Update on the Use of Antihypertensive Drugs in Pregnancy

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As the most common medical disorder of pregnancy, hypertension is reported to complicate 1 in 10 pregnancies[1,2] and affects an estimated 240 000 women in the United States each year.[3] Antihypertensive treatment rationale in this group represents a departure from the nonpregnant adult Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines.[4] First, during pregnancy, the priority regarding hypertension is in making the correct diagnosis, with the emphasis on distinguishing preexisting (chronic) from pregnancy induced (gestational hypertension and the syndrome of preeclampsia). Second, much of the obstetric literature distinguishes blood pressure (BP) levels as either mild (140 to 159/90 to 109 mm Hg) or severe (≥160/110 mm Hg), rather than as stages (as in Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; Table 1). Third, in contrast to hypertension guidelines in adults, which emphasize the importance of systolic BP, much of the obstetric literature focuses on diastolic rather than systolic BP, in part because of the lack of clinical trials to support one approach versus another. The focus of treatment is the 9 months of pregnancy, during which untreated mild-to-moderate hypertension is unlikely to lead to unfavorable long-term maternal outcomes. In this setting, antihypertensive agents are mainly used to prevent and 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 BP to target. The choice of antihypertensive agents is less complex, because only a small proportion of currently available drugs have been adequately evaluated in pregnant women, and many others are contraindicated. Appropriate use of antihypertensive drugs in specific pregnancy-associated hypertensive disorders, including therapeutic BP goals and criteria for selecting specific antihypertensive drugs, are discussed in this review.

Principles of Treatment of Specific Hypertensive Disorders

There are 4 major hypertensive disorders in pregnancy, each with unique pathophysiologic features that have implications for antihypertensive therapy, as described below.

Chronic hypertension, defined as BP >140/90 mm Hg either predating pregnancy or developing before 20 weeks' gestation, complicates ≈3% of pregnancies. Because the cause is largely essential hypertension, it 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 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 below), many will experience a physiological lowering of BP during pregnancy and a reduction in the requirement for antihypertensive medication. The goal of treatment is to maintain BP at a level that minimizes maternal cardiovascular and cerebrovascular risk. Prevention of preeclampsia is desirable; however, current evidence has not shown that either specific BP targets in pregnancy or specific antihypertensive agents modify the risk of superimposed preeclampsia in women with preexisting hypertension.[5]

Preeclampsia-eclampsia is a syndrome that manifests clinically as new-onset hypertension in later pregnancy (any time after 20 weeks, but usually closer to term), with associated proteinuria: 1+ on dipstick and, officially, ≥300 mg per 24-hour urine collection. 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] causing widespread endothelial dysfunction with multiorgan system clinical features, such as hypertension, proteinuria, and cerebral (edema, occipital headaches, or seizures) and hepatic dysfunction (extension to hemolysis elevation of liver enzymes, low platelets).[6] As currently understood, the hypertension of preeclampsia is secondary to placental underperfusion, thus, lowering systemic BP is not believed to reverse the primary pathogenic process, and antihypertensive medication has never been demonstrated to "cure" or reverse preeclampsia. Nevertheless, because preeclampsia may develop suddenly in young, previously normotensive women, prevention of cardiovascular and cerebrovascular consequences of severe and rapid elevations of BP is an important goal of clinical management, often requiring judicious use of antihypertensive medication.

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Table 1. BP Classification: JNC-7 vs NHBPEP

JNC-7 BP Classification (Nonpregnant), mm Hg	NHBPEP BP Classification (Pregnant), mm Hg
Normal	Normal/acceptable in pregnancy
SBP≤120 and DBP≤80	SBP≤140 and DBP≤90
Prehypertension	
SBP 120 to 139 or DBP 80 to 89	
Stage 1 hypertension	Mild hypertension
SBP 140 to 159 or DBP 90 to 99	SBP 140 to 150 or DBP 90 to 109
Stage 2 hypertension	Severe hypertension
SBP 160 to 179 or DBP 100 to 110	≥160 systolic or ≥110 diastolic
Stage 3 hypertension	
SBP 180 to 209 or DBP 110 to 119	

JNC-7 indicates the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[4]; NHBPEP, National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy.[1]

Superimposed preeclampsia complicates 25% of pregnancies in women with chronic hypertension, a much higher risk than that observed in the general population.[8] Principles of management are similar to those outlined above for preeclampsia, although women with preexisting hypertension and superimposed preeclampsia may be more likely to develop severe hypertension requiring multiple antihypertensive medications.

