancy: Overdiagnosis is appropriate

■ ABSTRACT

Hypertensive disorders of pregnancy are common and require special care to prevent maternal and fetal morbidity and mortality. Since the symptoms of preeclampsia, the most dangerous disorder, are variable, overdiagnosis is appropriate. Chronic hypertension complicates 5% of all pregnancies and is becoming more common due to delayed childbearing.

■ KEY POINTS

Preeclampsia used to be diagnosed by the “30-15” rule: systolic pressure more than 30 mm Hg above baseline and diastolic pressure more than 15 mm Hg above baseline. That rule, however, is now discredited because it is not specific enough.

Antihypertensive medications are used solely to prevent maternal morbidity. They have no effect on disease progression and do not prevent eclampsia.

All hypertensive patients should undergo increased surveillance, serial laboratory tests throughout pregnancy, serial ultrasound scans to follow growth, and antenatal testing.

A woman with early and severe preeclampsia should be evaluated for an underlying metabolic disorder such as the factor V Leiden mutation, antiphospholipid antibody syndrome, hyperhomocysteinemia, or protein S deficiency.

DIAGNOSING AND MANAGING hypertension in pregnancy consume a significant amount of resources and can challenge even the most experienced clinician. Since the presentation of preeclampsia is variable, and since the diagnostic criteria in previous guidelines missed some cases, a high index of suspicion is warranted.

Hypertensive disorders complicate 12% to 22% of all pregnancies, with results that range from inconsequential to catastrophic. They are a major cause of neonatal morbidity and mortality and are responsible for 17.6% of maternal deaths, making them the third leading cause after thromboembolism and hemorrhage. Chronic hypertension is becoming a more common problem because of delayed childbearing.

This article covers the classification, pathophysiology, diagnosis, and management of hypertension in pregnancy, as well as how to counsel patients postpartum.

■ FOUR CATEGORIES

The current classification system recognizes four categories of hypertensive disorders in pregnancy:^{1,2}

- Gestational hypertension
- Preeclampsia-eclampsia
- Chronic hypertension
- Preeclampsia superimposed on chronic hypertension.

■ GESTATIONAL HYPERTENSION

Gestational hypertension, formerly known as pregnancy-induced hypertension or PIH, is the new onset of hypertension after 20 weeks

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of gestation. The diagnosis requires that the patient have:

- Elevated blood pressure (systolic ≥ 140 or diastolic ≥ 90 mm Hg, the latter measured using the fifth Korotkoff sound)
- Previously normal blood pressures
- No protein in the urine
- No manifestations of preeclampsia-eclampsia.

Also known as transient hypertension, gestational hypertension is actually diagnosed retrospectively when the patient does not develop preeclampsia and if blood pressure returns to normal by the 6-week postpartum visit.

In other words, gestation hypertension is a nonspecific diagnosis that is assigned until a more specific diagnosis (preeclampsia with the onset of proteinuria, chronic hypertension if hypertensive at the 6-week postpartum visit) is made. In any event, the diagnosis of gestational hypertension mandates increased surveillance.

■ PREECLAMPSIA-ECLAMPSIA

Preeclampsia: Hypertension plus proteinuria

Preeclampsia is defined as elevated blood pressure after 20 weeks of gestation (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) plus proteinuria (> 0.3 g/24 hours). In clinical practice, we usually use the criteria of two elevated blood-pressure measurements 6 hours apart and two readings of 1+ proteinuria 6 hours apart.

This definition is intentionally permissive. Preeclampsia used to be diagnosed by the “30-15” rule: systolic pressure more than 30 mm Hg above baseline and diastolic pressure more than 15 mm Hg above baseline. That rule, however, is now discredited because it is too nonspecific. Similarly, facial edema may be impressive and was once considered a diagnostic criterion, but it is no longer regarded as one because it is too variable.

