

Hypertension in pregnancy

Tailoring treatment to risk



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Not all hypertensive gravidas should receive drug therapy. In fact, antihypertensive medications should be halted in some patients. Here, 2 experts present a comprehensive plan for high- and low-risk women.

The decision to use antihypertensive drug therapy in pregnant women is a tricky one—especially considering the ever-evolving nature of treatment. For instance, we now know that in some hypertensive gravidas, medical interventions may actually be deleterious.

With the aging of the obstetric population in the United States, hypertension in pregnancy—which currently affects 7% of gesta-

tions—will remain a major issue in preconception and prenatal care. Its reported risks, which include stroke, pulmonary edema, and death, underscore the importance of careful management (TABLE 1).

This article describes the indications for antihypertensive therapy in pregnancy, focusing on 2 basic categories—high-risk and low-risk patients—and offers guidance in choosing the optimal agent for each patient.

Correct classification helps direct management

First, identify chronic hypertension.

Chronic hypertension is defined as an elevation in blood pressure (BP) that exists prior to pregnancy. Unfortunately, because the pregestational BP is not always known, the diagnosis in many cases must be made on the basis of specific levels: systolic BP of at least 140 mm Hg or diastolic BP of at least 90 mm Hg on at least 2 occasions at least 4 hours apart prior to 20 weeks' gestation.¹

Even with these guidelines, however, diagnosis may be difficult, since early manifestations of preeclampsia can include hypertension prior to 20 weeks' gestation.^{2,3} In addition, the physiologic decrease in BP during the first and second trimesters—seen in many patients with chronic hypertension—may obscure the condition early in gestation and lead to the erroneous diagnosis of gestational hypertension or preeclampsia later in pregnancy.^{4,6}

Once a diagnosis of chronic hypertension is made, an accurate classification of the disease will help guide management and initiation of antihypertensive medication.

Mild versus severe hypertension. In pregnancy, chronic hypertension is classified as mild or severe. Mild hypertension has traditionally been defined as systolic BP less than 160 mm Hg and diastolic blood pressure less than 110 mm Hg.^{1,7} However, the American College of Obstetricians and Gynecologists recently changed its definition of mild hypertension to systolic BP less than 180 mm Hg.^{8,9} Most women with chronic hypertension in pregnancy have the mild form of the disease.

Low-risk hypertension. Patients with uncomplicated chronic mild hypertension are at low risk.

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TABLE 1

Maternal risks of severe hypertension in pregnancy

Stroke
Cerebral hemorrhage
Hypertensive encephalopathy
Congestive heart failure/pulmonary edema
Acute renal dysfunction/acute renal failure
Abruptio placentae
Disseminated intravascular coagulopathy
Death

High-risk hypertension. Patients at high risk have either chronic severe hypertension or chronic mild hypertension in association with any of the complicating factors listed in TABLE 2.

History and laboratory studies. To properly classify the disease when first evaluating a patient with chronic hypertension, a thorough history is essential. Ask about related medical illnesses as well as target organ damage. Pay special attention to cardiac, renal, thyroid, and cerebrovascular disease, as well as diabetes. The outcomes of prior pregnancies also are important, espe-

KEY POINTS

- The treatment goal is to reduce blood pressure to a safe level to prevent maternal cerebral complications. This goal must be weighed against the risks of fetal exposure to antihypertensive drugs and the effects on uteroplacental blood flow.
- Gravidas with uncomplicated mild hypertension are at low risk; however, those with severe hypertension or associated complicating factors are at high risk of complications and adverse outcomes.
- Antihypertensive medications should not be used routinely in low-risk patients.
- Women with high-risk chronic hypertension are at risk for postpartum complications such as pulmonary edema, hypertensive encephalopathy, and renal failure.

TABLE 2

Criteria for low- versus high-risk chronic hypertension

LOW-RISK CHRONIC HYPERTENSION

Chronic mild hypertension (systolic blood pressure 140–160 mm Hg and diastolic blood pressure 90–110 mm Hg) **in the absence of complicating factors**

HIGH-RISK CHRONIC HYPERTENSION

Either:

Chronic severe hypertension (systolic blood pressure \geq 180 mm Hg and diastolic blood pressure \geq 110 mm Hg)

or

Chronic mild hypertension (systolic blood pressure 140–160 mm Hg and diastolic blood pressure 90–110 mm Hg) **in association with any of the following:**

- Hypertension for >4 years
- Maternal age >40 years
- Renal disease
- Cardiomyopathy
- Coarctation of the aorta
- Retinopathy
- Diabetes (classes B to F)
- Collagen vascular disease
- Antiphospholipid antibody syndrome with perinatal loss
- Previous severe preeclampsia with perinatal death

Overall, regardless of the treatment, perinatal mortality is not improved with antihypertensive medications for mild hypertension.

cially complications such as abruptio placentae, preeclampsia, preterm delivery, growth restriction, fetal death, and neonatal complications.