Gestational hypertension occurs in ≈6% of pregnancies and is hypertension developing in the latter half of pregnancy not associated with the systemic features of preeclampsia (eg, proteinuria). The precise diagnosis is frequently made in hindsight; if laboratory tests remain normal and BP decreases postpartum, then the diagnosis is gestational hypertension (formerly called "transient hypertension" in previous texts and guidelines). Women with gestational hypertension should be considered to be at risk for preeclampsia, which may develop at any time, including the first postpartum week. Approximately 15% to 45% of women initially diagnosed with gestational hypertension will develop preeclampsia, and this is more likely with earlier presentation, previous miscarriage, and previous hypertensive pregnancy, as well as higher BP.[9,10] 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 BP control prevents preeclampsia.

Occasionally, women with apparent gestational hypertension remain hypertensive after delivery. These women most likely have pre-existing chronic hypertension, which was masked in early pregnancy by physiological vasodilation. The natural history of hypertension in the postpartum period and the maximum time to normalization (beyond which chronic hypertension should be diagnosed) are not known. In general, hypertension >140/90 mm Hg persisting beyond 3 months postpartum is diagnosed as chronic hypertension. This is further discussed in a later section.

Although all 4 types of hypertension in pregnancy may lead to maternal and perinatal complications, preeclampsia (regardless of BP level) and severe hypertension (regardless of type) are those associated with the highest maternal and perinatal risks. The main risks to the mother are placental abruption, accelerated hypertension leading to hospitalization, and target organ damage, such as cerebral vascular catastrophe.[1] Fetal risks include growth restriction and prematurity because of worsening of maternal disease necessitating early delivery.[11]

Principles for Treatment of Mild-to-Moderate Hypertension in Pregnancy

The benefits of antihypertensive therapy for mild-to-moderately elevated BP in pregnancy (≤160/110 mm Hg), either chronic or pregnancy induced, have not been demonstrated 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 140 to 169 mm Hg systolic BP and 90 to 109 mm Hg diastolic BP).[5,12–15] Of note, with antihypertensive treatment, there seems to be less risk of developing severe hypertension (risk ratio: 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.[5]

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[1] with no set treatment target; in Canada, therapy is considered at ≥140/90 mm Hg targeting diastolic pressure to 80 to 90 mm Hg,[16] and in Australia, elevations ≥160/90 mm Hg are treated to a target of ≥110 systolic.[17] A recent retrospective review of 28 patients who suffered stroke in the setting of preeclampsia demonstrated that the cause of stroke was usually arterial hemorrhage, that the average BP before stroke was 159 to 198 mm Hg systolic and 81 to 133 mm Hg diastolic, and that 54% of women died.[18] Of note, systolic hypertension (155 to 160 mm Hg) was more prevalent than diastolic hypertension (most women did not reach a diastolic BP of 110 mm Hg) in women who suffered strokes. This case series underscores the need for clinical trials and evidence-based guidelines for antihypertensive treatment in pregnant women. Our practice is to initiate treatment when BP is ≥150 systolic and 90 to 100 mm Hg diastolic.

When the diagnosis is preeclampsia, the gestational age, as well as the level of BP, influences the use of antihypertensive therapy. At term, women with preeclampsia are likely to be delivered, treatment of hypertension (unless severe) can be delayed, and BP can be reevaluated postpartum. If preeclampsia develops remote from term, and expectant management is undertaken, treatment of severe hypertension is initiated, and BP can usually be safely lowered to 140/

