

Managing Hypertensive Disorders in Pregnancy

An internist's perspective

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The diagnosis and management of hypertension in pregnancy require a basic knowledge of the physiologic changes occurring in pregnancy and the relative risks and benefits of various management strategies. Primary care clinicians are in a unique position to counsel patients with hypertension before they become pregnant and to provide long-term follow-up to women who develop hypertension in pregnancy. They are also an integral component of the multidisciplinary team necessary for the optimal management of these patients.

This article will discuss the normal changes in blood pressure that occur during pregnancy and what changes may be abnormal. It will also provide diagnostic guidelines and treatment options for chronic hypertension in pregnancy and preeclampsia.

PHYSIOLOGIC CHANGES IN PREGNANCY

Blood pressure falls early in pregnancy because of a marked reduction in systemic vascular resistance. The average fall is 9 mm Hg systolic and 17 mm Hg diastolic; it reaches a nadir at 16 to 20 weeks. Chronic hypertension may thus be masked in early pregnancy. During the third trimester, blood pressure slowly rises until, by the end of the pregnancy, it reaches

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ABSTRACT: The goals for managing hypertension in pregnant women differ from those in the general population—the emphasis during pregnancy is on preventing acute complications and avoiding fetal compromise. Many women with mild-to-moderate chronic hypertension may not require medication during pregnancy, but severe hypertension should be treated with an antihypertensive drug that is safe for both mother and fetus. Preeclampsia may develop in normotensive women, or it may be superimposed on chronic hypertension. Symptoms or signs suggestive of preeclampsia require prompt evaluation and notification of the obstetrician. (*Women Health Primary Care* 1999;2(7):559-568)

pre-pregnancy levels.

At the same time, pregnancy increases blood volume and the glomerular filtration rate, resulting in reduced serum levels of creatinine (the normal range in pregnancy is 0.3 to 0.8 mg/dL or 27 to 71 μmol/L) and uric acid (the

upper limit of normal in pregnancy is 4.5 mg/dL or 0.27 mmol/L). Therefore, levels considered normal in non-pregnant women may reflect renal impairment in pregnant women.

Increased renal excretion of protein may also be seen in pregnancy because of changes in tubular function and the increase in the glomerular filtration rate. Urinary protein excretion is not considered abnormal until it exceeds 300 mg in 24 hours.

BLOOD PRESSURE MEASUREMENT

Office measurement: When the blood pressure of a pregnant woman is taken, she should be sitting with her arm at the level of her heart, and an appropriately sized cuff should be used. The supine position should be avoided for two reasons:

- ◆ Vena caval compression by the gravid uterus may cause a fall in the systolic pressure from reduced venous return.
- ◆ Aortic compression may mimic coarctation of the aorta, with elevation of upper limb blood pressure.

As with nonpregnant patients, it is important to confirm high readings on two occasions.

Use of Korotkoff phase V (the absence of sounds)

in determining diastolic blood pressure is considered most accurate. In cases in which the sounds are audible at very low levels, it is recommended that both Korotkoff phase IV (muffling of sounds) and Korotkoff phase V be recorded.

Ambulatory measurement: Ambulatory blood pressure monitoring provides a better estimate of blood pressure variability and of actual blood pressure levels throughout the day than does office blood

Ambulatory blood pressure monitoring may also be helpful in optimizing the timing and dosage of antihypertensive therapy. Whether the advantages of ambulatory blood pressure monitoring have any clinical relevance in pregnancy is not yet clear.

DEFINITIONS

One of the major difficulties in reading the literature about hypertension in pregnancy is the lack

tional High Blood Pressure Education Program Working Group.³ This practical and concise scheme classifies all hypertension occurring in pregnancy into one of four categories: chronic hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, and transient hypertension.

Chronic hypertension is defined as elevated blood pressure diagnosed before pregnancy, before 20 weeks' gestation, or during pregnancy if it persists longer than 6 weeks after delivery. Guidelines for the treatment of chronic hypertension are listed in Table 1.

