Antihypertensive Drugs in Pregnancy

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Summary: Blood pressure targets and medications that are safe differ in pregnant women compared with nonpregnant individuals. The principles of treatment for mild, moderate, and severe hypertension in pregnancy, chronic versus gestational versus preeclampsia, and women hypertensive at term versus remote from term are reviewed. The choice of antihypertensive drugs also is discussed; methyldopa, labetalol, and nifedipine, among others, appear safe for use in pregnancy, whereas angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be avoided. The management of increased blood pressure in the postpartum period, and agents to use in lactation, are also discussed.

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Hypertension, the most common medical disorder of pregnancy, is reported to complicate 1 in 10 gestations,1,2 and affects an estimated 240,000 women in the United States each year.3 The principles of antihypertensive treatment in pregnancy represents a departure from the nonpregnant adult (7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC-7]) guidelines.4 First, during pregnancy the priority is to distinguish pre-existing (chronic) from hypertension specific to pregnancy (gestational hypertension and preeclampsia). Second, much of the obstetric literature categorizes blood pressure levels as either mild (140-159/90-109 mm Hg) or severe (≥160/110 mm Hg), rather than by stages (as in JNC-7) (Table 1). Third, in contrast to hypertension guidelines in adults, which emphasize the importance of systolic blood pressure, much of the obstetric literature focuses on diastolic blood pressure in part because of a lack of clinical trials to support one approach versus another. Finally, the focus of treatment is primarily limited to the 9 months of pregnancy, a time frame that permits the trade-off of slightly higher blood pressures than targeted in nonpregnant individuals to minimize fetal exposure to antihypertensive medications. In this setting, antihypertensive medications are mainly used to prevent or treat severe hypertension, to prolong pregnancy for as long as safely possible thereby maximizing the gestational age of the infant, and to minimize fetal exposure to medications that may have adverse effects. During pregnancy, the challenge is in deciding when to use antihypertensive medications, and what level of blood pressure to target. The choice of antihypertensive agents is less complex because only a small proportion of currently available drugs have been evaluated adequately in pregnant women and many are contraindicated; some carry Food and Drug Administration (FDA) classifications that suggest or demand their avoidance in pregnancy (classes D and X). Appropriate use of antihypertensive drugs in specific pregnancy-associated hypertensive disorders, including therapeutic blood pressure goals and criteria for selecting specific antihypertensive drugs, are discussed in this review.

TREATMENT OF SPECIFIC HYPERTENSIVE DISORDERS

There are four major hypertensive disorders in pregnancy, each with unique pathophysiologic features that have implications for antihypertensive therapy:
Chronic Hypertension

Chronic hypertension, defined as blood pressure (BP) of 140/90 mm Hg or greater either predating pregnancy or developing earlier than 20 weeks' gestation, complicates approximately 3% of pregnancies. The cause is largely essential hypertension, which is more frequent in African American patients and women who are of advanced maternal age, or who are obese. Women of childbearing age with stage 1 (mild) essential hypertension (Table 1) who are free of target organ damage and are in good health have an excellent prognosis for pregnancy. Although at increased risk for superimposed preeclampsia (see later), many will naturally experience a physiologic lowering of blood pressure during pregnancy, and a reduction in the requirement for any previously prescribed antihypertensive medication. The goal of treatment is to maintain blood pressure at a level that minimizes maternal cardiovascular and cerebrovascular risk. Prevention of preeclampsia is desirable, however, current evidence has not shown that either specific blood pressure targets in pregnancy or specific antihypertensive agents modify the risk of superimposed preeclampsia in women with pre-existing hypertension.5

Preeclampsia-Eclampsia

Preeclampsia-eclampsia is a syndrome characterized by new-onset hypertension in later pregnancy (usually after 20 weeks, but often closer to term), with associated proteinuria: 1+ on dipstick and by definition at least 300 mg/24-hour urine. This syndrome occurs in 5% to 8% of all pregnancies, and is thought to be a consequence of abnormalities in the maternal vessels supplying the placenta, leading to poor placental perfusion and release of factors.6,7 This leads to widespread endothelial dysfunction with multi-organ system clinical features, such as hypertension, proteinuria, and cerebral (edema, occipital headaches, seizures) and hepatic dysfunction (extension to hemolysis elevation of liver enzymes, low platelets).6 As currently understood, the hypertension of preeclampsia is a consequence of placental underperfusion, thus lowering systemic blood pressure is not believed to reverse the primary pathogenic process, and antihypertensive medication has never been shown to cure or reverse preeclampsia. Nevertheless, control of hypertension may allow for expectant management of preeclampsia, prolonging pregnancy remote from term. As well, in women with preeclampsia-eclampsia, intracerebral hemorrhage remains the most common cause of death,8 so control of severe and rapid increases of blood pressure is the main goal of clinical management, often requiring the use of antihypertensive medication.