Table 2. Drugs for Gestational or Chronic Hypertension in Pregnancy

Drug (FDA Risk)*	Dose	Concerns or Comments
Preferred agent		
Methyldopa (B)	0.5 to 3.0 g/d in 2 divided doses	Drug of choice according to NHBEP; safety after first trimester well documented, including 7 years follow-up of offspring
Second-line agents†		
Labetalol (C)	200 to 1200 mg/d in 2 to 3 divided doses	May be associated with fetal growth restriction
Nifedipine (C)	30 to 120 mg/d of a slow-release preparation	May inhibit labor and have synergistic action with magnesium sulfate in BP lowering; little experience with other calcium entry blockers
Hydralazine (C)	50 to 300 mg/d in 2 to 4 divided doses	Few controlled trials, long experience with few adverse events documented; useful in combination with sympatholytic agent; may cause neonatal thrombocytopenia
β-Receptor blockers (C)	Depends on specific agent	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
Hydrochlorothiazide (C)‡	12.5 to 25.0 mg/d	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
Contraindicated ACE-Is and angiotensin type 1 receptor antagonists (D)‡		Leads to fetal loss in animals; human use associated with cardiac defects, fetopathy, oligohydramnios, growth restriction, renal agenesis and neonatal anuric renal failure, which may be fatal

No antihypertensive has been proven safe for use during the first trimester. Drug therapy was indicated for uncomplicated chronic hypertension when diastolic BP was $\geq$100 mm Hg (Korotkoff V). Treatment at lower levels may be indicated for patients with diabetes mellitus, renal disease, or target organ damage. NHBPEP indicates National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy.

*Food and Drug Administration classification.

†We omit some agents (eg, clonidine and α-blockers) because of limited data on the use for chronic hypertension in pregnancy.

‡We would classify this in category X.

90 mm Hg with oral medications as described below. It should be emphasized that there are no studies addressing safe BP treatment targets for pregnant women, and guidelines and reviews generally recommend treating to BP levels that are likely to be protective against acute adverse cerebrovascular or cardiovascular events, which is usually in the range of 140 to 155/90 to 105 mm Hg.[19] When antihypertensive therapy is used in women with preeclampsia, fetal monitoring is helpful to recognize any signs of fetal distress that might be attributable to reduced placental perfusion. Indeed, temporizing management of early onset preeclampsia ($<$34 weeks) includes judicious use of antihypertensive medications along with work cessation, bed rest, and close in-hospital maternal and fetal monitoring, followed by delivery for specific maternal and fetal indications. This approach has been shown to delay delivery in selected cases for an average of 2 weeks, which has been associated with improved outcomes later in childhood.[20] It must be emphasized that daily of 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 elevated BP before pregnancy, it is reasonable to expect that pressures may decrease early in pregnancy because of physiological vasodilation, and if there is no known target organ damage, clinicians can consider discontinuing antihypertensive treatment and monitoring, provided patients are closely followed. Therapy can then be initiated if the BP again rises to 140 to 150/90 to 100 mm Hg.[21] In women with underlying renal dysfunction, it may be reasonable to choose a slightly lower threshold for treatment.[8] There are a wide variety of agents available for use, and orally administered antihypertensive agents can be used in standard doses in pregnancy (Table 2). First-line agents for nonsevere hypertension are methyldopa and labetalol, with nifedipine as second line, followed by others in third line.

Treatment of Severe Hypertension

There is consensus that severe hypertension in pregnancy, defined as $>$160/110 mm Hg, requires treatment, because these women are at an increased risk of intracerebral hemorrhage, and that treatment decreases the risk of maternal death.[1,22] Those with hypertensive encephalopathy, hemorrhage, or eclampsia require treatment with parenteral agents to lower mean arterial pressure (2/3 diastolic +1/3 systolic

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

Drug (FDA Risk*)	Dose and Route	Concerns or Comments†
Labetalol (C)	10 to 20 mg IV, then 20 to 80 mg every 20 to 30 minutes, maximum of 300 mg; for infusion: 1 to 2 mg/min	Because of a lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine; avoid in women with asthma or congestive heart failure
Hydralazine (C)	5 mg, IV or IM, then 5 to 10 mg every 20 to 40 minutes; once BP controlled repeat every 3 hours; for infusion: 0.5 to 10.0 mg/h; if no success with 20 mg IV or 30 mg IM, consider another drug	A drug of choice according to NHBEP; long experience of safety and efficacy
Nifedipine (C)	Tablets recommended only: 10 to 30 mg PO, repeat in 45 minutes if needed	We prefer long-acting preparations; although obstetric experience with short acting has been favorable, it is not approved by the FDA for management of hypertension
Diazoxide (C)	30 to 50 mg IV every 5 to 15 minutes	Use is waning; may arrest labor; causes hyperglycemia
Relatively contraindicated nitroprusside (C)‡	Constant infusion of 0.25 to 5.00 μg/kg per minute	Possible cyanide toxicity if used for >4 hours; agent of last resort

Drugs indicated for acute elevation of diastolic BP≥105 mm Hg; the goal is gradual reduction to 90 to 100 mm Hg. NHBPEP indicates National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy; FDA, Food and Drug Administration.