Preeclampsia can range from mild to severe. **Severe preeclampsia** is defined as any of the following:

- Markedly elevated blood pressure measurements (systolic ≥ 160 mm Hg or diastolic ≥ 110 mm Hg) taken at least 6 hours apart with the patient on bed rest
- Proteinuria (≥ 5 g/24 hours or $\geq 3+$ on two random samples 4 hours apart)

- Manifestations of end-organ disease: oliguria (< 500 mL in 24 hours), cerebral or visual disturbances, pulmonary edema, cyanosis, epigastric or right-upper-quadrant pain, impaired liver function, thrombocytopenia, or fetal growth restriction.

Eclampsia: Preeclampsia with seizures

Eclampsia is defined as the new onset of grand mal seizures in a woman with preeclampsia. These seizures do not occur as isolated events; they are part of the spectrum of severe preeclampsia.

Approximately one third of cases of eclampsia develop during pregnancy, one third during labor, and one third postpartum. If seizures occur more than 2 or 3 days after delivery, one should look for another cause, because eclampsia rarely develops so late.

Risk factors for preeclampsia

Several factors are associated with preeclampsia:

- First pregnancy (the most important risk factor)
- Multifetal gestation
- Preeclampsia in a previous pregnancy (especially if the onset was early and severe)
- Chronic hypertension
- Pregestational diabetes
- Nephropathy
- Vascular and connective tissue disorders (eg, lupus, lupus nephritis, antiphospholipid antibody syndrome)
- Obesity
- Age greater than 35 years
- African-American ethnicity (inconsistent finding).

Causes of preeclampsia:

An immunologic role?

Preeclampsia occurs only in humans. Without animal models, the underlying cause remains unknown despite decades of investigation. The most popular theory is immunologic.

During a normal pregnancy, fetal syncytial trophoblasts penetrate and remodel maternal spiral arteries, causing them to dilate into large, flaccid vessels. This remodeling accommodates the vast, increased maternal circulation needed for adequate placental perfusion.

Criteria for diagnosing preeclampsia are intentionally permissive

This remodeling is somehow prevented in preeclamptic pregnancies: the placenta is unable to properly burrow into the maternal blood vessels, leading to intrauterine growth restriction and other fetal manifestations of the disorder.

Investigators speculate that this incomplete placentation is due to maternal immunologic intolerance of foreign fetal genes. Evidence in support of this theory is that the risk of preeclampsia is highest in a first pregnancy and decreases with the length of time a woman has lived with the father before becoming pregnant. Furthermore, risk is also increased in multiparous women who are pregnant by a new partner.

Pathophysiology of preeclampsia: Vasospasm, endothelial injury, coagulopathy

The underlying pathophysiologic processes in preeclampsia are global vasospasm, endothelial injury, and coagulopathy. Intense vasospasm occurs in the microcirculation and leads to tissue hypoxia and eventually end-organ injury. The vasospasm is probably due to an imbalance between vasodilators (eg, prostacyclin and nitric oxide) and vasoconstrictors (eg, thromboxane A_2).

The expression of the syndrome is variable. Some women present with mild hypertension, edema of the face and hands, and new-onset proteinuria; others present with decreased fetal movement or intrauterine demise. Still others present with eclampsia. For this reason, overdiagnosis of the condition is appropriate.

Vascular changes. Intense vasospasm results in hypertension, capillary leak, hemoconcentration, and a collapsed intravascular space as fluid escapes from the vessels to the interstitial spaces.

Gant et al,³ in a classic study, infused angiotensin II into women during their first pregnancy. As early as 14 weeks of gestation, blood vessels in those who later developed preeclampsia demonstrated increased tone and a propensity to spasm, showing that the pathophysiology existed for months before clinical hypertension developed.

Hematologic changes include:

- Thrombocytopenia—platelets are dra-

matically reduced, probably consumed by endothelial injury. Counts can be as low as 20 to $50 \times 10^9/L$.

- Hemoconcentration—doctors used to follow preeclampsia with serial hematocrits.
- Microangiopathic hemolysis—eventually, red cells are sheared through the microcirculation.

Hepatic changes are usually limited to hepatocellular necrosis, demonstrated by elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Occasionally there is subcapsular hemorrhage and even hepatic rupture, which has a 60% maternal mortality rate.

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) used to be classified as a separate syndrome, but current thinking categorizes it as a manifestation of preeclampsia, occurring in about 20% of severe cases. It is associated with significant maternal and perinatal morbidity.