Superimposed Preeclampsia

Superimposed preeclampsia complicates approximately 25% of pregnancies in women with chronic hypertension, five times the rate observed in the general population.9 At times it

<table>
<thead>
<tr>
<th>JNC-7 Blood Pressure Classification (Nonpregnant), mm Hg</th>
<th>NHBPEP Blood Pressure Classification (Pregnant), mm Hg</th>
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<tbody>
<tr>
<td>Normal: SBP ≤120 DBP ≤80</td>
<td>Normal/acceptable in pregnancy: SBP ≤140 and DBP ≤90</td>
</tr>
<tr>
<td>Prehypertension: SBP 120-139 or DBP 80-89</td>
<td>Mild hypertension: SBP 140-150 or DBP 90-109</td>
</tr>
<tr>
<td>Stage 1 hypertension: SBP 140–159 or DBP 90–99</td>
<td>Severe hypertension: ≥160 systolic or ≥110 diastolic</td>
</tr>
<tr>
<td>Stage 2 hypertension: SBP 160-179 or DBP 100-110</td>
<td>—</td>
</tr>
<tr>
<td>Stage 3 hypertension: SBP 180-209 or DBP 110-119</td>
<td>—</td>
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</tbody>
</table>

may be difficult to distinguish exacerbation of chronic hypertension from superimposed preeclampsia, but it is usually prudent to err toward treating the latter. Principles of management are similar to those outlined earlier for preeclampsia, although women with pre-existing hypertension and superimposed preeclampsia may be more likely to develop severe hypertension, requiring multiple antihypertensive medications.

Gestational Hypertension

Gestational hypertension, formerly called transient hypertension in previous texts and guidelines, occurs in approximately 6% of pregnancies and is defined as de novo hypertension developing in the latter half of pregnancy not associated with the systemic features of preeclampsia (e.g., proteinuria). The precise diagnosis frequently is made in hindsight; if laboratory tests remain normal, and blood pressure decreases postpartum, then the diagnosis was gestational hypertension rather than preeclampsia or chronic hypertension. Women with gestational hypertension should be considered to be at risk for preeclampsia because approximately 15% to 45% of women initially in the gestational hypertension category develop preeclampsia. Progression to preeclampsia is more likely if gestational hypertension appears early, there is a history of prior miscarriage or hypertension during a previous pregnancy, as well as in those with higher blood pressure. As in women with chronic hypertension, antihypertensive medications should be prescribed with the goal of preventing maternal consequences of severe hypertension because there is no evidence that targeted blood pressure control prevents preeclampsia.

Occasionally, women with apparent gestational hypertension remain hypertensive after delivery. These women most likely have pre-existing chronic hypertension that was masked in early pregnancy by physiologic vasodilation. The natural history of hypertension in the postpartum period, and the maximum time to normalization (beyond which chronic hypertension should be diagnosed), appears to be hypertension of 140/90 mm Hg or greater persisting beyond 3 months postpartum. This is discussed further in a later section.

Although all four types of hypertension in pregnancy may lead to maternal and perinatal complications, preeclampsia (regardless of blood pressure level) and severe hypertension (regardless of type) are those associated with the highest maternal and perinatal risks. The mothers usually do well, but the main risks are placental abruption, accelerated hypertension leading to hospitalization, and target organ damage, such as cerebral vascular catastrophe. The fetus is far more vulnerable; risks include growth restriction, accelerated hypertension leading to hospitalization, and pre-maturity owing to worsening of maternal disease necessitating early delivery.

MILD TO MODERATE HYPERTENSION IN PREGNANCY

The benefits of antihypertensive therapy for mild to moderately increased blood pressure in pregnancy (≤160/110 mm Hg), either chronic or de novo, have not been shown in clinical trials. Recent reviews, including a Cochrane meta-analysis, concluded that there are insufficient data to determine the benefits and risks of antihypertensive therapy for mild to moderate hypertension (defined as blood pressure 140-160 mm Hg systolic or diastolic blood pressure 90–109 mm Hg). Of note, with antihypertensive treatment, there seems to be less risk of developing severe hypertension (relative risk, 0.50; with a number needed to treat of 10) but no difference in outcomes of preeclampsia, neonatal death, preterm birth, and small for gestational age babies with treatment.

International guidelines for the treatment of hypertension in pregnancy vary with respect to thresholds for starting treatment and targeted BP goals, but all are higher than the Joint National Committee guidelines for treatment of (nonobstetric) hypertension. Therapy is recommended in the United States for a BP of 160/105 mm Hg or greater, with no set treatment target; in Canada for women with no comorbid conditions therapy is recommended for blood pressure of 140 to 150/90 mm Hg or greater, targeting diastolic pressure to 80 to 90 mm Hg and in those with comorbid conditions targeting 130 to 139/80 to
89 mm Hg; and in Australia increases of 160/90 mm Hg or greater are treated to a target of no less than 110 systolic. A retrospective review of 28 patients who suffered stroke in the setting of preeclampsia (54% died) showed that the cause of stroke was usually arterial hemorrhage, and the average blood pressure prestroke was 159 to 198/81 to 133 mm Hg. In this case series, systolic hypertension (155-160 mm Hg) was more prevalent than diastolic hypertension (ie, most women did not reach a diastolic BP of 110 mm Hg). This report underscores the need for clinical trials and evidence-based guidelines for antihypertensive treatment in pregnant women. Our practice is to initiate treatment when blood pressure is 150 systolic or greater or 90 to 100 mm Hg diastolic. Other clinicians may wait until diastolic BPs reach 100 mm Hg before treating. One should note that in the presence of any signs of end-organ damage (electrocardiogram or imaging changes suggesting cardiac hypertrophy, alterations in the optic fundi, borderline high or frankly abnormal creatinine levels) the patient’s hypertension is treated as if she were not pregnant.