Preeclampsia is a condition unique to pregnancy, typically occurring after 20 weeks' gestation and characterized by hypertension, proteinuria, and edema. The hypertension is defined as a blood pressure greater than 140/90 mm Hg, and proteinuria is defined as more than 300 mg of protein in a 24-hour urine collection.

Preeclampsia superimposed on chronic hypertension is a diagnosis that is often difficult to make, but the distinction is critical: Management and risks to mother and fetus are very different from those associated with chronic hypertension alone. Elevation of blood pressure cannot be used as the sole criterion for superimposed preeclampsia, because blood pressure normally rises toward the end of pregnancy. Other evidence, such as new-onset proteinuria, hyperuricemia, thrombocytopenia, or elevated liver enzyme levels, is required to support the diagnosis of preeclampsia superimposed on chronic hypertension.

Transient hypertension is a diagnosis that is made retrospectively. It is the development of hypertension during pregnancy or in the first 24 hours postpartum, without evidence of preeclampsia or underlying chronic hypertension. Because preeclampsia may initially be nonproteinuric, and because

pressure measurement alone, and it has particular value in diagnosing "white coat" hypertension. Several monitors have now been assessed for use in pregnancy, such as SpaceLabs' 90207 (SpaceLabs Medical Inc, Redmond, Washington) and A & D's TM-2420 (A & D Co, Ltd, Tokyo, Japan) monitors.¹

of common terminology. Various terms have been used, including preeclampsia, pregnancy-induced hypertension, and gestational hypertension. The classification scheme most widely used was proposed by the American College of Obstetricians and Gynecologists in 1972² and endorsed in 1990 by the Na-

Table 1. Managing chronic hypertension before and during pregnancy

1. Discuss pregnancy before conception. If the patient is planning to become pregnant in the near future, assess her antihypertensive regimen and switch her medication to a "safer" drug if the one she is taking is not optimal. If it has not been done previously, assess the patient for secondary causes of hypertension. Obtain baseline "preeclampsia" laboratory measurements (complete blood cell count; urinalysis; serum levels of uric acid, creatinine, and aspartate aminotransferase; and 24-hour urinary protein excretion).
2. Once pregnancy is confirmed, consider stopping the antihypertensive medication if the patient's blood pressure is likely to remain below 160/100 mm Hg. Check blood pressure at least monthly.
3. Blood pressure decreases early in pregnancy, reaching a nadir at 16 to 20 weeks. Tell the patient to call you if she has any lightheadedness or presyncope, and adjust medications as appropriate.
4. After 20 weeks, watch for preeclampsia. Instruct the patient to call you or her obstetrician if she has headaches, visual changes, rapid weight gain, or epigastric discomfort.
5. Expect the blood pressure to begin rising toward baseline in the third trimester. If the blood pressure is elevated towards the end of a dosing interval, consider increasing the frequency of dosing. Many drugs have increased clearance and a greater volume of distribution during pregnancy and may require more frequent dosing.
6. If the patient has any signs or symptoms of preeclampsia, perform appropriate laboratory tests (complete blood cell count; measurements of serum creatinine, uric acid, and aspartate aminotransferase levels; urinalysis with or without 24-hour urinary protein excretion) and contact her obstetrician. Consider admission to hospital if indicated by test results.
7. After delivery, the patient can usually be given her pre-pregnancy antihypertensive medication. Most antihypertensive drugs are compatible with breast-feeding.

chronic hypertension may be masked by the normal decrement in blood pressure that occurs in the first and second trimesters, transient hypertension is a diagnosis of exclusion. Until the diagnosis becomes clear, patients with this disorder should be assumed to have preeclampsia, given the increased risks associated with that condition. Transient hypertension often recurs in subsequent pregnancies and may be a predictor for the later development of chronic hypertension.

