REVIEW

Use of Antihypertensive Drugs during Pregnancy and Lactation

Firas A Ghanem & Assad Movahed

Section of Cardiology, Department of Medicine, The Brody School of Medicine East Carolina University, Greenville, North Carolina, USA

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Correspondence
Assad Movahed, M.D., Section of Cardiology, Department of Medicine, The Brody School of Medicine, East Carolina University, Greenville, NC 27834-435, USA.
Tel.: 252-744-4651, Fax: 252-744-5884,
E-mail: movaheda@ecu.edu.

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The decision to treat elevated arterial pressure in pregnancy depends on the risk and benefits imposed on the mother and the fetus. Treatment for mild-to-moderate hypertension during pregnancy may not reduce maternal or fetal risk. Severe hypertension, on the other hand, should be treated to decrease maternal risk. Methyldopa and β-adrenoceptor antagonists have been used most extensively. In acute severe hypertension, intravenous labetalol or oral nifedipine are reasonable choices.

Introduction

Elevated arterial blood pressure is seen in 6% to 8% of all pregnancies and is a major contributor to maternal, fetal, and neonatal morbidity (American College of Obstetricians and Gynecologists 1996). Hypertension (arterial pressure >140/90 mmHg) in pregnancy is classified into one of four conditions: (1) chronic hypertension that precedes pregnancy; (2) preeclampsia-eclampsia, a systemic syndrome of elevated arterial pressure, proteinuria (> 300 mg protein/24 h) and other findings (seizures or coma in the case of eclampsia); (3) preeclampsia superimposed upon chronic hypertension; and (4) gestational hypertension, or nonproteinuric hypertension of pregnancy where arterial pressure returns to normal by 12 weeks postpartum (Lenfant 2001).

Because of the potential for teratogenicity and other adverse events to the fetus or newborn, drug prescription to pregnant women has been subject to varying levels of concerns and controversies. The Food and Drug Administration (FDA) has classified medications in term of use in pregnancy under one of five letter categories—A, B, C, D, and X (table 1) (FDA 2001). This classification may be ambiguous, sometimes, due to oversimplification that reflects occasional lack of knowledge rather than actual proven harm. Due to ethical dilemmas in treating vulnerable populations such as pregnant women, a large bulk of the available data on medication risk in pregnancy have been derived form retrospective analysis subjecting conclusions to selection, recall, and attrition biases as well as the bias of change in methods and confounders over time. As perinatal mortality or the use of a placebo as control is no longer realistic or ethical in most trials of antihypertensive drugs in pregnancy, practitioners may find themselves armed with data favoring the use of older and potentially safer medications over newer medications with possibly more approved indications.

There are significant variations in defining hypertension stages during pregnancy (like using only diastolic blood pressure) reflecting how elevated arterial pressure was defined during the design of each study. Largely, mild-to-moderate hypertension during pregnancy is defined as systolic blood pressure 140 to 169 mmHg or diastolic blood pressure 90 to 109 mmHg whereas severe hypertension is defined as 160 to 170 mmHg or more systolic blood pressure or 110 mmHg or more diastolic blood pressure. (Abalos et al. 2007).

Although antihypertensive therapy for mild-to-moderate hypertension in pregnancy may reduce the risk for severe hypertension, it does not seem to decrease the incidence of preeclampsia nor affect maternal or perinatal outcomes (Abalos et al. 2007). Avoidance of drug therapy

Table 1 Classification of antihypertensive drugs used to treat hypertension in pregnancy.

Category	Basis for classification
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus. However, there are no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies; adequate, well controlled, or observational in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies; adequate, well controlled, or observational in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

is, therefore, suggested in mild hypertension where non-pharmacological therapies may suffice and the benefits from short-term therapy may be lacking (table 2). Because no interventions have been proven to decrease the risk of development of preeclampsia, delivery of the fetus and placenta remains the only effective treatment (Longo et al. 2003). Chronic hypertension therapy can be stopped during pregnancy under close observation, or alternatively, a woman whose arterial pressure was well controlled by antihypertensives before pregnancy may continue with the same agents (if not contraindicated). The National Institutes of Health-sponsored Working Group on High Blood Pressure in Pregnancy recommend antihypertensive therapy for blood pressures exceeding a threshold of 150 to 160 mmHg systolic or 100 to 110 mmHg diastolic or in the presence of target organ damage, such as left ventricular hypertrophy or renal insufficiency (Lenfant 2001).