When the diagnosis is preeclampsia, the gestational age, as well as the level of BP, influence the use of antihypertensive therapy. At or near term, women with preeclampsia are likely to be delivered. Severe hypertension should always be treated, but the treatment of moderate hypertension can be reassessed postpartum. If preeclampsia develops remote from term, and expectant management is undertaken, treatment of severe hypertension should be initiated, and blood pressure lowered to 140/90 mm Hg with oral medications, as described later. It should be emphasized that there are no studies addressing safe blood pressure treatment targets for pregnant women, and guidelines and reviews generally recommend treating to blood pressure levels that are likely to be protective against acute adverse cerebrovascular or cardiovascular events, which is usually in the range of 135 to 155/85 to 90 mm Hg. When antihypertensive therapy is used in women with preeclampsia, fetal monitoring is advisable to recognize fetal distress, which might be attributable to reduced placental perfusion. Management of early onset preeclampsia (<34 wk) includes judicious use of antihypertensive medications, avoiding both high (>160/110 mm Hg) as well as low (<120/80 mm Hg) blood pressures. Although not found to be effective by Cochrane and other analyses, bed rest, and close in-hospital maternal and fetal monitoring, frequently are prescribed. Control of hypertension and careful monitoring have been shown to permit postponement of delivery in selected cases for an average of 2 weeks, which has been associated with improved outcomes later in childhood. It must be emphasized that daily assessment of both maternal (review of symptoms, BP, and blood work) and fetal well-being are necessary in such cases, and delivery may be necessary if either deteriorate.

For women with chronic hypertension and mild to moderately increased BP before pregnancy, it is reasonable to expect that pressures may decrease early in pregnancy, owing to physiologic vasodilation, and if there is no known target organ damage, clinicians can consider discontinuing antihypertensive treatment and monitoring, provided patients are followed up closely. Therapy then can be initiated if the BP again increases to 140 to 150/90 to 100 mm Hg. In women with underlying renal dysfunction, it is reasonable to choose a slightly lower threshold for treatment. There are a wide variety of agents available for use, and orally administered antihypertensives can be used in standard doses in pregnancy (Table 2). First-line recommended agents for nonsevere hypertension are methyldopa and labetalol, with nifedipine as second-line, although the latter is now used quite commonly.

**SEVERE HYPERTENSION**

There is consensus that treatment is indicated for severe hypertension in pregnancy, defined as 160/110 mm Hg or greater, to prevent intracerebral hemorrhage and maternal death. Those with hypertensive encephalopathy, hemorrhage, or eclampsia require treatment with parenteral agents to lower mean arterial pressure (two-thirds diastolic + one-third systolic blood pressure) by 25% over minutes to hours, and then to further lower blood pressure to 160/100 mm Hg over
In treating severe hypertension, it is important to avoid hypotension because the degree to which placental blood flow is autoregulated likely is limited, and aggressive lowering may cause fetal distress. In women with preeclampsia, treatment of acute severe hypertension should be initiated at lower than usual doses because these pa-

<table>
<thead>
<tr>
<th>Drug (FDA Risk Classification)</th>
<th>Dose (oral)</th>
<th>Concerns or Comments</th>
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<tbody>
<tr>
<td>Preferred agent</td>
<td>0.5-3.0 g/d in 2-4 divided doses</td>
<td>Drug of choice according to NHBPEP working group; safety after first trimester well documented, including 7-year follow-up evaluation of offspring</td>
</tr>
<tr>
<td>Second-line agents*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol (C)</td>
<td>200-1,200 mg/d in 2-3 divided doses</td>
<td>May be associated with fetal growth restriction</td>
</tr>
<tr>
<td>Nifedipine (C)</td>
<td>30-120 mg/d of a slow-release preparation</td>
<td>May inhibit labor; little experience with other calcium entry blockers</td>
</tr>
<tr>
<td>Hydralazine (C)</td>
<td>50-300 mg/d in 2-4 divided doses</td>
<td>Few controlled trials, long experience with few adverse events documented; useful in combination with sympatholytic agent; may cause neonatal thrombocytopenia</td>
</tr>
<tr>
<td>β-receptor blockers (C)</td>
<td>Depends on specific agent</td>
<td>May decrease uteroplacental blood flow; may impair fetal response to hypoxic stress; risk of growth restriction when started in first or second trimester (Atenolol); may be associated with neonatal hypoglycemia at higher doses</td>
</tr>
<tr>
<td>Hydrochlorothiazide (C)†</td>
<td>12.5-25 mg/d</td>
<td>Majority of controlled studies in normotensive pregnant women rather than hypertensive patients; can cause volume contraction and electrolyte disorders; may be useful in combination with methyldopa and vasodilator to mitigate compensatory fluid retention</td>
</tr>
<tr>
<td>Contraindicated</td>
<td>—</td>
<td>Leads to fetal loss in animals; human use associated with cardiac defects, fetopathy, oligohydramnios, growth restriction, and neonatal anuric renal failure, which may be fatal; direct renin inhibitors—no reports in pregnancy: avoid</td>
</tr>
</tbody>
</table>