CHRONIC HYPERTENSION

Between 1% and 5% of all pregnancies occur in women with chronic hypertension. Most women with mild-to-moderate hypertension can expect favorable pregnancy outcomes. However, there is an increased risk of superimposed preeclampsia. When a woman with chronic hypertension becomes pregnant, useful baseline studies include measurements of urinary protein excretion and serum levels of uric acid, creatinine, platelets, and liver enzymes.

SECONDARY CAUSES

If there has been no prior evaluation for any secondary causes of hypertension (such as renal vascular disease, Cushing's disease, or coarctation of the aorta), one should be performed. A few secondary causes deserve special comment, because they are affected by or have an impact on pregnancy.

Pheochromocytoma is a rare cause of hypertension that, if left untreated, carries a significant risk of maternal mortality during labor and delivery. Therefore, any suspicion of it raised by the history or the physical examination should prompt evaluation with a 24-hour urine test for metanephrines.

Renal parenchymal disease also increases the risks associated with pregnancy. Women with mild renal insufficiency (serum creatinine lev-

el below 1.5 mg/dL or 133 μ mol/L) usually have good pregnancy outcomes. However, those who have moderate-to-severe disease face a number of additional risks, including a greater risk of superimposed preeclampsia, worsening of maternal renal function, and increased perinatal morbidity and mortality. Women with severe renal insufficiency (serum creatinine level above 3 mg/dL or 265 μ mol/L) are at particularly high risk.

Because gestation lasts only 40 weeks and most adverse effects of hypertension develop over years, the emphasis during pregnancy is on the prevention of short-term rather than long-term complications. In addition, any strategies taken need to avoid compromising fetal well-being.

There is no definite evidence that treating mild-to-moderate hypertension (systolic blood pressure below 160 mm Hg and diastolic

There is no definite evidence that treating mild-to-moderate chronic hypertension (systolic blood pressure below 160 mm Hg and diastolic blood pressure below 100 mm Hg) in pregnancy provides benefit to the mother or fetus.

Coarctation of the aorta is a rare cause of hypertension that carries an increased risk of aortic dissection and rupture during pregnancy. It can be diagnosed by checking for a radial-femoral pulse delay.

Hyperaldosteronism is one cause of hypertension that often improves during pregnancy because of the high progesterone levels. The increased progesterone levels may result in normalization of the hypertension and hypokalemia associated with this condition. Hyperaldosteronism (as well as postpartum preeclampsia) should be considered when a woman who was normotensive during pregnancy presents with hypertension after delivery.

MANAGEMENT

The goals for managing hypertension in pregnant women differ from those in the general population.

blood pressure below 100 mm Hg) in pregnancy provides benefit to the mother or fetus. When blood pressure is above this level, treatment should be instituted to prevent both maternal hypertensive vascular damage and placental abruption (the risk of which may be increased). It should be noted that the treatment of chronic hypertension has not been shown to protect against the development of preeclampsia.⁴

Nonpharmacologic treatment: Close supervision of the hypertensive mother is the mainstay of therapy. Nonpharmacologic strategies that are used in nonpregnant patients, such as salt restriction (which may further compromise an already reduced intravascular volume), are not recommended. Restriction of activity may be effective in lowering blood pressure in patients with mild-to-moderate hypertension, thereby avoiding the