Pathophysiology

During normal pregnancy maternal vascular and hemodynamic changes occur that have the potential to change the pharmacokinetics of drugs. Peripheral vascular resistance progressively falls in pregnancy leading to a reduction in arterial pressure despite the increases in cardiac output, ventricular stroke volume, and heart rate (Robson et al. 1989). The dramatic increase in maternal plasma volume leads to a progressive fall in plasma albumin concentration and consequently plasma protein binding of certain drugs is reduced and the volume of distribution of some drugs is altered. Due to an increase in cardiac output in pregnancy, there is a 50% increase of effective renal plasma flow, glomerular filtration rate, and creatinine clearance resulting in a parallel increase in the clearance of drugs that undergo renal excretion. Placental transfer of low molecular weight, lipid-soluble drugs is more efficient than the slow transfer of hydrophilic drugs and this may limit fetal exposure to certain drugs. Ultimately, the fetal concentrations equilibrate slowly with the maternal circulation. These changes in hemodynamic conditions return to normal in the postpartum period (Morgan 1997). Maternal hepatic clearance augmented by the increase in blood flow is also altered by changes in drug-metabolizing enzymes during pregnancy because estrogens and progesterone can induce some cytochrome P450 enzymes and inhibit others (Loebstein et al. 1997). In most cases the transfer of drugs to the fetus is inevitable. The teratogenic effects of drugs on the fetus are mainly due to exposure during the first trimester, whereas exposure thereafter will not produce a major anatomical defect, but possibly a functional one

Table 2 Therapy of hypertension in pregnancy.

Mild hypertension	Moderate-to-severe hypertension	
	Commonly used drugs	Daily dose range (mg)
Drugs, bed rest, and hospitalization are not routinely recommended	Methyldopa	250–1000 t.i.d.
The evidence for use of fish oils, marine oil, or other prostaglandin precursor supplements is insufficient	Clonidine	0.1–1.2 b.i.d.
Salt restriction is not helpful for preeclampsia prevention	Prazosin	1–10 b.i.d.
Calcium supplementation may lead to reduction in arterial blood pressure and preeclampsia	Propranolol	40–120 b.i.d. or t.i.d.
Alcohol and smoking cessation always advised	Labetalol	100–1200 b.i.d.
	Nifedipine	10–30 t.i.d. or q.i.d.
	Hydrochlorothiazide	12.5–50 q.d.

q.d., once daily; b.i.d., twice daily; t.i.d., three times daily; q.i.d, four times daily.

(Shehata and Nelson-Piercy 2000). Elimination of medications from the fetus is predominantly controlled by maternal elimination processes; lowering of maternal concentrations allows medications to diffuse back across the placenta to maternal circulation. Fetal pharmacokinetics of drugs differs in that the ability of fetal liver to metabolize drugs is much less than that in the adults. In addition, the fetal kidney is a poor route of elimination as the fetal renal blood flow is only 3% of cardiac output, compared with 25% in the adult, and the renal tubular anion secretion is absent. Furthermore, renally excreted drug enters the amniotic fluid and recirculates via fetal swallowing (Morgan 1997).

Preeclampsia is diagnosed when hypertension and proteinuria (due to increased glomerular permeability and damage) occur after 20 weeks' gestation. Edema is often seen but is not essential to make the diagnosis. Eclampsia is the occurrence of seizures as a complication of preeclampsia (Longo et al. 2003). In preeclampsia, narrowed spiral arteries and subsequent reduction in uteroplacental perfusion leads to maternal enodothelial activation/dysfunction. This leads to an enhanced formation of endothelin and thromboxane, increased vascular sensitivity to angiotensin II (attenuated in normal pregnancy), and decreased formation of vasodilators such as nitric oxide and prostacyclin. These abnormalities, in turn, cause blood pressure elevation by impairing natriuresis and increasing total peripheral resistance (Granger 2001). Platelet and coagulation cascade activation occurs in preeclampsia and is manifested by high circulating concentrations of von Willebrand factor, endothelin, cellular fibronectin, and an increased thromboxane/prostacyclin ratio (Roberts and Redman 1993). Varying degrees of abnormal cerebral perfusion pressure (both over-perfusion and under-perfusion states) exist in preeclampsia even when peripheral vasoconstriction and elevated blood pressure are less evident. These abnormalities coincide with headache and blurred vision commonly seen in preeclampsia (Belfort et al. 1999) and with cerebral edema, cerebral hemorrhage, temporary blindness, and seizures associated with eclampsia (Longo et al. 2003).