Neurologic changes are common and include headache, blurred vision, scotoma (seeing spots or “snow”), hyperreflexia, and rarely, cortical blindness, and the generalized seizures of eclampsia.

Renal changes. Glomerular endotheliosis is the pathognomonic lesion of preeclampsia: the glomeruli are enlarged, distorted, and filled with occlusions, with hypertrophy of the intracapillary cells. Laboratory testing shows a decreased glomerular filtration rate, decreased renal blood flow (the former more than the latter), and nonselective proteinuria (ie, all proteins including albumin; what a urine dip stick detects).

Fetal changes. Intrauterine growth restriction is very common. Oligohydramnios also occurs, because the amniotic fluid is essentially fetal urine; with poor perfusion through the placenta, the fetus has diminished urine output. Intrauterine demise and placental abruption are not uncommon.

Doppler waveforms are typically abnormal, and antenatal testing suggests that the fetus is in jeopardy. We use the ratio of forward flow of blood in the umbilical artery during systole to that during diastole (the “umbilical artery S:D ratio”) to assess the degree of resistance to flow in the placenta. The higher the ratio, the less diastolic flow. The greater

Glomerular endotheliosis is a clear indicator of preeclampsia

the resistance to flow, the greater the peril to the fetus.

Physical findings vary

Preeclampsia affects individual patients differently and is associated with myriad signs, symptoms, and laboratory findings. Typical findings are manifestations of end-organ dysfunction and include:

- Hypertension and proteinuria
- Edema of the face and hands (swelling in the legs and feet is typical of all pregnant women)
- Rapid weight gain
- Headache
- Blurred vision
- Epigastric or right-upper-quadrant pain
- Decreased fetal movement.

Once preeclampsia is diagnosed, laboratory evaluation is aimed at searching for evidence of end-organ disease such as hemolysis, thrombocytopenia, hemoconcentration, and liver involvement. It includes:

- A complete blood cell count, including hematocrit, platelet count, and inspection of smear for schistocytes (red blood cell fragments)
- Blood urea nitrogen (BUN), creatinine, and uric acid
- ALT and AST.

Managing preeclampsia: Balancing maternal and fetal risk

Preeclampsia places both mother and fetus at risk. It is, however, a maternal disorder. The fundamental pathophysiology of vasospasm and global tissue hypoxia begins long before the clinical presentation *and will progress* as the pregnancy goes on. Delivery is always the best decision for the mother's health, but may not be for the fetus.

Therefore, the mainstay of treatment is early detection and managed delivery to minimize both maternal and fetal risks.

If the pregnancy is at term, the decision is easy: the baby should be delivered. If remote from term, the mother should be admitted for evaluation. She will need:

- Baseline and serial laboratory tests (complete blood cell count, BUN, creatinine, uric acid, ALT, AST)
- Ultrasonography to measure fetal growth

and amniotic fluid volume

- Antenatal testing (nonstress test or biophysical profile). The biophysical profile is an assessment of fetal well-being. Fetuses that are well oxygenated behave normally by twisting, squirming, flexing and extending extremities, and breathing. Fetuses that are hypoxic lie still, trying to conserve oxygen.
- A 24-hour urine collection for protein.

Outpatient management is appropriate only if one can be certain that the disease is progressing slowly. A patient with severe preeclampsia must be admitted at once to a skilled center where obstetric anesthesia is available in addition to advanced obstetric, nursing, and neonatal services.

Magnesium sulfate is still the drug of choice for preventing and arresting eclamptic seizures. Several large, multicenter, randomized, control trials have found it more effective than placebo, phenytoin,⁴ diazepam, and antihypertensive medications. It is safe for both the mother and the fetus.

Invasive hemodynamic monitoring may be required if a patient has oliguria or anuria despite fluid challenge, pulmonary edema, or refractory hypertension.

Intravenous hydration for oliguria must be given cautiously to avoid pulmonary edema. If there is no evidence of pulmonary edema, a trial of fluid resuscitation (500 mL over an hour) should be given. If the patient does not respond to two trials, central hemodynamic monitoring by pulmonary capillary wedge pressure should be obtained. (Monitoring central venous pressures is not helpful in preeclampsia—or in pregnancy in general.) Only if the wedge pressure is low should fluids be given.