Table 2. Pharmacologic treatment of hypertension in pregnancy

Agent	Dosage	Comments
1st-line drug		
Methyldopa	250 mg bid – 1 g tid	Agent of choice. Only drug with long-term follow-up of children that shows normal mental and physical development at 10 years. Major side effect is somnolence. Use with caution in patients with depression. Compatible with breast-feeding.
2nd-line drugs		
Labetalol	100 mg bid – 500 mg tid	Use if methyldopa is not tolerated or not effective. Long record of use in pregnancy, but there is not as much data on long-term safety as there is for methyldopa. Short-term safety is equal to that of methyldopa. Compatible with breast-feeding.
β-blockers	Varies with agent	Pindolol and oxprenolol are the preferred agents. There is concern regarding possible intrauterine growth restriction. Many β-blockers are compatible with breast-feeding; check specific agent.
Nifedipine (slow-release)	30 mg qd – 60 mg bid	Limited experience with use throughout pregnancy. Use as a tocolytic agent in third trimester produces no ill effects. Compatible with breast-feeding.
3rd-line drugs		
Hydralazine ¹³	25 mg tid – 75 mg qid	Extensive experience with use in pregnancy. Because it can cause reflex tachycardia, hydralazine has limited effectiveness as a single agent, but it is a good choice if a second drug is required. Compatible with breast-feeding.
Clonidine	0.05 mg bid – 0.4 mg bid	As effective as methyldopa, but follow-up studies have associated this drug with night terrors in children. Concentrated in breast milk. No hypotension observed in infants, but other effects are not known.
Special indications		
Diuretics	Varies with agent	There is concern related to reduction in normal pregnancy-associated volume expansion. Not for routine use, but may be indicated in patients with renal or cardiac disease. Hydrochlorothiazide and chlorthalidone are compatible with breast-feeding.
Drugs to avoid		
Angiotensin-converting enzyme inhibitors	Varies with agent	Contraindicated except in extreme circumstances (eg, scleroderma crisis) because of their association with stillbirth and renal failure in exposed fetuses. Not teratogenic; therefore, first trimester exposure is not associated with adverse fetal effects. Captopril and enalapril are compatible with breast-feeding.
Angiotensin II receptor antagonists	Varies with agent	Experience with angiotensin II receptor antagonists in pregnancy is limited, but they are likely to have effects similar those of the angiotensin-converting enzyme inhibitors.

need for pharmacologic therapy. As noted earlier, ambulatory blood pressure monitoring may be useful in differentiating true hypertension from “white coat” hypertension. Use of alcohol and tobacco should be discouraged in any pregnant woman.

Pharmacologic treatment: When a patient with pharmacologically treated chronic hypertension presents early in pregnancy, her clinician has three options. The first is to stop her medication and follow her closely. Many women with mild-to-moderate hypertension may not require medication during pregnancy because of the physiologic drop in blood pressure and the revised goals for treatment. If the patient has severe hypertension, however, this strategy is likely to fail and is not advisable.

The second option is to change her medication to methyldopa or another drug that is acceptable for use in pregnancy. Although most women tolerate methyldopa well, some women may experience side effects that require the use of an alternative agent.⁵ The third alternative is to have the patient continue to use her current medication, if it has not been shown to affect fetal well-being.

Table 2 summarizes the drugs available for treatment of hypertension in pregnancy. Information

about the use of these drugs during breast-feeding is included in the table, but for more details, the reader is referred to Briggs et al⁶ and the recommendations of the Committee on Drugs of the American Academy of Pediatrics.⁷

PREECLAMPSIA

A major cause of maternal and fetal morbidity, preeclampsia occurs in 5% to 10% of primigravid women. The cause of preeclampsia is not known, but most research indicates that genetic, immunologic, and placental factors contribute.

The development of clinical disease is related to widespread endothelial cell dysfunction. This dysfunction results in the dysregulation of vasomotor hormone release, with resultant vasospasm and hypertension, increased vascular permeability, and activation of the coagulation system.

RISK FACTORS

In comparison to parous women, primigravid women face a well-established 6- to 15-fold increased risk of preeclampsia. Most investigators have found, however, that the protective effect of previous pregnancies is lost when there is a change in partner.

The risk of preeclampsia is also increased in women with chronic hypertension, renal disease, dia-

betes, or a family or personal history of preeclampsia—particularly early-onset preeclampsia. In addition, pregnancies associated with increased placental mass (such as may occur when multiple gestation or hydatidiform mole is present) have a higher risk of preeclampsia.