The following section reviews different classes of drugs used to treat hypertension in pregnancy.

Centrally and Peripherally Acting α-Adrenergic Agents

Centrally acting agents (methyldopa, clonidine) stimulate α_2- adrenoceptors and/or imadozoline receptors on adrenergic neurons situated within the rostra ventrolateral medulla leading to a reduction in the sympathetic outflow. As with some vasodilators, salt and water retention can occur during escalating doses and prolonged use of drugs of this class and this tends to blunt their hypotensive effects necessitating the addition of diuretics to restore blood pressure control (Sica 2007). Selective α_1 postsynaptic adrenoceptor antagonists (doxazosin, terazosin, prazosin) cause vasodilation by blocking the binding of norepinephrine to the smooth muscle receptors, while producing minimal direct tachycardia or stimulation of renin release(Dommisse et al. 1983).

Methyldopa (B)

Methyldopa is the most studied among currently used antihypertensive drugs. It has the longest safety record and is considered by most clinicians to be the drug of choice in the treatment of hypertension in pregnancy (Sibai 1996). Treatment with methyldopa in the last trimester in women with pregnancy-induced hypertension reduced maternal blood pressure and heart rate but had no adverse effects on uteroplacental and fetal hemodynamics (Montan et al.1993). Although a decrease in neonatal head circumference has been reported after first-trimester

exposure to methyldopa (Moar et al. 1978), a follow-up study to the age of 4 years showed less developmental delay in those infants whose mothers were treated with methyldopa during pregnancy than those whose mothers were untreated (Ounsted et al. 1980). Published reports demonstrated neither short-term effects on the fetus or neonate nor long-term effects during infancy after the long-term use of methyldopa in pregnancy (Sibai 1996) although there are no sufficient data on its use in the first trimester of pregnancy. Additionally, methyldopa is a weak antihypertensive drug that needs to be given three or four times a day and frequently requires titration leading to potential maternal adverse effects, use of an additional medication or nonadherence to therapy (Redman et al.1977). Methyldopa is excreted in small amounts into breast milk and is considered compatible with breast-feeding (American Academy of Pediatrics 2001).

Clonidine (C)

Clonidine is another centrally acting α_2-adrenoceptor agonist with a potential for rebound hypertension following withdrawal. It has been used mainly in the third trimester without reports of adverse outcome or rebound hypertension in the neonates, yet experience during the first trimester is very limited (Horvath et al. 1985). Clonidine is excreted in human milk at concentrations roughly twice that in maternal serum and caution should be exercised when used by nursing mothers (Hartikanen-Sorri et al. 1987).

Prazosin (C)

Although the bioavailability and half-life of prazosin are increased in pregnancy, it appears both effective and safe when used during the last trimester to control blood pressure (Rubin et al. 1983). Prazosin leads to improved blood pressure control when used in conjunction with oxprenolol in women with moderately severe gestational hypertension but no data are available on its use during breast-feeding (Dommisse et al. 1983).

Only limited data are available on the use of other central α_2-adrenoceptors agonists and peripheral α_1-adrenoceptor antagonists in human pregnancy or lactation.

β-Adrenoceptor Antagonists

β-Adrenoceptor antagonists exert their effects through the blockade of β_1-adrenoceptors (reducing heart rate, blood pressure, myocardial contractility, and myocardial oxygen consumption) and β_2-adrenoceptors (inhibiting relaxation of smooth muscle in blood vessels, bronchi, gastrointestinal system, and genitourinary tract).

β-Adrenoceptor antagonists can be divided into nonselective (propranolol nadolol, timolol, and pindolol); β_1-selective antagonists (acebutolol, atenolol, bisoprolol, betaxolol, esmolol, and metoprolol); as well as the newer third-generation β-adrenoceptor antagonists with α_1-adrenoceptor blocking properties responsible for their vasodilator effects (labetalol, carvedilol, and bucindolol) (Bakris et al. 2006). β-Adrenoceptor antagonists have been used during pregnancy without evidence of teratogenic effects. Concerns have expressed, however, when these drugs are used throughout pregnancy as they may produce adverse reactions such as intrauterine growth retardation (IUGR), cardiorespiratory depression, bradycardia, hypoglycemia, and hypothermia. These concerns may be exaggerated and these drugs are probably in this respect not different from other antihypertensive drugs (Magee et al. 2000; Waterman et al. 2004;). A recent systematic review, published in Cochrane Database, compared β-adrenoceptor antagonists as a class (included acebutolol, atenolol, metoprolol, pindolol, and propranolol) to placebo in reducing the risk of severe hypertension and the need for additional antihypertensive drugs during pregnancy. The review found that there was insufficient evidence to draw conclusions about the effects of β-adrenoceptor antagonists on perinatal outcome (Magee and Duley 2003). Despite their wide use in pregnancy, experience with β-adrenoceptor antagonists in first trimester is either lacking or shown to lead to low birth weight.