*Food and Drug Administration classification, C indicates that either 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 only be given if the potential benefits justify the potential risk to the fetus.

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

‡We would classify in category D: there is positive evidence of human fetal risk, but the benefits of the 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 can not be used or are ineffective).

BP) by 25% over minutes to hours and then to further lower BP to 160/100 mm Hg over subsequent hours.[1] In treating severe hypertension, it is important to avoid hypotension, because the degree to which placental blood flow is autoregulated is not established, and aggressive lowering may cause fetal distress. In women with preeclampsia, consideration should be given to initiating agents for treatment of acute severe hypertension at lower doses, because these patients may be intravascularly volume depleted and may be at increased risk for hypotension. Principles of treatment are outlined in Table 3; of note, a recent meta-analysis of 24 trials (2949 women) in which different antihypertensive drugs were compared for the treatment of severe hypertension in pregnancy concluded that there is insufficient data to favor one agent over another,[23] although others have concluded that agents other than parenteral hydralazine (eg, parenteral labetalol or oral nifedipine) are preferable because of reduced maternal and fetal adverse effects.[24]

Choice of Antihypertensive Drug for Use in Pregnancy

The Food and Drug Administration reviews human and animal data to assign letter grades corresponding with risk of fetal exposure in pregnancy. Most antihypertensive agents used in pregnancy are designated as "category C," which states that human studies are lacking, animal studies are either positive for fetal risk or are lacking, and the drug should be given only if potential benefits justify potential risks to the fetus.[25] This category cannot be interpreted as no evidence of risk and is so broad to preclude usefulness in practice, leading some groups to suggest that the Food and Drug Administration classification be abandoned.[26,27] Information is, thus, based on clinical cases, small studies, and meta-analyses.

Sympathetic Nervous System Inhibition

Methyldopa remains one of the most widely used drugs for the treatment of hypertension in pregnancy. It is a centrally acting α_2-adrenergic agonist prodrug, which is metabolized to α-methyl norepinephrine and then replaces norepinephrine in the neurosecretory vesicles of adrenergic nerve terminals. BP control is gradual, over 6 to 8 hours, because of the indirect mechanism of action. It is not thought to be teratogenic based on limited data and a 40-year history of use in pregnancy. It has been assessed in a number of prospective trials in pregnant women compared with placebo[28–30] or with alternative antihypertensive agents.[30–33] Treatment with methyldopa has been reported to prevent subsequent progression to severe hypertension in pregnancy[34] and does not seem to have adverse effects on uteroplacental or fetal hemodynamics[35] or on fetal well being.[29] One placebo-controlled trial (>200 women with diastolic BP >90 mm Hg at entry) noted fewer midpregnancy losses in patients randomly assigned to methyldopa,[28] but this observation was not confirmed in a more recent trial of a similar size.[29] Importantly, birth weight, neonatal complications, and development during the first year were similar in children exposed to methyldopa as in the placebo group.[36,37] In a follow-up study of offspring who were exposed to methyldopa in utero, at 7.5 years of age, the children exhibited intelligence and neurocognitive development similar to control subjects.[38]

Adverse effects are consequences of central α_2-agonism or decreased peripheral sympathetic tone. These drugs act at sites in the brain stem to decrease mental alertness and impair sleep, leading to a sense of fatigue or depression in some patients. Frequently, decreased salivation, leading to xerostomia, is experienced. Methyldopa can also cause elevated liver enzymes in 5%; hepatitis and hepatic necrosis have also been

reported.[39] Some patients will develop a positive antinuclear antigen or antiglobulin (Coombs') test with chronic use, and this is occasionally associated with clinical hemolytic anemia. In these cases, medications from other classes are substituted.