Finally, laboratory evaluation should include urine analysis, urine culture, 24-hour urine protein, electrolytes, complete blood count, and glucose tolerance testing.

Other key examinations. In women with long-standing disease, ophthalmologic evaluation, electrocardiography, echocardiogra-

phy, and assessment of creatinine clearance may be indicated.

Objective of treatment:

Prevent complications

In the nonpregnant state, the aim of hypertensive management is to prevent long-term vascular complications such as stroke and cardiovascular disease.¹⁰ A reasonable treatment goal for patients with mild to moderate hypertension may be benefits that are apparent after 5 years of therapy¹⁰—an acceptable time frame due to the long-term nature of the disease.

In pregnant women, however, the duration of the condition (pregnant and hypertensive) is finite and relatively short; as a result, maternal health benefits may not be clear. For that reason, the objective is to reduce BP to a safe level to prevent maternal cerebral complications (systolic BP below 160 mm Hg and diastolic BP below 110 mm Hg). Of course, these short-term maternal benefits must be weighed against the potential risks of fetal exposure (TABLE 3).^{11,12}

Low-risk disease: Avoid routine antihypertensive therapy

A limited number of randomized trials have studied the effectiveness of antihypertensive treatment in preventing adverse maternal outcomes such as superimposed preeclampsia and abruptio placentae. Here are 2 key findings:

• No demonstrable maternal benefit.

Overall, there appears to be no clear benefit of antihypertensive treatment in women with mild hypertension. Indeed, the 2 largest studies had contradictory findings regarding preeclampsia,^{6,13} and there was no demonstrable benefit in regard to abruptio placentae.

• Antihypertensive drugs may adversely affect fetal growth.

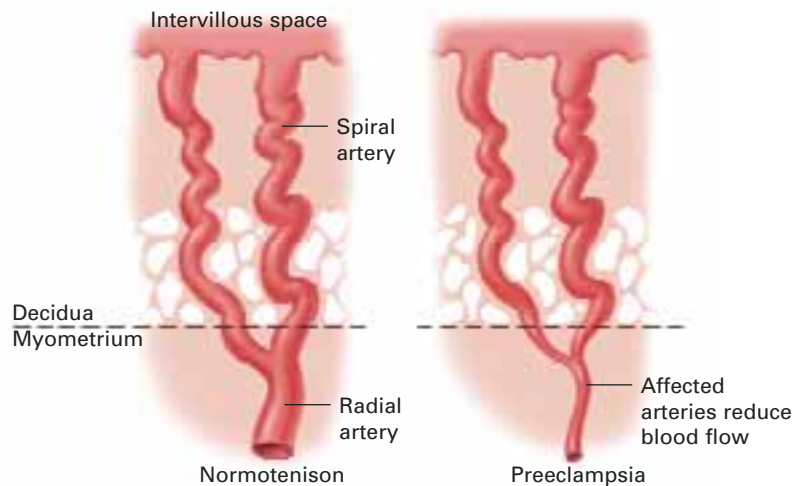
A recent meta-analysis examining antihypertensive medications in patients with mild to moderate hypertension investigated the relationship between a fall in

mean arterial blood pressure and the delivery of small-for-gestational-age (SGA) infants.¹⁴ The authors concluded that antihypertensive medications induce BP drops that may adversely affect fetal growth (see FIGURE). Prior to this observation, prospective studies had shown no association between antihypertensive medications and SGA infants. (The only exception was atenolol; 3 separate studies found a relationship between treatment with atenolol and low birth weight.¹⁵⁻¹⁷)

Overall, maternal and perinatal data indicate that, regardless of the treatment, perinatal mortality is not improved with antihypertensive medications for mild hypertension. In fact, the indiscriminate use of such medications may have deleterious effects. Consequently, antihypertensive medications should not be used routinely in low-risk patients.^{18,19}