Propranolol (C)

Propranolol is a nonselective β-adrenoceptor antagonist used frequently in pregnancy with plasma concentrations, clearance, and half-life during pregnancy not different from those in nonpregnant women (O'Hare et al. 1984). Fetal and neonatal effects have been reported with propranolol and include bradycardia, hypoglycemia, IUGR, hyperbilirubinemia, polycythemia, and prolonged labor (Gladstone et al. 1975). Livingstone et al. (1983), however, reported similar blood pressure efficacy of propranolol as compared with methyldopa with no significant difference in the birth weights of the infants in either group. Propranolol and its metabolites were found to cross into breast milk with the maximum dose likely to be ingested by the infant being about 0.1% of the maternal dose, an amount unlikely to cause adverse effects (American Academy of Pediatrics 2001; Livingstone et al. 1983).

Atenolol (D)

Although in an early randomized and double-blind prospective study the selective β_1-adrenoceptor antagonist

atenolol was shown to have no adverse effects on maternal or fetal outcome (Rubin et al. 1983), a similar study later reported that atenolol given from the end of the first trimester in patients with mild hypertension is associated with IUGR and possible prolongation of β-blockade (Butters et al. 1990). Lip et al. (1997) reviewed the records of 398 women referred to an antenatal hypertension clinic between 1980 and 1995. Atenolol therapy was found to have the lowest mean birth weight compared with calcium channel antagonists, diuretics, methyldopa, other β-adrenoceptor antagonists, or no-drug therapy. In a retrospective cohort study, Bayliss et al. (2002) has shown that atenolol, taken at the time of conception and/or during the first trimester of pregnancy, was associated with low birth weight compared with other antihypertensive drugs, an effect that was lost when atenolol was used in the second trimester of pregnancy. There is no evidence, however, to suggest any short- or medium-term pediatric complications after the use of atenolol in late pregnancy as shown in a prospective study of 120 women who developed hypertension in the third trimester of pregnancy and randomized to atenolol or placebo for 5 weeks (Reynolds et al. 1984). As a result, atenolol should be avoided in the early stages of pregnancy and given with caution in the later stages. Atenolol is concentrated into human milk with peak concentrations 3.6 times higher than simultaneous plasma concentrations after single-dose administration and 2.9 times higher after continuous-dose administration warranting infant evaluation for signs of β-blockade especially in the presence of fetal renal dysfunction (White et al. 1984).

Metoprolol (C)

Sandström (1978) compared the effect of metoprolol alone or in combination with hydralazine to those treated with hydralazine in hypertensive pregnant women. Perinatal mortality and fetal growth retardation were lower in the metoprolol group with no significant adverse effects of β-blockade reported in the fetus. Oumachigui et al. (1992), in a similar cohort of patients, suggested better blood pressure control and improved fetal outcome in the metoprolol group compared to methyldopa. Although metoprolol accumulates in breast milk, breast-feeding may not need to be interrupted in an infant with normal liver function (Liedholm et al. 1981).

Labetalol (C)

Labetalol, a combined α_1- and β-adrenoceptor antagonist with vasodilatory effects, can decrease blood pressure in pregnancy without compromising uteroplacental blood flow (Lunell et al. 1982). In a placebo-controlled study treatment in mild-to-moderate gestational hypertension, labetalol demonstrated its efficacy without any increase in IUGR or neonatal hypoglycemia with a trend toward reduction in preterm delivery, neonatal respiratory distress syndrome, and jaundice in the labetalol-treated group (Pickles et al. 1989). Plouin et al. (1988) compared labetalol with methyldopa in a randomized controlled trial involving 176 pregnant women with mild-to-moderate hypertension. Blood pressure reduction, average birth weight, heart rate, blood glucose, and respiratory rate were similar in both groups. In a more recent trial comparing the two drugs, labetalol achieved faster and more efficient blood pressure control, having a beneficial effect on renal functions and was better tolerated than methyldopa (el-Qarmalawi et al. 1995). The use of labetalol versus hydralazine did not show any difference in the outcome of birth weight nor clinical signs of adrenergic blockade at 24 h of age (Hjertberg et al. 1993). Although labetalol is secreted into human milk, concentration varies and it is considered to be compatible with breast-feeding (American Academy of Pediatrics 2001; Lunell et al. 1985).