Table 2. Drugs for Gestational or Chronic Hypertension in Pregnancy

No antihypertensive agent has been proven safe for use during the first trimester. Drug therapy indicated for uncomplicated chronic hypertension when diastolic BP was 100 mm Hg or greater (Korotkoff V). Treatment at lower levels may be indicated for patients with diabetes mellitus, renal disease, or target organ damage.

Abbreviation: NHBPEP, National High Blood Pressure Education Program.

Modified from reference 113.

*We omitted some agents (eg, clonidine, α-blockers) because of limited data on use for chronic hypertension in pregnancy.

†We would classify in category X.
Patients may be intravascularly volume depleted and at increased risk for hypotension. Principles of treatment are outlined in Table 3; of note, a meta-analysis of 24 trials (2,949 women) in which different antihypertensive drugs were compared for the treatment of severe hypertension in pregnancy concluded that there are insufficient data to favor one agent over another, although other studies have concluded that agents other than parenteral hydralazine (eg, parenteral labetalol or oral nifedipine) are preferable owing to reduced maternal and fetal adverse effects.

## CHOICE OF ANTIHYPERTENSIVE DRUGS

The FDA reviews human and animal data to assign letter grades corresponding to risk of fetal exposure in pregnancy. Most antihypertensive agents used in pregnancy are designated as category C, which states that human studies are lacking and animal studies are either positive for fetal risk or are lacking, and that the drug should be given only if potential benefits justify potential risks to the fetus. This category cannot be interpreted as no evidence of risk, and is so broad to preclude usefulness in

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**Table 3. Drugs for Urgent Control of Severe Hypertension in Pregnancy**

<table>
<thead>
<tr>
<th>Drug (FDA Risk)*</th>
<th>Dose and Route</th>
<th>Concerns or Comments†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol (C)</td>
<td>10-20 mg IV, then 20-80 mg every 20-30 min, maximum, 300 mg; for infusion, 1-2 mg/min IV</td>
<td>Because of a lower incidence of maternal hypotension and other side effects, its IV use now supplants that of hydralazine; avoid in women with asthma or congestive heart failure</td>
</tr>
<tr>
<td>Hydralazine (C)</td>
<td>5 mg, IV or IM, then 5-10 mg every 20-40 min; once BP controlled repeat every 3 h; for infusion, 0.5-10 mg/h; if no success with 20 mg IV or 30 mg IM, consider another drug</td>
<td>A drug of choice according to NHBPEP working group; long experience of safety and efficacy</td>
</tr>
<tr>
<td>Nifedipine (C)</td>
<td>Tablets recommended only: 10-30 mg oral dose, repeat in 45 min if needed</td>
<td>We prefer long-acting preparations; although obstetric experience with short-acting preparations has been favorable it is not approved by US FDA for management of hypertension</td>
</tr>
<tr>
<td>Diazoxide (C)</td>
<td>30-50 mg IV every 5-15 min</td>
<td>Use is waning; may arrest labor; causes hyperglycemia</td>
</tr>
<tr>
<td>Relatively contraindicated nitroprusside (C)‡</td>
<td>Constant infusion of 0.25-5 μg/kg/min IV</td>
<td>Possible cyanide toxicity if used for &gt;4 h; agent of last resort</td>
</tr>
</tbody>
</table>

*US Food and Drug Administration classification, C indicates that studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and/or there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.

†Adverse effects for all agents, except as noted, may include headache flushing, nausea, and tachycardia (primarily owing to precipitous hypotension and reflex sympathetic activation).

‡We would classify in category D: there is positive evidence of human fetal risk, but the benefits of use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
practice, leading some groups to suggest that the FDA classification be abandoned, or at least modified so as to be more useful to the clinician.28,29 The following information is thus based on clinical case series, small studies, and meta-analyses.

SYMPATHETIC NERVOUS SYSTEM INHIBITORS

Methyldopa is still widely used for treatment of hypertension in pregnancy and remains one of the only drugs for which a 7.5-year follow-up evaluation of the newborn of treated mothers is available. It is a centrally acting α₂-adrenergic agonist prodrug, which is metabolized to α-methyl norepinephrine and then replaces norepinephrine in the neurosecretory vesicles of adrenergic nerve terminals. Blood pressure control is gradual, over 6 to 8 hours, owing to the indirect mechanism of action. It is not thought to be teratogenic based on limited data and a more than 40-year history of use in pregnancy. It has been assessed in a number of prospective trials in pregnant women, compared with placebo30-32 or with alternative antihypertensive agents.32-35 Treatment with methyldopa has been reported to prevent subsequent progression to severe hypertension in pregnancy36 and does not appear to have adverse effects on uteroplacental or fetal hemodynamics7 or on fetal well being.31 One placebo-controlled trial (>200 women with diastolic BP ≥90 mm Hg at entry) noted fewer midpregnancy losses in patients randomized to methyl-
dopa30 but this observation was not confirmed in a more recent trial of similar size.31 Importantly, birth weight, neonatal complications, and development during the first year were similar in children exposed to methyldopa as in the placebo group.38,39 Also in the earlier-noted follow-up study of offspring who were exposed to methyldopa in utero, at 7.5 years of age, intelligence and neurocognitive development were similar to controls.40 It is unfortunate that this landmark 1993 study did not result in a standard method of evaluation applied to all antihypertensive drugs prescribed to pregnant women.