DIAGNOSIS

When diagnosing preeclampsia, primary care providers should be aware of its presenting features, obtain appropriate laboratory testing when it is indicated, and refer possible cases to an obstetrician for evaluation.

Preeclampsia may become clinically apparent at any time after 20 weeks’ gestation. Symptoms of preeclampsia include migrainous headache or visual phenomena, epigastric pain, and rapid weight gain. Signs of preeclampsia include hypertension (blood pressure above 140/90 mm Hg), right upper quadrant tenderness, hyperreflexia, and edema; however, the latter is an unreliable sign that is common in normal pregnancy.

Ideally, there should be documentation of the patient’s normal pre-pregnancy blood pressure. If a record of pre-pregnancy blood pressure is not available, elevated blood pressures require careful interpretation, and it may be necessary to rely on other indicators

Table 3. Acute treatment of severe hypertension in pregnancy

Agent	Dosage	Comments
Hydralazine ¹³	5 mg IV bolus, then 5 – 10 mg every 20 – 30 minutes	May cause tachycardia and headache. Onset of action is 10 minutes; half-life is 1 hour.
Labetalol	10 mg IV bolus, then 10 – 80 mg every 10 minutes (up to 300 mg)	Onset of action is 5 – 10 minutes; half-life is 5 hours.
Nifedipine (short-acting)	10 mg PO (chew and swallow)	Use cautiously; can cause a precipitous drop in pressure, particularly when used in combination with magnesium. Onset of action is 30 minutes; half-life is 2 hours.
Diazoxide	50 mg every 5 – 10 minutes until desired effect is achieved	Associated with arrest of labor and maternal and neonatal hyperglycemia. Onset of action is 2 – 5 minutes; half-life is 20 – 60 hours.

of preeclampsia.

Proteinuria is an important feature of preeclampsia. When preeclampsia is suspected, a 24-hour urine collection is the most reliable way of determining the presence of proteinuria.

Hyperuricemia is an important sign that is often found in women with preeclampsia but usually not in patients with chronic hypertension. It reflects impaired renal tubular function, precedes proteinuria and rising serum creatinine levels, and has been correlated with fetal outcome.⁸

A subtype of preeclampsia called the *HELLP syndrome* (hemolysis, elevated liver enzymes, and low platelets) is characterized by coagulation disturbances and hepatic dysfunction. Any pregnant patient presenting with discomfort in the epigastrium or right upper quadrant and malaise should be evaluated for the HELLP syndrome. The work-up should include a complete blood cell count, platelet measurement, and liver function tests.

COMPLICATIONS

Life-threatening complications of preeclampsia include pulmonary edema, acute renal failure, hepatic rupture, convulsions, cerebral hemorrhage, and abruptio placentae. Disseminated intravascular coagulation may occur as a result of placental abruption or secondary to preeclampsia itself. Risks to the fetus include growth retardation, prematurity, hypoxemia, acidosis, and death.

MANAGEMENT

There is currently no well-established prophylactic treatment for preeclampsia. Low-dose acetylsalicylic acid is not effective in the prevention of preeclampsia,⁹ even in women at high risk.¹⁰

Early diagnosis, close observation, and careful timing of delivery are important in the management

Hypertensive Disorders in Pregnancy

PRIMARY POINTS

Blood pressure begins to fall early in pregnancy, reaching a nadir at 16 to 20 weeks and rising to pre-pregnancy levels by term.

Hypertension occurring in pregnancy can be divided into four categories: chronic hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, and transient hypertension.

Given the physiologic drop in blood pressure early in pregnancy, women with mild-to-moderate chronic hypertension may not require antihypertensive medication during pregnancy. Drug therapy is indicated for blood pressures greater than 160/100 mm Hg. Methyldopa is the agent of choice.