Pindolol (B)

Pindolol is a nonselective β-adrenoceptor antagonist with intrinsic sympathomimetic activity and additional vasodilatory effect. Ellenbogen et al. (1986) reported that women with gestational hypertension randomized to pindolol had more significant drop in blood pressure and improvement in renal function than those treated with methyldopa. Montan et al. (1992) described the outcome in 29 women with gestational hypertension in the third trimester randomized to pindolol or atenolol. Pindolol achieved similar blood pressure reduction to atenolol but without the increase in peripheral vascular resistance, the decrease in the umbilical venous blood flow, or the decrease in maternal and fetal heart rate seen with atenolol. Despite FDA pregnancy risk classification of B, first-trimester and breast-feeding data with pindolol are lacking.

Acebutolol (B)

Acebutolol is cardioselective β-adrenoceptor antagonist with intrinsic sympathomimetic activity. Targeting a diastolic blood pressure of 80 mmHg or less, acebutolol was compared to methyldopa in a prospective open study (Williams and Morrissey 1983). There was no difference between the two groups in duration of pregnancy, birth weight, Apgar score, or placental weight, and no evidence of bradycardia, hypoglycemia, or respiratory difficulty

in the babies born to mothers taking acebutolol. Clinical symptoms of β-blockade have been observed, on the other hand, in infants of nursing mothers receiving acebutolol and, therefore, this drug should be used with caution in this situation (Boutroy et al. 1986).

Oxprenolol

Oxprenolol is a nonselective β-adrenoceptor antagonist not available in the USA. In an early study, the pregnancy outcome was better in the group treated with oxprenolol than in patients treated with methylopda, with greater maternal plasma volume expansion and placental and fetal growth, whereas blood sugar levels were higher in the oxprenolol group (Gallery et al. 1979). In a randomized trial Plouin et al. (1990) followed 155 hypertensive women with mean gestation time at entry of 28 weeks. Women treated with oxprenolol had lower incidence of delivery by caesarian section and of fetal distress as compared to those receiving placebo ($\pm$ hydralazine). There was no effect on fetal growth. The American Academy of Pediatrics (2001) considers oxprenolol to be compatible with breast-feeding.

Other β-Adrenoceptor Antagonists

Less experience is available on the use of other oral β-adrenoceptor antagonists (bisoprolol, carvedilol, nadolol) for hypertension in pregnancy and generally their use is limited in this situation.

Calcium Channel Antagonists

Calcium channel antagonists (CCAs) prevent the opening of voltage-gated calcium channels and reduce calcium entry into cardiac or vascular smooth muscle cells during phase 2 of an action potential exhibiting different selectivity for cardiac versus vascular calcium channels (Salhanick and Shannon 2003). Animal studies dealing with some CCAs have shown a decrease in uteroplacental blood flow, IUGR, fetal death, and skeletal and cardiovascular malformations; yet a prospective, multicenter cohort study following 78 women with first-trimester exposure to CCAs showed no increase in major malformations. They may, however, cause cessation of uterine contraction and limited information is available on their use in the first trimester (Magee et al 1996).

Nifedipine (C)

Despite its efficacy, nifedipine has long been considered a second-line therapy. In 1987 Constantine et al. (1987) used slow-release nifedipine in the treatment of severe hypertension in 23 pregnant women. In 22 of them nifedipine was used in combination with other drugs, and in 18 of them the other drug was atenolol. A high rate of premature delivery and a high rate of smaller infants were reported. It was not clear whether these findings were related to severe maternal disease or to drug therapy. To test its use as first-line therapy, Jayawardana and Lekamge (1994) allocated a total of 126 patients with gestational hypertension in their third trimester alternately to either nifedipine or methyldopa. Both drugs achieved similar blood pressure reduction and maternofetal safety profile. Mari et al. (1989) demonstrated that short-term nifedipine therapy in preeclampsia remote from term did not adversely affect fetal and uteroplacental circulation. Over long-term follow-up period (18 months) no abnormalities in child development were found in infants born to women treated with nifedipine during pregnancy (Bortolus et al. 2000). Because of the lipophilic nature of nifedipine, the levels of the drug in the umbilical serum and breast milk were relatively high, but pregnancy outcome was favorable in all cases (Manninen and Juhakoski 1991). The American Academy of Pediatrics (2001) considers the use of nifedipine to be compatible with breast-feeding. The use of short-acting nifedipine in acutely severe hypertension will be discussed later.