Clonidine, a selective α_2-agonist, acts similarly and is comparable to methyldopa with respect to safety and efficacy,[40] 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.[41] 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,[31,32,42,43] there are still some unresolved issues regarding their use in pregnancy, largely a result of a few small studies that suggest an association with lower birth weight infants. None of the β-blockers have been associated with teratogenicity. In meta-analysis and Cochrane review,[44] individual agents were not distinguishable in their perinatal effects with the exception of atenolol, which in 1 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.[45] This observation was supported in a subsequent retrospective review comparing atenolol with alternative therapies.[46] 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 nonclinically significant neonatal bradycardia,[14,47] although in a systematic review of trials, labetalol does not (along with oral methyldopa, nifedipine, or hydralazine) seem to cause neonatal heart rate effects.[48] Parenteral therapy has been found to increase the risk of neonatal bradycardia, requiring intervention in 1 of 6 newborns.[14] Further reassurance is derived from a 1-year postpartum follow-up study, which showed normal development of infants exposed to atenolol in utero.[49] Maternal outcomes are improved with the use of β-blockers, with effective control of maternal BP, decreased incidence of severe hypertension, and decreased rate of preterm admission to hospital[14]; they have been found in a recent Cochrane analysis to be more effective in lowering BP compared with methyldopa in 10 trials.[5]

Labetalol, a nonselective β-blocker with vascular α_1-receptor blocking capabilities, has gained wide acceptance in pregnancy. When administered orally to women with chronic hypertension, it seems as safe[29,33,50,51] and effective as methyldopa, although neonatal hypoglycemia with higher doses has been reported.[52] Of some concern, 1 placebo controlled study reported an association with fetal growth restriction in the management of preeclampsia remote from term.[51] Parenterally it is used to treat severe hypertension, and because of a lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine.[24]

Adverse effects may be predicted as consequences of β-receptor blockade. Fatigue, lethargy, exercise intolerance (because of β_2-blocking effects in skeletal muscle vasculature), peripheral vasoconstriction, sleep disturbance (with use of more lipid-soluble drugs), and bronchoconstriction may be seen; however, discontinuation because of adverse effects is uncommon.[5]

Peripherally acting α-adrenergic antagonists are second-line antihypertensive drugs in nonpregnant adults. These are indicated during pregnancy in the management of hypertension because of suspected pheochromocytoma, and both prazosin and phenoxybenzamine have been used, with β-blockers used as adjunctive agents after α-blockade is accomplished.[53,54] Because there is but limited experience with these agents in pregnancy, their routine use cannot be advocated.

Calcium Channel Antagonists

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 and verapamil do not seem to pose teratogenic risks to fetuses exposed in the first trimester.[55] Most investigators have focused on the use of nifedipine, although there are reports of nicardipine,[56,57] isradipine,[58] felodipine,[59] and verapamil.[60] Although used in pregnancy, the dihydropyridine amlodipine is yet unstudied in this population. Maternal adverse effects of the calcium channel blockers include tachycardia, palpitations, peripheral edema, headaches, and facial flushing.[61] Nifedipine does not seem to cause a detectable decrease in uterine blood flow.[62,63] 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.[64] Administration of short-acting nifedipine capsules has been, in case reports, associated with maternal hypotension and fetal distress.[65,66] If rapid BP 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,[67] and given possible untoward fetal effects of short-acting sublingual nifedipine,[65,66] we also advocate use of the long-acting preparation.

A concern with the use of calcium antagonists for BP control in preeclampsia has been the concomitant use of magnesium sulfate to prevent seizures; drug interactions between nifedipine and magnesium sulfate were reported to cause neuromuscular blockade, myocardial depression, or circulatory collapse in some cases.[68–70] In practice[21,71,72] and in a recent evaluation,[73] these medications are commonly used together without increased risk.

Diuretics

Diuretics are commonly prescribed in essential hypertension before conception 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 through gestation (with an attempt made to lower the dose) or used in combination with other

agents, especially for women deemed likely to have salt-sensitive hypertension.[1] Older anecdotal studies suggested that diuretics might prevent preeclampsia, a finding that was supported by a meta-analysis (published in 1985) of 9 randomized trials involving >7000 subjects.[74] Although volume contraction might be expected to limit fetal growth, outcome data have not supported these concerns.[74] 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.