Adverse effects are consequences of central α₂-agonism or decreased peripheral symp-
pathetic tone. These drugs act at sites in the brainstem to decrease mental alertness and impair sleep, leading to a sense of fatigue or to depression in some patients. Frequently, decreased salivation leading to xerostomia is experienced. Methyldopa also can cause liver enzyme increases in 5% of patients; both hepatitis and hepatic necrosis have been reported.41 Some patients will develop a positive antinuclear antigen, or antiglobulin (Coombs) test with chronic use, and this occasionally is associated with clinical hemolytic anemia. In these cases, medications from other classes are substituted.

Clonidine (Catapres; Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT), a selective α₂-agonist, acts similarly and is comparable with methyldopa with respect to safety and efficacy,42 but of some concern is a small controlled follow-up study of 22 neonates that reported an excess of sleep disturbance in clonidine-exposed infants.43 In pregnancy, it is mainly used as a third-line agent for multidrug control of refractory hypertension.

PERIPHERALLY ACTING ADRENERGIC-RECEPTOR ANTAGONISTS

β-blockers have been used extensively in pregnancy. Although several randomized trials comparing β-blockers with either placebo or other agents have been conducted,33,34,44,45 there are still unresolved issues regarding their use in pregnancy because of a few small studies that suggested an association with lower birth weight infants. None of the β-blockers have been associated with teratogenicity. In a meta-analysis and Cochrane review,46 individual agents were not distinguishable in their perinatal effects with the exception of atenolol (Tenormin; AstraZeneca Pharmaceuticals), which in one small study was started at 12 to 24 weeks’ gestation and resulted in clinically significant fetal growth restriction and decreased placental weight compared with placebo.47 This observation was supported by a subsequent retrospective review comparing atenolol with alternative therapies.48 Given differences in β-blockers with respect to lipid solubility and receptor specificity, the potential for clinically relevant differences between agents exists, but has not been investigated in
pregnancy. Oral β-blockade had been associated with non-clinically significant neonatal bradycardia, though in a systematic review of trials, labetalol did not (along with oral methyldopa, nifedipine, or hydralazine) appear to cause neonatal heart rate effects. Parenteral therapy has been found to increase the risk of neonatal bradycardia, requiring intervention in one of six newborns. Further reassurance is derived from a 1-year postpartum follow-up study that showed normal development of infants exposed to atenolol in utero.

Maternal outcomes are improved with the use of β-blockers, with effective control of maternal blood pressure, decreased incidence of severe hypertension, and decreased rate of preterm admission to the hospital; they have been found in a recent Cochrane analysis to be more effective in lowering blood pressure compared with methyldopa in 10 trials.

Labetalol (Trandate; Prometheus Laboratories, Inc, San Diego, CA), a nonselective β-blocker with vascular α1-receptor blocking capabilities has gained wide acceptance in pregnancy. When administered orally to women with chronic hypertension, it appears as safe and effective as methyldopa, although neonatal hypoglycemia with higher doses has been reported. Of some concern, one placebo-controlled study reported an association with fetal growth restriction in the management of preeclampsia remote from term. Parenterally it is used to treat severe hypertension, and because of a lower incidence of maternal hypotension and other side effects, many find this drug preferable to hydralazine.

Adverse effects may be predicted as consequences of β-receptor blockade. Fatigue, lethargy, exercise intolerance (owing to β2-blocking effects in skeletal muscle vasculature), peripheral vasoconstriction, sleep disturbance (with use of more lipid-soluble drugs), and bronchoconstriction may be seen, however, discontinuation owing to side effects is uncommon.

Peripheral acting α1-adrenergic antagonists are second-line antihypertensive drugs in non-pregnant adults. These are indicated during pregnancy in the management of hypertension owing to suspected pheochromocytoma; both prazosin (Minipres; Pfizer Inc, New York, NY) and phenoxybenzamine (Dibenzyline; Well-Spring Pharmaceutical Corp) have been used, with β-blockers as adjunctive agents after α-blockade is accomplished. Because there is limited experience with these agents in pregnancy, their routine use cannot be advocated.