Nicardipine (C)

Nicardipine has been used for the treatment of hypertension in pregnancy. In a study published in 1993, Carbonne et al. (1993) treated 40 pregnant patients (mild or moderate hypertension) with oral nicardipine starting at 28 weeks' gestation through the seventh-postpartum day. Twenty patients with severe preeclampsia received intravenous nicardipine. Both regimens achieved a significant decrease in blood pressures without reported fetal or neonatal adverse effects. Jannet et al. (1994) compared the effect of the dihydropyridine nicardipine and metoprolol in 100 patients with mild or moderate hypertension during pregnancy. Nicardipine was found to be more effective than metoprolol in decreasing maternal BP, although the neonatal outcome was not significantly different despite a trend toward higher birth weights in the nicardipine group. There no data are available on the use of nicardipine in nursing mothers.

Other CCAs

Isradipine (C) was studied in 27 women with gestational hypertension in the third trimester. The drug significantly reduced mean arterial pressure without altering uteroplacental or fetal blood flows (Lunell et al. 1991). The data are inadequate on diltiazem (C), verapamil (C), or amlodipine (C) to provide reliable information on their

efficacy and safety in the treatment of hypertension in pregnancy.

Vasodilators

Hydralazine (C)

Oral hydralazine (arteriolar dilator) has no effect on placental or maternal renal vascular resistance despite reflex tachycardia and hypotensive effect (Gudmundsson et al. 1995). Due to its weak hypotensive effect, hydralazine is commonly used to augment the action of methyldopa or of β-adrenoceptor antagonists (Barron and Lindheimer 1995). Hydralazine is secreted into breast milk and the American Academy of Pediatrics (2001) considers hydralazine to be compatible with breast-feeding. The parenteral use of hydralazine and other vasodilators will be discussed under treatment of acute hypertension.

Diuretics

Due to their widespread use, many young women with chronic hypertension may find themselves pregnant while taking diuretics. An old small controlled trial using a diuretic combined with methyldopa or hydralazine for chronic hypertension in multiparas claimed that treatment prevented "pregnancy-aggravated" hypertension (Arias and Zamora 1979). The benefit of diuretics-reducing preeclempsia has been claimed on the basis of their ability to reduce edema that has been included in the past as an essential diagnostic criterion of preeclampsia. The presence of hypovolemia and decreased central venous pressures in preeclempsia led to concerns about the use of diuretics in this population despite concurrent generalized edema (Maclean et al. 1978). In hypertensive pregnancies, diuretics may prevent normal plasma volume expansion an effect that may be damaging to the fetal growth (Sibai et al. 1984). A Cochrane review by Churchill et al. (2007) confirmed the lack of the efficacy of diuretics in the prevention of preeclampsia and association of more nausea and vomiting with diuretic therapy. In the absence of preeclampsia or reduced fetal growth, the Working Group Report on High Blood Pressure in Pregnancy concluded that gestation does not preclude use of diuretic drugs to reduce or control blood pressure in women whose hypertension predated conception or manifested before midpregnancy (Lenfant 2001).

Thiazide Diuretics

Collins et al. (1985) reviewed nine randomized trials comparing thiazide therapy (chlorothiazide (C), hydrochlorothiazide (B), bendroflumethiazide (C), chlorthalidone (B), dihydrotrichlorothiazide or cyclopenthiazide) with no treatment in nearly 7000 pregnant women. This comparison failed to provide reliable evidence of either the presence or the absence of any worthwhile effects of treatment with diuretics on perinatal mortality. In addition, reported adverse effects of thiazides (neonatal thrombocytopenia and jaundice; maternal pancreatitis, hypokalemia, and hyponatremia) were not significantly different in treated versus untreated women. Thiazides are distributed into breast milk and have been used to inhibit lactation, yet the American Academy of Pediatrics (2001) considers chlorothiazide, hydrochlorothiazide, bendroflumethiazide, and chlorthalidone to be compatible with breast-feeding.