Hydrochlorothiazide may be continued during pregnancy; the use of low doses (12.5 to 25 mg daily) may minimize untoward metabolic effects, such as impaired glucose tolerance and hypokalemia.[21] Triamterene and amiloride are not teratogenic based on small numbers of case reports.[21] Spironolactone is not recommended because of its antiandrogenic effects during fetal development, although this was not borne out in an isolated case.[75]

Serotonin$_2$ Receptor Blockers

Serotonin-induced vasodilation is mediated by S_1 receptors and subsequent release of prostacyclin and NO. Endothelial dysfunction and loss of endothelial S_1 receptors allows serotonin, of which the levels are greatly increased in pregnancy, to react only with S_2 receptors, resulting in vasoconstriction and platelet aggregation. Ketanserin is a selective S_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 humans and has been studied primarily in Australia and South Africa in small trials, which suggest that it may be safe and useful in the treatment of chronic hypertension in pregnancy, preeclampsia, and hemolysis elevation of liver enzymes, low platelets syndrome.[76,77] Ketanserin has not been Food and Drug Administration approved in the United States.

Direct Vasodilators

Hydralazine selectively relaxes arteriolar smooth muscle by an as-yet-unknown mechanism. Its greatest use 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 due to excessive vasodilation or 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 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.[78] 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 adverse effect profiles.[79] For acute severe hypertension later in pregnancy, intravenous hydralazine has been associated with more maternal and perinatal adverse effects than intravenous labetalol or oral nifedipine,[24] such as maternal hypotension, cesarean sections, placental abruptions, Apgar scores <7, and oliguria.[14] Furthermore, the common adverse effects, such as headache, nausea, and vomiting, mimic the symptoms of deteriorating preeclampsia. Effects on uteroplacental blood flow are unclear, likely because of variation in the degree of reflex sympathetic activation, and fetal distress may result via a precipitous drop in maternal pressure.[80–82] A recent meta-analysis of the use of intravenous hydralazine in severe hypertension in pregnancy concluded that parenteral labetalol or oral nifedipine were preferable first-line agents, with hydralazine as a suitable second-line agent.[24]

Isosorbide dinitrate, an NO donor, has been investigated in a small study of gestational hypertensive and preeclamptic pregnant patients. It was found that cerebral perfusion pressure is unaltered by isosorbide dinitrate, despite significant changes in maternal BP, thus decreasing the risk for ischemia and infarction when BP is lowered.[83]

Sodium nitroprusside is a direct NO donor, which 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, and this toxicity usually occurs after 24 to 48 hours of infusion unless its excretion is delayed due to renal insufficiency. It is seldom used in pregnancy, usually only in cases of life-threatening refractory hypertension in the moments before delivery.[84] Adverse effects include excessive vasodilation and cardioneurogenic (ie, paradoxical bradycardia) syncope in volume-depleted preeclamptic women.[85] The risk of fetal cyanide intoxication remains unknown. Given the long experience with hydralazine and alternative use 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 blocking agents are contraindicated 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 neonatal anuric renal failure, leading to death of the fetus.[86,87] Angiotensin receptor blocker use in pregnancy has also caused fetal demise, attributed primarily to renal failure.[88–90]

First-trimester exposure to ACE-I has been associated recently 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 risk ratio of congenital malformation of 2.71 when compared with no antihypertensive medication or other types of antihypertensive medication.[91] Whether adverse outcomes are because of a hemodynamic effect in the fetus or specific (nonhemodynamic)

requirements for angiotensin II as a fetal growth factor is unknown. As such, first-trimester use of ACE-I and angiotensin receptor blocking agent medications should be avoided. Because exposure to ACE inhibitors 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 angiotensin receptor blocking agents, the risk of birth defects rises from 3% to 7%[91]; it has not been our practice to recommend pregnancy termination. Of note, direct renin inhibitors might be expected to have similar effects as ACE-I and angiotensin receptor blocking agents in pregnancy; however, we are unaware of any reports of their use in pregnancy, and, consequently, they should be avoided in this setting.