**CALCIUM-CHANNEL BLOCKERS**

Calcium-channel antagonists have been used to treat chronic hypertension, mild preeclampsia presenting late in gestation, and urgent hypertension associated with preeclampsia. Orally administered nifedipine (Adalat [Bayer Healthcare Pharmaceuticals, Calgary, Alberta], Procardia [Pfizer Inc]) and verapamil (Isoptin; Ranbaxy Pharmaceuticals Inc) do not appear to pose a teratogenic risk to fetuses exposed in the first trimester. Most investigators have focused on the use of nifedipine, although there are reports of nicardipine (Cardene; EKR Therapeutics, Inc), isradipine, felodipine (Plendil [AstraZeneca Pharmaceuticals], Renedin [Sanofi-Aventis]), and verapamil (Isoptin). Amldopidine (Norvasc; Pfizer Inc), the dihydropyridine calcium-channel blocker widely used for treatment of hypertension in nonpregnant hypertensive patients, has not been studied extensively in pregnancy. We are only aware of one small case series in pregnancy, however, it is commonly used in pregnancy and appears safe. Maternal side effects of the calcium-channel blockers include tachycardia, palpitations, peripheral edema, headaches, and facial flushing. Nifedipine does not appear to cause a detectable decrease in uterine blood flow. Short-acting dihydropyridine calcium antagonists, particularly when administered sublingually, are now not recommended for the treatment of hypertension in nonpregnant patients because of reports of myocardial infarction and death in hypertensive patients with coronary artery disease. Administration of short-acting nifedipine capsules has been, in case reports, associated with maternal hypotension and fetal distress. If rapid blood pressure control is desired, then we recommend using parenteral labetalol or hydralazine until the desired target is achieved. One study has shown efficacy and safety of long-acting oral nifedipine in pregnant...
patients with severe hypertension in pregnancy,\textsuperscript{70} and given possible untoward fetal effects of short-acting sublingual nifedipine,\textsuperscript{68,69} we also advocate use of the long-acting preparation.

A concern with the use of calcium antagonists for BP control in preeclampsia relates to the concomitant use of magnesium sulfate to prevent seizures; additive effects between nifedipine and magnesium sulphate were observed in a few cases, leading to neuromuscular blockade, myocardial depression, or circulatory collapse.\textsuperscript{71-73} However, these agents are commonly used together in practice\textsuperscript{23,74,75} and a recent evaluation\textsuperscript{76} provided evidence that they may be used together without increased risk.

\textbf{Diuretics}

Diuretics commonly are prescribed in patients with essential hypertension and, given their apparent safety, the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy concluded that they may be continued during pregnancy (with an attempt made to decrease the dose; see later) or used in combination with other agents, especially for women deemed likely to have salt-sensitive hypertension.\textsuperscript{1} Older anecdotal studies suggested that diuretics might prevent preeclampsia, a finding that was supported by a (now discredited) meta-analysis (published in 1985) of nine randomized trials involving more than 7,000 subjects.\textsuperscript{77} Although volume contraction might be expected to limit fetal growth, outcome data have not supported these concerns.\textsuperscript{77} However, mild volume contraction with diuretic therapy may lead to hyperuricemia, and in so doing invalidate serum uric acid levels as a laboratory marker in the diagnosis of superimposed preeclampsia.

In women already taking, hydrochlorothiazide may be continued during pregnancy; the use of low doses (12.5-25 mg/d) may minimize untoward metabolic effects such as impaired glucose tolerance and hypokalemia.\textsuperscript{23} Triamterene and amiloride do not appear to be teratogenic based on a small number of case reports.\textsuperscript{23} Spironolactone is not recommended because of its antiandrogenic effects noted during fetal development in animal models, although this was not borne out in an isolated clinical case.\textsuperscript{78}

\textbf{SEROTONIN\textsubscript{2}-RECEPTOR BLOCKERS}

Serotonin-induced vasodilation is mediated by \textit{S\textsubscript{1}} receptors and subsequent release of prostacyclin and nitric oxide. Endothelial dysfunction and loss of endothelial \textit{S\textsubscript{1}} receptors allows serotonin, whose levels are greatly increased in pregnancy, to react only with \textit{S\textsubscript{2}} receptors, resulting in vasoconstriction and platelet aggregation. Ketanserin is a selective \textit{S\textsubscript{2}}-receptor-blocking drug that decreases systolic and diastolic BP in nonpregnant patients with acute or chronic hypertension. Ketanserin has not been found to be teratogenic in animals or human beings, and has been studied during pregnancy primarily in Australia and South Africa in small trials, which suggest it may be safe and useful in the treatment of chronic hypertension in pregnancy, preeclampsia, and hemolysis elevation of liver enzymes, low platelets syndrome.\textsuperscript{79,80} Ketanserin has not been FDA approved in the United States.