Antihypertensive medications are used solely to prevent maternal morbidity and have no effect on disease progression or preventing eclampsia. Very high blood pressure should be managed: we usually treat women if the diastolic blood pressure is greater than 100 or 110 mm Hg. Medications must be given with caution: if blood pressure is lowered too fast, it can have a dramatic effect on uteroplacental perfusion and can cause an already compromised fetus to rapidly decompensate and become bradycardic.

The disease process in eclampsia begins early and will progress as pregnancy goes on



Preferred medications are hydralazine (5–10 mg intravenous bolus every 10–15 minutes), labetalol, nicardipine, and sodium nitroprusside. Sodium nitroprusside is best for bringing down blood pressure in a controlled manner, but it carries the risk of fetal cyanide toxicity if used for longer than 4 hours.

Diuretics are usually contraindicated because of the already collapsed intravascular volume. However, if the pulmonary capillary wedge pressure is high, diuretics are necessary.

Antenatal corticosteroids should be considered to accelerate not only lung maturation, but maturation in all organ systems. They also reduce the risk of intracerebral hemorrhage and necrotizing colitis. To derive benefit, one must wait 48 hours from the first injection until delivery, which may not be possible.

Tests to evaluate the fetus

Management must also include intensive antenatal surveillance. There are many tools available for this:

Fetal kick counts. The mother counts the baby's movements each day. There should be at least 10 kicks or turns in 4 hours.

The nonstress test, so-called because it is done when a woman is not in labor, consists of external fetal monitoring and correlating the fetal heart rate with fetal movements. It is inexpensive, is straightforward to interpret, and has a very high negative predictive value: one can be 97% certain that the fetus will still be alive in 1 week if fetal heart rate patterns are in the normal range. However, this is based on studies of pregnant women with a variety of disorders; the prognosis in preeclampsia is worse because the condition steadily deteriorates.

Ultrasonography helps to assess fluid volume and fetal growth and anatomy.

Fetuses that are “starved” because of poor placentation have certain characteristics in common: the head and brain tend to be spared and have a normal circumference because of preferential blood flow, but the abdominal circumference lags behind. The liver takes up about two thirds of the cross-sectional area of the abdomen: as the fetus starves, the liver shrinks as its glycogen stores are depleted. Therefore, a comparison of the

head circumference with the abdominal circumference shows an asymmetric growth pattern. The estimated fetal weight is low because the abdomen is also a large part of this value. In addition, the smaller abdominal circumference leads to a smaller estimated fetal weight than expected for a particular gestational age, or “intrauterine growth restriction.” This carries a high risk for intrauterine demise.

One can also see a lack of amniotic fluid, or anhydramnios. Even the bladder may be empty. The amniotic fluid index reflects the amount of fluid and is correlated with fetal outcome.⁵

Placental resistance to forward flow (from the fetus to the placenta) can be assessed by Doppler ultrasonography. The placenta is normally a low-resistance, high-flow vascular bed, allowing blood driven by the fetal circulation to easily flow forward through systole and diastole. With hypertension, placental senescence increases resistance to forward flow. There is forward flow in systole but substantially decreased forward flow in diastole. As the condition worsens, the ratio of forward flow in systole to that in diastole increases, and the point is reached when there is so much resistance to forward flow that blood moves forward in systole but backward during diastole. At this point, prompt delivery of the baby is required.

The biophysical profile assesses fetal behavior with ultrasound visualization. Normal, well-oxygenated fetuses are usually surrounded by ample amniotic fluid. They are active, moving around and showing breathing movements. In contrast, oxygen-deprived fetuses lie very still to conserve oxygen. The biophysical profile is a very reliable test at any point in time but also carries the caveat that conditions for the mother with preeclampsia can be expected to worsen daily. It is labor-intensive, sometimes requiring 30 minutes.

Amniocentesis to assess lung maturity can play a pivotal role in deciding whether to deliver the baby.