Management of Hypertension Postpartum

In the postpartum period, previously normotensive women have been noted to have a rise in BP, which reaches a maximum on the fifth postpartum day, and in 1 study 12% of patients had a diastolic BP exceeding 100 mm Hg.[92] This is thought to be a consequence of physiological volume expansion and fluid mobilization in the postpartum period. The natural history of gestational hypertension and preeclampsia in the postpartum period and the maximum time to normalization (beyond which chronic hypertension should be diagnosed) are not known. As such, and noted in a recent Cochrane analysis, the need for treatment, the management of antihypertensive medication, and patient counseling have been unguided by the literature.[93] Postpartum, no guidelines currently exist, but Tan and de Swiet[94] have suggested that antihypertensive drugs should be given if the BP exceeds 150 mm Hg systolic or 100 mm Hg diastolic in the first 4 days of the puerperium. Choice of antihypertensive agent in the postpartum period is often influenced by breast feeding,[95] but in general the agents commonly used in the antepartum period may be continued postpartum (Table 4). The medication may then be discontinued when BP normalizes. This may occur days to several weeks postpartum, and home BP monitoring by the patient may be helpful in this regard.

In select cases of women with severe preeclampsia, there seems to be some benefit to a brief course of furosemide diuresis in the days postpartum, particularly for patients with hypertension accompanied by symptomatic pulmonary or peripheral edema.[96] A few case reports have suggested that nonsteroidal anti-inflammatories may contribute to BP elevation postpartum,[97] and the effects on BP in nonpregnant individuals are well documented. Thus, in postpartum patients who are already hypertensive, these drugs should be used cautiously or should perhaps be avoided.

Antihypertensive Use in Breastfeeding

There are 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.[98,99] 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.

Table 4. Maternal Antihypertensive Medications Usually Compatible With Breastfeeding

Captopril
Diltiazem
Enalapril
Hydralazine
Hydrochlorothiazide
Labetalol
Methyldopa
Minoxidil
Nadolol
Nifedipine
Oxprenolol
Propranolol
Spironolactone
Timolol
Verapamil

Data are from Reference 104. Diuretics (furosemide, hydrochlorothiazide, and 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.

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 physiological pH. Even when drugs are ingested by nursing infants, exposure depends on volume ingested, intervals between drug administration 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 is generally 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 seems low.[100] Although milk concentrations of diuretics are low and considered safe, these agents can decrease milk production significantly.[101] There are reports of calcium channel blocker transfer into breast milk,[102] apparently without adverse effects. Sufficient data exist for the safety of 2 ACE-Is, captopril and enalapril; the concentration of captopril was 1% of that found in blood, with the infant receiving 0.03% of the regular dose,[103] and clinically insignificant amounts of enalapril were excreted into breast milk as well; based on these findings, the American Academy of Pediatrics deems these drugs compatible with breast feeding.[104] There are currently insufficient data on angiotensin II receptor blockers; varied animal data show detectable milk levels, and recommendation regarding their safety cannot at this time be given.

Summary

The 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. Currently, there is little evidence to support the concept that BP control in pregnant women with chronic hypertension will prevent the subsequent occurrence of preeclampsia, itself the cause for most adverse outcomes in these patients. As BP falls in early pregnancy, decreasing or even discontinuing medication

and monitoring is often possible in women with mild or moderate hypertension. Acknowledging limitations in evidenced-based data and other concerns discussed above regarding gestational age, 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 worsening hypertension in the mother. Acceptable agents include methyldopa, labetalol, and nifedipine in standard doses. Atenolol use should probably be avoided in pregnancy, because it has been associated with slightly lower birth weights. 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. Recent data suggest that they should also be avoided in the first trimester. Finally, control of severe hypertension has been studied in a recent meta-analysis, and this suggests that intravenous labetalol or oral nifedipine is as effective as intravenous hydralazine, with fewer adverse effects.

Many research questions surrounding hypertension in pregnancy and preeclampsia remain unanswered. Advancement of clinical knowledge requires studies that are large, collaborative, and multicentered. For example, to better understand the need for antihypertensive therapy in mild-to-moderate chronic hypertension, a study designed to detect a moderate (20%) relative risk reduction in preeclampsia or intrauterine growth restriction would require a randomized trial with enrollment of 1000 to 3000 women with chronic hypertension. Preconception management of hypertension, the necessity for antihypertensive agents, specific drug agents, racial differences, BP 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[105]; 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 numbers of women exposed to particular agents are required to guide treatment efficacy, advance our knowledge of drug safety, and ultimately improve treatment options.

Disclosures

None.

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