Loop Diuretics

Loop diuretics, especially furosemide (C), have been used in pregnancy to treat pulmonary edema, severe hypertension in the presence of chronic kidney disease, or congestive heart failure despite the potential risk of neonatal hyperbilirubinemia (Turmen et al. 1982). There is, however, a lack of adequate data on their use in pregnant women.

Loop diuretics cross into breast milk and may suppress lactation but the American Academy of Pediatrics (2001) has no recommendation regarding their use in lactating mothers.

Other Diuretics

Little data is available on the use of potassium-sparing diuretics (spironolactone (D), amiloride (B), triamterene (D)) to treat hypertension during pregnancy although spironolactone is contraindicated due to concerns about its antiandrogenic properties in animals (Messina et al. 1979). Spironolactone is considered compatible with breast-feeding (American Academy of Pediatrics 2001).

Drugs Acting on the Renin-Angiotensin-Aldosterone System

Accumulating evidence suggests that angiotensin II plays an important role in nephrogenesis through its type 1 receptor (vascular smooth muscle cells differentiation) and type 2 receptor (mesenchymal proliferation and apoptosis) (Lasaitiene et al. 2006). Intrauterine exposure to angiotensin-converting enzyme (ACE) inhibitors has been accompanied by severe disturbance of fetal and neonatal renal function, such as oligohydramnios, long-lasting neonatal anuria as well as pulmonary hypoplasia (Hanssens et al. 1991). Similar abnormalities have been reported after fetal exposure to angiotensin

type 2 receptor blockers (ARBs) (Martinovic et al. 2001). Currently, all ACE inhibitors, ARBs, and the new direct renin inhibitor aliskiren, are considered pregnancy category C in the first trimester and category D in the second and third trimesters. Recently, Cooper et al. (2006) reported that infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95% confidence interval, 1.72 to 4.27). Given the possible teratogenic effect of ACE inhibitors, renin-angiotensin-aldosterone system antagonists should be avoided throughout pregnancy and in women planning to conceive.

The American Academy of Pediatrics (2001) considers captopril and enalapril compatible with breast-feeding. There are no data describing the use of other ACE inhibitors or ARBs during human lactation.

Treatment of Acute Severe Hypertension

Antihypertensive treatment in pregnancy is needed to protect the mother from the dangers of severe uncontrolled hypertension particularly cerebral hemorrhage in the context of severe preeclampsia (Kyle and Redman 1992). Martin et al. (2005) described 28 women who had hemorrhagic strokes associated with severe preeclampsia and eclampsia. Twenty-four of them had prestroke systolic arterial pressure that exceeded 155–160 mmHg. In contrast, only 3 of 24 patients (12.5%) exhibited prestroke diastolic pressures of 110 mmHg or greater and only 5 of 28 reached 105 mmHg. This may suggest the need to consider antihypertensive therapy for severely preeclamptic and eclamptic patients when systolic blood pressure reaches or exceeds 155–160 mmHg in addition to the recommendation by the American College of Obstetricians and Gynecologists Practice Guidelines to initiate therapy for diastolic blood pressure levels of 105–110 mmHg or higher (American College of Obstetricians and Gynecologists 2002). Hydralazine, labetalol, or nifedipine are the most frequently employed agents for the rapid reduction of acute severe hypertension (Table 3).

Parenteral labetalol (C) has been shown to be effective for the treatment of uncontrolled severe hypertension in pregnancy by producing rapid dose-dependent decreases in arterial pressure without reflex tachycardia or significant reduction in heart rate and by reducing the incidence of dangerous ventricular arrhythmias that might occur with hydralazine (Mabie et al. 1987). In a recent report by Belfort et al. (2002) labetalol significantly reduced the cerebral perfusion pressure in preeclamptic gravidas without affecting cerebral perfusion, primarily by a decrease in systemic arterial pressure.