Labor and delivery in preeclampsia

Obstetric consultation is advised early in labor. Vaginal delivery is preferable to cesarean section, provided that time and fetal and mater-

Management must include intensive antenatal surveillance

nal well-being allow it. Hemorrhage is particularly dangerous because the mother is already volume-depleted intravascularly. Neuraxial (epidural or spinal) anesthesia is usually preferable to general anesthesia.

Resolution after delivery

Once the placenta is delivered, the disease rapidly improves. Large fluid shifts should occur immediately postpartum, and diuresis indicates that the syndrome is resolving. However, women with severe and early onset of disease may worsen before getting better.

The physiologic changes of preeclampsia are completely reversible after delivery. However, maternal morbidity caused by severe hypertension, hemorrhage, or anesthetic complications may be permanent.

■ CHRONIC HYPERTENSION IN PREGNANCY

Chronic hypertension is high blood pressure that either precedes pregnancy, is diagnosed within the first 20 weeks of pregnancy, or does not resolve by the 6-week postpartum check-up. Two categories of severity are recognized: mild (up to 179 mm Hg systolic and 109 mm Hg) and severe (≥ 180 systolic or 110 diastolic).

Chronic hypertension complicates about 5% of all pregnancies, and prevalence rates are increasing due to delayed childbearing.

Chronic hypertension accounts for a disproportionate amount of maternal and perinatal morbidity and mortality, mostly because of an increased risk of superimposed preeclampsia. There is an increased risk of prematurity, birth of infants who are small for their gestational age, intrauterine death, placental abruption, and cesarean delivery.

Complication rates are directly related to the severity and duration of elevated blood pressures. For instance, patients with severe hypertension in the first trimester have a greater than 50% risk of developing superimposed preeclampsia. If superimposed preeclampsia develops, the risk of prematurity is 100%, compared with 38% without preeclampsia. The risk of growth restriction is 78% vs 15% without preeclampsia, and overall perinatal mortality is 48% vs 0%. If proteinuria is found early in pregnancy, the odds ratio for prematurity is 3.1, and the odds ratio for growth restriction is 2.8.⁶

Women with hypertension who are considering pregnancy should be apprised of the risks.

Diagnosis a challenge after 20 weeks

Chronic hypertension is difficult to diagnose if blood pressure was never documented before pregnancy or during the first trimester. Both systolic and diastolic blood pressures are normally at their lowest levels during the second trimester of pregnancy. Hence, if a woman presents at 28 weeks with a diastolic pressure of 86 mm Hg, it is difficult to determine if her blood pressure is progressing towards gestational hypertension, or if in fact it is lower than her baseline level, due to the hemodynamic changes of pregnancy.

Most patients with chronic hypertension are already known to have essential primary hypertension. If a young patient with no known history of hypertension presents with severe hypertension, it may be appropriate to rule out secondary hypertension.

Baseline tests

It is prudent to order at least a 24-hour urine collection for total protein and baseline laboratory tests of renal function (BUN and creatinine). Depending on the duration and severity of hypertension, other baseline tests, including ALT, AST, and a complete blood cell count may be useful for comparison if preeclampsia develops later in pregnancy.

An ultrasound scan to date the pregnancy can also prove useful later and should be done as early as possible. At 8 weeks of gestation, the accuracy is plus or minus 3 days; by the third trimester there is tremendous variability in size, making dating the pregnancy more difficult. By the third trimester, the accuracy for dating is plus or minus 3 weeks.

Management of chronic hypertension

All hypertensive patients should undergo increased surveillance, serial laboratory tests throughout pregnancy, serial ultrasound scans to follow growth, and antenatal testing. The baby should be delivered vaginally if possible.

We have no known method to prevent preeclampsia in these high-risk patients. Many agents, including low-dose aspirin, calcium supplementation, and magnesium supplementation, have been tried in large, multi-

Ultrasonographic dating of the pregnancy should be done as early as possible



center randomized controlled trials without proof of benefit. Studies of vitamins A and C are ongoing.

Review antihypertensive medications

Medications should be reviewed when pregnancy is first diagnosed. We cannot recommend with certainty to either stop, start, or continue antihypertensive medications: evidence is mixed whether such actions improve outcome.