Clinical care. When a woman with low-risk hypertension presents for prenatal care, it is our policy to discontinue antihypertensive medications at the first prenatal visit. Although many women will not require antihypertensive treatment during the pregnancy, careful management remains essential, as such patients can become high-risk at any time. Therapy should be initiated if her condition changes to severe hypertension (systolic BP of 180 mm Hg or more, or a diastolic blood pressure of 110 mm Hg or more).⁸

Low-risk women should be monitored closely for evidence of preeclampsia and fetal growth restriction. Thus, they should have a baseline ultrasound at 16 to 20 weeks' gestation, with serial monthly ultra-

FIGURE**Placental effects of hypertension**

In hypertensive gravidas, placental blood flow is reduced—particularly in cases of preeclampsia. Antihypertensive therapy in low-risk women may induce blood pressure drops that further compromise fetal growth.

TABLE 3**Rates of adverse pregnancy outcomes among patients with mild and severe chronic hypertension**

OUTCOME	MILD HYPERTENSION (%)	SEVERE HYPERTENSION (%)
Preeclampsia	10-25	25-50
Abruptio placentae	0.7-1.5	2-5
Fetal growth restriction	8.0-15.5	10-20
Preterm birth	12-34.4	25-30

sounds beginning at 30 to 32 weeks to follow fetal growth. Nonstress testing or biophysical profiles are indicated in the presence of severe hypertension, preeclampsia, or abnormal fetal growth.

Patients with uncomplicated low-risk hypertension may continue pregnancy until 40 weeks' gestation. However, beyond 37 weeks, the presence of complications such as severe hypertension, documented growth restriction, and superimposed preeclampsia are indications for hospitalization and delivery.

TABLE 4**Agents for treating chronic hypertension in pregnancy**

DRUG	STARTING DOSE	MAXIMUM DAILY DOSE	COMMON SIDE EFFECTS
Labetalol	100 mg every 8 h	1,200–2,400 mg	Headache Tremulousness
Thiazide diuretic	12.5 mg twice daily	50 mg	Hypokalemia
Nifedipine Short acting	10 mg every 8 h	120 mg	Hypotension Headache Tachycardia
Long acting	30 mg/d	240 mg	
Alpha methyldopa	250 mg twice daily	4 g	Thirst Drowsiness Elevation of liver enzymes

**High-risk disease:
Initiate medical therapy**

Randomized, controlled trials do not exist for gravidas with high-risk hypertension—that is, women with severe hypertension or complicating factors—due to concerns about the potential adverse consequences of uncontrolled disease, such as cerebrovascular accident, congestive heart failure, and renal failure.²⁰ It is interesting to note, however, that

Labetalol provides the added benefit of alpha-adrenergic blockade, which offers the theoretical advantage of vasodilation.

although controlling hypertension in such patients may help prolong pregnancy, there is no evidence that it reduces the rates of preeclampsia or abruptio placentae.^{20,21}

When to start treatment. For women with high-risk hypertension, hospitalization at the time of the first prenatal visit facilitates complete cardiovascular and renal evaluation, and is therefore often beneficial. If a woman has target organ damage, treatment should be initiated at a systolic BP of 140 mm Hg or a diastolic BP of 90 mm Hg. Indeed, many such women are already receiving treatment for

their hypertension, in which case antihypertensive medications should be continued, though physicians should consider altering the regimen to optimize fetal safety.

Choosing the best agent. Before choosing an antihypertensive drug, review the patient's history. If her disease was well controlled on a particular medication, that agent is probably a reasonable first choice, provided there is adequate published literature establishing the safety of her medication during pregnancy. Obviously, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, and atenolol should be avoided because of the potential adverse effects on the fetus, including renal failure. The most commonly used medications for control of hypertension during pregnancy are listed in TABLE 4.

■ **Labetalol.** We consider labetalol a first-line agent for controlling hypertension in pregnancy. This beta-blocking drug provides the added benefit of alpha-adrenergic blockade, which offers the theoretical advantage of vasodilation—not seen with traditional beta-blockers. Overall, labetalol has an excellent record of safety in pregnancy.

In a randomized, controlled trial involving 86 mildly hypertensive patients who initiated labetalol therapy between 6 and 13 weeks' gestation, no major congenital malformations were identified.⁶ Although there have

been reports of an increased risk for SGA infants in patients treated with labetalol for mild pregnancy-induced hypertension during the second and third trimesters, this association has not been documented in women with chronic hypertension.⁶

■ **Thiazide diuretics.** If labetalol fails to control blood pressure, we typically add either the calcium-channel blocker nifedipine or a thiazide diuretic. Use of the latter has been well documented in pregnancy. Indeed, thiazide diuretics can be given in the first trimester and throughout gestation without associated risks of major fetal malformations or adverse fetal-neonatal complications.