Patients with mild-to-moderate chronic hypertension can expect a good pregnancy outcome, whereas preeclampsia is associated with significant risk. Proteinuria, hyperuricemia, and thrombocytopenia may be useful markers of superimposed preeclampsia in patients with chronic hypertension.

The only cure for preeclampsia is delivery, but close surveillance and temporizing measures, such as blood pressure control and seizure prophylaxis, may be useful when delivery must be temporarily delayed because of fetal immaturity.

Most women with preeclampsia have no underlying medical conditions, but those with early-onset or recurrent preeclampsia have a higher incidence of renal, collagen vascular, or thrombotic disorders.

Any pregnant patient with discomfort in the epigastrium or right upper quadrant and malaise should be evaluated for the HELLP syndrome. The work-up should include a CBC, platelet measurement, and liver function tests.

Pregnancy may unmask latent hypertension, and those women who develop transient hypertension in pregnancy are at greater risk for chronic hypertension. Conversely, women who remain normotensive during their pregnancies are less likely to develop chronic hypertension than is the average person.

of preeclampsia. Because delivery is the only cure for severe preeclampsia, a delay in delivery should only occur because of uncertainty in the diagnosis or extreme prematurity of the fetus.

Fetal surveillance is also important in preeclampsia. This may include such modalities as ultrasonography, non-stress/stress testing, and biophysical profiles.

Nonpharmacologic treatment: Bed rest has been proposed to be of value in preeclampsia by maximizing uteroplacental blood flow, lowering blood pressure, and promoting diuresis. There is, however, no evidence that it improves pregnancy outcome.¹¹

Pharmacologic treatment: Drug therapy for preeclampsia is recommended when systolic blood pressure is greater than 169 mm Hg or diastolic pressure is greater than 109 mm Hg, to prevent intracerebral hemorrhage and encephalopathy. In the absence of evidence of target organ damage, treatment of lower blood pressure levels is controversial, because the effect on placental blood flow is not known and there is no evidence that treatment of mild preeclampsia decreases the frequency of adverse outcomes. Antihypertensive treatment options are summarized in Tables 2 and 3.

Anticonvulsant drugs are used to prevent and treat seizures in women with preeclampsia. Magnesium sulfate is more effective than is phenytoin.¹²

Important indicators of worsening preeclampsia that may indicate the necessity for delivery include headache, visual symptoms, abdominal pain, pulmonary edema, deteriorating renal and hepatic functioning, and falling platelet counts. Physical findings may include hyperreflexia, epigastric or hepatic tenderness, and retinal


arteriolar vasospasm.

Vaginal delivery is the preferred mode of delivery. When the gestational age is less than 34 weeks and the mother is stable, delivery should be delayed by 24 to 48 hours, if possible, to allow for glucocorticoid administration. This should decrease the risk of intracranial hemorrhage and accelerate fetal lung maturity.

FOLLOW-UP AND PROGNOSIS

The vast majority of women with preeclampsia have no underlying medical problems and are not at increased risk of subsequent medical morbidity. However, the incidence of underlying thrombophilia, collagen vascular disease, or renal disease is increased in women with severe preeclampsia that develops before 34 weeks' gestation.

In women with recurrent preeclampsia, careful follow-up postpartum to ensure that blood pressure and all laboratory test results (including measurements of serum creatinine, blood urea nitrogen, and 24-hour urinary protein excretion) have normalized is important to confirm the absence of underlying chronic hypertension or renal disease. Investigation for a thrombophilia should be considered in women with severe, early, or recurrent preeclampsia.

Most women who develop preeclampsia during pregnancy are at no greater risk for chronic hypertension than are other women. However, the incidence of chronic hypertension is increased among women with early-onset or recurrent preeclampsia and in all African-American women; these women need long-term follow-up. Women with transient hypertension are also at greater risk for chronic hypertension, which may suggest that latent hypertension is unmasked by pregnancy. 

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