\textbf{DIRECT VASODILATORS}

Hydralazine (Apresoline; Novartis Pharmaceuticals Corp) selectively relaxes arteriolar smooth muscle by an as yet unknown mechanism. Its greatest utility is in the urgent control of severe hypertension, or as a third-line agent for multidrug control of refractory hypertension. It is effective orally, intramuscularly, or intravenously; parenteral administration is useful for rapid control of severe hypertension. Adverse effects are mostly those caused by excessive vasodilation or reflex sympathetic activation, and include headache, nausea, flushing, or palpitations. Chronic use can lead, in rare cases, to a pyridoxine-responsive polyneuropathy or to immunologic reactions including a drug-induced, lupus-like syndrome. Hydralazine has been used in all trimesters of pregnancy and data have not shown an association with teratogenicity, although neonatal thrombocytopenia and lupus have been reported.\textsuperscript{81} It has been widely used for chronic hypertension in the second and third trimesters, but its use has been supplanted by agents with more favorable side-effect profiles.\textsuperscript{82} For acute severe hyperten-
sion later in pregnancy, intravenous hydralazine has been associated with more maternal and perinatal adverse effects than intravenous labetalol or oral nifedipine,26 such as maternal hypotension, cesarean deliveries, placental abruptions, Apgar scores less than 7, and oliguria.15 Furthermore, common side effects of hydralazine, such as headache, nausea, and vomiting, mimic the symptoms of deteriorating preeclampsia. Effects on uteroplacental blood flow are unclear, likely owing to variation in the degree of reflex sympathetic activation, and fetal distress may result via a precipitous decrease in maternal pressure.83-85

Isosorbide dinitrate (Isordil; Valeant Pharmaceuticals International), a nitric oxide donor acting primarily on capacitance vessels, has been investigated in a small study of gestational hypertensive and preeclamptic pregnant patients. It did not affect cerebral perfusion pressure despite significant changes in maternal blood pressure, thus decreasing the risk for ischemia and infarction when blood pressure is decreased.86

Sodium nitroprusside is a direct nitric oxide donor that nonselectively relaxes both arteriolar and venular vascular smooth muscle. Administered only by continuous intravenous infusion, it is easily titrated because it has a near-immediate onset of action and duration of effect of 3 minutes. Nitroprusside metabolism releases cyanide, which can reach toxic levels with high infusion rates; cyanide is metabolized to thiocyanate, whose own toxicity usually occurs after 24 to 48 hours of infusion unless its excretion is delayed owing to renal insufficiency. Nitroprusside is seldom used in pregnancy, usually only in cases of life-threatening refractory hypertension in the moments before delivery.87 Adverse effects include excessive vasodilation and cardioneurogenic (ie, paradoxic bradycardia) syncope in volume-depleted preeclamptic women.88 The risk of fetal cyanide intoxication remains unknown; in one literature review of 24 exposed fetuses there did not appear to be an association between sodium nitroprusside use and fetal demise.89

Given the long experience with hydralazine and alternative utility of parenteral labetalol or oral calcium-channel blockers, this drug is considered as a last resort.

**ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR ANTAGONISTS**

Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARBs) are both class D drugs according to FDA classification, although we approach them as if contraindicated, especially in the second or third trimesters, because of toxicity associated with reduced perfusion of the fetal kidneys. Use is associated with a fetopathy similar to that observed in Potter’s syndrome (ie, bilateral renal agenesis) including renal dysgenesis, oligohydramnios as a result of fetal oliguria, calvarial and pulmonary hypoplasia, intrauterine growth restriction, and fatal neonatal anuric renal failure.90,91 ARB use in pregnancy also has caused similar fetal renal abnormalities, as well as fetal demise, attributed primarily to renal failure.92-94

First trimester exposure to ACE-I recently has been associated with a greater incidence of malformations of the cardiovascular and central nervous systems. Of 29,096 pregnancies analyzed, 209 were exposed to ACE-I in the first trimester alone, associated with a relative risk of congenital malformation of 2.71, when compared with no antihypertensive medication or other types of antihypertensive medication.95 Whether adverse outcomes are owing to a hemodynamic effect in the fetus or to specific (nonhemodynamic) requirements for angiotensin II as a fetal growth factor is unknown. A more recent study of pregnancies recorded in the Swedish Birth Registry reported an increase in cardiac malformations in fetuses exposed to ACE-Is in the first trimester, however, similar risks also were observed in women who reported taking other antihypertensive drugs, particularly β-blockers.96 As such, first trimester use of ACE-I and ARB medications should be avoided. Because exposure to ACE-Is during the first trimester cannot be considered safe, it may be best to counsel women to switch to alternate agents while attempting to conceive. However, in those who inadvertently become pregnant while taking ACE-I or ARBs,
the risk of birth defects increases from 3% to 7%\textsuperscript{95}; it has not been our practice to recommend pregnancy termination. Of note, direct renin inhibitors might be expected to have similar effects as ACE-Is and ARBs in pregnancy, however, we are unaware of any reports of their use in pregnancy; they should be avoided in this setting.

**POSTPARTUM HYPERTENSION**

In the postpartum period, previously normotensive women have been noted to have an increase in BP that reaches a maximum on the fifth postpartum day, and in one study 12% of patients had a diastolic BP exceeding 100 mm Hg.\textsuperscript{97} This is thought to be a consequence of physiologic volume expansion and fluid mobilization in the postpartum period. Postpartum there are currently no management guidelines (as also noted in a recent Cochrane analysis\textsuperscript{98}), but Tan and de Swiet\textsuperscript{99} suggested that antihypertensive drugs should be given if the blood pressure exceeds 150 mm Hg systolic or 100 mm Hg diastolic in the first four days postpartum. Medications may be continued until blood pressure normalizes and then may be stopped. This may occur days to several weeks postpartum, and home blood pressure monitoring by the patient may be helpful in this regard. In the postpartum period, hypertension as a result of gestational hypertension and preeclampsia appears to normalize by 3 months.\textsuperscript{100} Beyond this period, if patients continue to require antihypertensive agents to maintain a normal blood pressure, chronic hypertension may be diagnosed. Choice of antihypertensive agent in the postpartum period often is influenced by breastfeeding, although it is concentrated in human milk. Acebutolol and atenolol should not be used in nursing mothers.