■ **Calcium-channel blockers.** Calcium-channel-blocking agents also have an excellent safety profile in pregnancy. They have been studied both as antihypertensive medications (primarily in the second and third trimesters) and as tocolytic agents. In a prospective, multicenter, cohort study in which 78 women were exposed to calcium-channel blockers (mainly nifedipine and verapamil) during the first trimester, there was no increase in the rate of birth defects.²²

A separate prospective, randomized trial evaluated the benefit of nifedipine in pregnancy. A total of 283 women—47% of whom had chronic hypertension—were enrolled between 12 and 34 weeks' gestation (mean: 24 weeks). Researchers found patients on nifedipine therapy experienced no improvement in maternal or neonatal outcomes compared to subjects assigned to no treatment.²³ Follow-up at 18 months of 94 of the infants exposed to nifedipine in utero showed no adverse effects on development.²⁴

■ **Methyldopa.** For many obstetricians, methyldopa remains a first-line agent for the treatment of chronic hypertension in pregnancy.¹ It has a well-documented safety record in both short-term²⁵ and long-term follow-up of

Medical factors guiding selection of antihypertensive medication

If the patient has...	It's generally best to start with...
Diabetes Vascular disease	Calcium-channel blocker
Salt-wasting hypertension* Left ventricular systolic dysfunction Mitral stenosis	Thiazide diuretic

*Mostly African-American women

children exposed in utero.²⁶ Indeed, many studies have evaluated use of this medication to manage mild to moderate hypertension, with no evidence of adverse maternal or fetal outcome. However, it is now rarely used in the nonpregnant population, and the safety of other medications, such as labetalol and nifedipine, has prompted us to stop giving it.

In women with diabetes, calcium-channel blockers have a reno-protective effect and are our first-line agent in pregnancy.

■ **Other considerations.** Finally, when choosing an antihypertensive drug, the physician must consider the benefits and response of specific agents in particular risk groups (TABLE 5).

In women with diabetes, calcium-channel blockers have a reno-protective effect and are our first-line agent in pregnancy, since ACE inhibitors, which also offer this benefit, must be avoided beyond 16 weeks' gestation because of the potential adverse fetal effects.

Young African-American women frequently have low-renin, salt-sensitive hypertension, and therefore thiazide diuretics or nifedipine may be better first-line agents in this population.

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TABLE 6

Medications for treating acute severe hypertension

DRUG	DOSE	ONSET OF ACTION	DURATION OF ACTION	SIDE EFFECTS
Hydralazine	5-10 mg IV every 20 min	10-20 min	3-6 h	Tachycardia Headache Flushing Angina
Labetalol	20-80 mg IV every 10 min	5-10 min	3-6 h	Scalp tingling Vomiting Heart block
Sodium nitroprusside*	0.25-5 mcg/kg/min	Immediate	1-2 min	Nausea Vomiting Muscle twitching Thiocyanate and cyanide intoxication
Nicardipine*	5-15 mg/h IV	5-10 min	1-4 h	Tachycardia Headache Phlebitis

*Drugs to use in the presence of hypertensive encephalopathy.

Severe gestational hypertension and preeclampsia

Women who develop severe gestational hypertension (systolic BP of 160 mm Hg or more or diastolic BP of 110 mm Hg or more) and/or preeclampsia require antihypertensive treatment during management

Because nitroprusside is both a vasodilator and a venodilator, it is an ideal agent for gravidas with hypertensive encephalopathy.

remote from term. In this case, the aim of antihypertensive drug treatment is to keep systolic BP between 150 and 159 mm Hg and diastolic BP between 100 and 109 mm Hg in order to not compromise uteroplacental blood flow.

The drugs to use are oral labetalol and/or oral nifedipine. If maternal BP is not adequately controlled with maximum doses of labetalol plus nifedipine, the patient should be delivered.

Severe hypertension and encephalopathy

Hypertensive encephalopathy is a medical emergency. This rare complication of hypertension in pregnancy²⁷ is marked by severely elevated BP, with the diastolic level frequently exceeding 130 mm Hg. Associated findings include headache, visual disturbances, nausea, vomiting, seizures, confusion, stupor, and coma. Also possible are retinal hemorrhage, exudates, papilledema, and evidence of renal or cardiac disease. Transient focal neurologic findings may be present as well, but more often suggest vascular disease, hemorrhage, embolism, or thrombosis.