Methyldopa is the most studied of all antihypertensive medications and is generally the first choice in pregnancy because it has a limited effect on uteroplacental blood flow. Sometimes an alternative must be found because of elevated liver enzymes or complaints of headache.

Labetalol, a combined alpha-blocker and beta-blocker, is the first alternative to methyldopa and is becoming a first-line choice as experience with the drug during pregnancy increases. It is generally well tolerated and has an easier (twice-a-day) dosing schedule than methyldopa.

Calcium channel blockers, particularly nifedipine, are being used more frequently, probably because doctors have become familiar with their use to stop premature labor. They seem to be safe and effective, but evidence is sparse.

Diuretics have been used in pregnancy despite the theoretical risk of preventing normal blood volume expansion. Most studies have not found adverse pregnancy outcomes. Nonetheless, caution should be used in cases of impaired uteroplacental perfusion, such as preeclampsia or intrauterine growth restriction.

Atenolol and other pure beta-blockers should be avoided: they have been associated with babies born small for their gestational age.

Angiotensin-converting enzyme (ACE) inhibitors are contraindicated in the second and third trimester because they are associated with a myriad of congenital anomalies, including renal failure, oligohydramnios, renal dysgenesis, reduced ossification, pulmonary hypoplasia, and fetal and neonatal death. Patients presenting in the first trimester on an ACE inhibitor should either be taken off antihypertensive medications or switched to another agent. Exposure during

TABLE 1

Risks for pregnant women with chronic hypertension

COMPLICATION	IF NO PREECLAMPSIA	IF PREECLAMPSIA DEVELOPS
Prematurity	38%	100%
Small for gestational age	15%	78%
Perinatal mortality	< 1%	48%

this time is not an indication for pregnancy termination, however.

Angiotensin II receptor antagonists are considered guilty by association because of their similarity to ACE inhibitors, but there are no data to confirm this.

■ PREECLAMPSIA SUPERIMPOSED ON CHRONIC HYPERTENSION

Preeclampsia superimposed on chronic hypertension is defined as any of the following in a woman with chronic hypertension diagnosed before 20 weeks of gestation:

- New-onset proteinuria
- Sudden increase in baseline proteinuria
- Sudden worsening of hypertension.

Women with severe hypertension in the first trimester have a 50% chance of developing preeclampsia.⁷ This significantly increases the risk of an already high-risk pregnancy (TABLE 1).

Women with preeclampsia superimposed on chronic hypertension are also more likely to progress very rapidly from mild to severe disease. These women must be carefully watched, as this can happen within days or even hours.

■ POSTPARTUM COUNSELING

The likelihood that preeclampsia will recur in future pregnancies depends on the onset and severity of the syndrome. Mild preeclampsia diagnosed after 36 weeks has a low recurrence rate. At the other extreme, the risk is 40% for women with severe disease diagnosed before 30 weeks of gestation. The risk is lower for a woman who develops preeclampsia in her first pregnancy than for a woman who develops it in a later pregnancy, and the risk is intermediate

Methyldopa is generally the first choice in hypertension during pregnancy



for a woman who has had children before but develops preeclampsia after becoming pregnant with a new partner.

The recurrence risk for the HELLP syndrome is 5%.

A woman with early and severe preeclampsia should be evaluated after pregnancy for an underlying metabolic disorder, such as the factor V Leiden mutation, antiphospholipid antibody syndrome, hyperhomocysteinemia, or protein S deficiency.

Long-term prognosis

The risk for essential hypertension later in life is increased for women who develop:

- Preeclampsia for the first time after multiple pregnancies

- Early-onset and severe preeclampsia
- Gestational hypertension
- Preeclampsia in the first pregnancy, followed by gestational hypertension, chronic hypertension, or preeclampsia in the second pregnancy.

Preeclampsia is not associated with later cardiovascular disease. In a classic study, Chesley et al⁸ followed a large cohort of women for over 20 years and found no difference in later-life hypertension rates and overall mortality between women who had eclampsia and women who did not. However, women who had eclampsia in subsequent pregnancies fared worse, which may indicate they had an underlying cardiovascular disorder.

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