**BREASTFEEDING**

We could locate no well-designed studies assessing neonatal effects of maternally administered antihypertensive drugs delivered via breast milk. The pharmacokinetic principles that govern drug distribution to milk and ensuing exposure to the infant are well established.\textsuperscript{104,105} Milk, secreted by alveolar cells, is a suspension of fat globules in a protein-containing aqueous solution with a pH lower than that of maternal plasma. Factors that favor drug passage into milk are a small maternal volume of distribution, low plasma protein binding, high lipid solubility, and lack of charge at physiologic pH. Even when drugs are ingested by nursing infants, exposure depends on volume ingested, intervals between drug administration

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**Table 4. Maternal Antihypertensive Medications Usually Compatible With Breastfeeding**

<table>
<thead>
<tr>
<th>ACE-I</th>
<th>Calcium-Channel Blocker</th>
<th>(\beta)-Blocker</th>
<th>Diuretics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Diltiazem</td>
<td>Labetalol</td>
<td>Furosemide</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Nifedipine</td>
<td>Nadolol</td>
<td>Hydrochlorothiazide</td>
<td>Methylodopa</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Verapamil</td>
<td>Oxprenolol</td>
<td>Spironolactone</td>
<td>Minoxidil</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diuretics (furosemide, hydrochlorothiazide, spironolactone) may reduce milk production. Metoprolol is classified as compatible with breastfeeding, although it is concentrated in human milk. Acebutolol and atenolol should not be used in nursing mothers.

Data from the American Academy of Pediatrics.\textsuperscript{111}
and nursing, oral bioavailability, and the capacity of the infant to clear the drug. Neonatal exposure to methyldopa via nursing is likely low and it generally is considered safe (Table 4). Atenolol and metoprolol are concentrated in breast milk, possibly to levels that could affect the infant; by contrast, exposure to labetalol and propranolol appears low. Although milk concentrations of diuretics are low and considered safe, these agents, by inducing volume contraction in the mother, can decrease milk production significantly. There are reports of calcium-channel blocker transfer into breast milk, but relative infant doses of nifedipine, verapamil, and diltiazem are low, and all are safe during breast feeding. Sufficient data exist for the safety of three ACE-Is: captopril, enalapril, and quinapril; the concentrations are 1% to 2% of that found in blood, with the infant receiving approximately 0.03% of the regular dose. Based on these findings the American Academy of Pediatrics deems these drugs compatible with breast feeding. There are currently insufficient data on angiotensin II-receptor blockers; varied animal data show detectable milk levels and at this time our recommendation is not to use.

CONCLUSIONS

Use of antihypertensive agents in pregnancy for control of mild to moderate hypertension or for control of severe hypertension is summarized in Tables 2 and 3. As of 2011 there appeared to be little evidence to support the concept that blood pressure control in pregnant women with chronic hypertension will prevent the subsequent occurrence of preeclampsia, which is the cause for most adverse outcomes in these patients. Because blood pressure decreases in early pregnancy, decreasing or even discontinuing medication and monitoring often is possible in women with mild or moderate hypertension. Preventing worsening hypertension in the mother appears to be the greatest benefit in pregnancy according to available meta-analytic data, and we recommend a threshold for treatment of most pregnant hypertensive women of 140 to 150 mm Hg systolic, and/or 95 to 100 mm Hg diastolic, to prevent such worsening hypertension. Acceptable agents include methyldopa, labetalol, and nifedipine, in standard doses. ACE-Is and angiotensin-receptor blockers should be avoided in all trimesters; when administered in the second and third trimesters they are associated with a characteristic fetopathy, neonatal renal failure, and death, and thus are contraindicated. Cohort data lead to recommendations to avoid in the first trimester as well. Finally, control of severe hypertension in pregnancy has been studied in a recent meta-analysis, and this suggests that intravenous labetalol or oral nifedipine are as effective as intravenous hydralazine, with fewer side effects.

Many research questions surrounding hypertension in pregnancy and preeclampsia remain unanswered. Preconception management of hypertension, the necessity for antihypertensive agents, specific drug agents, racial differences, and blood pressure levels for initiation of therapy and treatment targets all remain to be determined. Current guidelines rely only on evidence from small, largely underpowered trials and expert opinion. Finally, studies of antihypertensive medication in pregnancy often evaluate the effectiveness of a drug without examining fetal outcomes associated with harm. Future studies must include detailed outcomes of risk and benefit for both the mother and baby. Better surveillance systems to routinely monitor adverse events and the number of women exposed to particular agents are required to guide treatment efficacy, advance our knowledge of drug safety, and, ultimately, improve treatment options.

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