Pathophysiology. In hypertensive encephalopathy, loss of autoregulation leads to generalized cerebral vasodilation. Under normal conditions, when the mean arterial pressure is between 60 and 130 mm Hg, patients maintain constant cerebral blood flow. In hypertensive patients, however, autoregulation occurs between mean arterial pressures of 110 and 180 mm Hg as a result of arteriolar thickening. When BP

exceeds the ability of the vessels to autoregulate, blood flow hyperperfusion the brain, causing fluid to leak into the perivascular tissue and resulting in vasogenic cerebral edema. Altered vascular reactivity to normally circulating pressor agents, deficient levels of vasodilating prostaglandins, endothelial dysfunction, and activation of the coagulation cascade may further exacerbate this condition.²⁸

Treatment options. Clinically, it may be impossible to differentiate hypertensive encephalopathy from eclampsia, and magnesium sulfate should be considered for seizure prophylaxis. The most frequently used antihypertensive medications for this syndrome are shown in TABLE 6. Nitroprusside lowers BP most predictably, but because of the associated risks of fetal cyanide toxicity, other medications may be more desirable first-line agents in the pregnant woman.

Importantly, because sudden drops in BP may impair cerebral perfusion, we recommend that the mean arterial pressure be lowered no more than 25% from baseline (TABLE 7). If pulmonary edema develops, oxygen and furosemide should be administered, and consultation with subspecialists considered. (We suggest such consultation for cases of renal dysfunction and cerebral complications, as well.) Because nitroprusside is both a vasodilator and a venodilator, it is an ideal agent in this situation.

Postpartum management

Monitor BP for at least 48 hours. Women with high-risk chronic hypertension are more likely to suffer postpartum complications such as pulmonary edema, hypertensive encephalopathy, and renal failure than normotensive patients.⁸ This risk is even higher when these women also have target organ involvement, superimposed preeclampsia, abruptio placentae, morbid obesity, or long-standing hypertension.

TABLE 7

Principles of management for severe hypertension and encephalopathy

Acute severe hypertension

- Control blood pressure to prevent hemorrhage, encephalopathy, and heart failure*

Hypertensive encephalopathy

- Control blood pressure*
- Control pulmonary edema
- Prevent seizures
- Use computed tomography to rule out hemorrhage and cerebral edema. If positive, obtain a neurology consult.

*Lower mean arterial pressure no more than 25% from baseline.

In these patients, BP must be closely monitored and controlled for at least 48 hours after delivery. Intravenous labetalol or hydralazine can be administered for acute elevations of BP²⁹; diuretics should also be used for women with circulatory congestion and pulmonary edema.³⁰

Methyldopa remains the first-line agent for breastfeeding patients without compelling indications for another drug.

Oral antihypertensive therapy may be needed to maintain BP control.

In choosing the appropriate agent, it is important to consider whether factors compel the choice of one medication over another. For example, for patients with a history of myocardial infarction, beta blockers and ACE inhibitors are excellent choices to decrease mortality.³¹ In patients with diabetes mellitus, as mentioned earlier, ACE inhibitors offer a renoprotective effect.¹⁰

Consider drug concentrations in breast milk. Another significant consideration in the postpartum period is whether the mother wishes to breastfeed her infant. All antihypertensive medications are found in

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breast milk to varying degrees,³² and the long-term effects of these medications on breastfeeding infants has not been specifically studied.

Because concentrations of methyldopa in milk are low and considered safe, it remains the first-line agent for patients without compelling indications for another antihypertensive drug. Concentrations of labetalol and propranolol also are low in breast milk; therefore, these may be better choices than atenolol and metoprolol, which are more highly concentrated in breast milk.¹²

Although diuretic agents have low concentrations in breast milk, they may decrease milk production.³²

Little information exists regarding the excretion of calcium-channel blockers in breast milk, but no untoward effects are apparent.³³ ACE inhibitors and angiotensin II receptor antagonists should be avoided because of potential deleterious effects on neonatal renal function, even though their concentrations in breast milk appear to be low. If ACE inhibitors are indicated for the breastfeeding mother, current data suggest that captopril and enalapril are safe.³⁴ ■

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