Nifedipine (C) has a clinical advantage because it is given by mouth in the absence of an intravenous route. The use of oral short-acting nifedipine for acute hypertension has decreased due to numerous reports of serious adverse effects such as stroke, severe hypotension, acute myocardial infarction, cardiac conduction disturbances, fetal distress, and death (Grossman et al. 1996). Nifedipine has been used, however, by Walters and Redman (1984) in 21 women during the second and third trimesters for the treatment of severe uncontrolled hypertension. A rapid and significant fall in arterial pressure by an average of 26/20 mmHg was seen at 20 min after administration with no adverse fetal effects. In another prospective comparative study, Visser and Wallenburg (1995) compared nifedipine capsules to intravenous dihydralazine (closely related to hydralazine) in 20 patients with severe preeclampsia between 27 and 35 weeks' gestation. Both drugs achieved similar blood pressure reduction but no signs of fetal distress occurred in the nifedipine-treated patients. Five of the patients treated with dihydralazine exhibited maternal hypotension and fetal heart rate deceleration. Despite multiple reports on exaggerated hypotension following concurrent use of parenteral magnesium sulfate with nifedipine, Scardo et al. (1996) studied the effects of oral nifedipine in 10 severely preeclamptic patients receiving magnesium sulfate infusion during a hypertensive emergency. All patients had systolic arterial pressure higher than or equal to 170 mmHg or the diastolic arterial pressure higher than or equal to 105 mmHg on repeat measurements 15 minutes apart at 24 weeks' or longer periods of gestation. Nifedipine decreased mean arterial pressure, systemic vascular resistance, and increased cardiac index without producing any undesirable maternal or fetal hemodynamic effects.

Nicardipine (C) was used in 20 patients with severe preeclampsia (diastolic arterial pressure greater than 110 mmHg and 24-hour proteinuria greater than 500 mg). Intravenous nicardipine decreased diastolic blood pressure below 90 mmHg, at least temporarily, in all 20 patients (Carbonne et al. 1993). In another report Hanff et al. (2005) confirmed that nicardipine can be used effectively in early-onset preeclampsia (median gestational age of 27 weeks) when other antihypertensive drugs (ketanserin, dihydralazine, or labetalol) have failed. Magnesium sulfate was administered during nicardipine treatment in three patients, but failed to increase the antihypertensive response.

Intravenous hydralazine (C), a potent arterial vasodilator, has long been the standard therapy for the management of hypertensive emergencies complicating pregnancy. Different randomized trials have suggested that nifedipine and labetalol are superior or equivalent to

Table 3 Antihypertensive drugs used in the treatment of severe hypertension in pregnancy. Maternal adverse effects and special considerations.

Drug	Dose	Maternal adverse effects	Special considerations
Hydralazine	5 mg i.v. bolus, then 10 mg every 20–30 min to a maximum of 25 mg, repeat in several hours as necessary	Hypotension, tachycardia, flushing, headache, vomiting, aggravation of angina, Lupus-like symptom	Fetal distress Neonatal thrombocytopenia
Labetalol	20 mg i.v. bolus, then 40 mg 10 min later, 80 mg every 10 min for two additional doses to a maximum of 220 mg	Nausea, vomiting, scalp tingling, bronchoconstriction, dizziness, heart block, orthostatic hypotension. Avoid in heart failure	Neonatal bradycardia, hypotension, and hypoglycemia
Nifedipine	10 mg p.o., repeat every 20 min to a maximum of 30 mg	Tachycardia, headache, flushing, tocolysis Caution with magnesium sulfate (hypotension)	Extended release formulation most available, but more data is needed for use in hypertensive emergency
Sodium nitroprusside	0.25 μg/kg/min to a maximum of 5 μg/kg/min	Nausea, vomiting, muscle, twitching, sweating, thiocynate, and cyanide intoxication	Fetal cyanide poisoning if used > 4 hours Used rarely, when others fail
Diazoxide	30–50 mg i.v. every 5–15 min	Hypotension, uterine atony, and hyperglycemia	Fetal hyperglycemia and distress
Nitroglycerin	5–100 μg/min as i.v. infusion	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Use in coronary ischemia and pulmonary edema

i.v., intravenous; min, minute; p.o., oral. Adapted from the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2003.

hydralazine for severe hypertension in pregnancy with possibly less fetal distress (Aali and Nejad 2002; Mabie et al. 1987). A recent *meta*-analysis of randomized controlled trials (between 1966 and 2002) of short-acting antihypertensives for severe hypertension in pregnancy has showed that hydralazine was associated with poorer maternal and perinatal outcomes than other antihypertensive drugs, particularly labetalol or nifedipine. Several adverse outcomes such as maternal hypotension, placental abruption, and adverse effects on fetal heart rate do not support the use of hydralazine as first line for treatment of severe hypertension in pregnancy (Magee et al. 2003).

Intravenous sodium nitroprusside (C) is an ultrafast antihypertensive drug. It produces arterial and venous vasodilatation, thereby decreasing both preload and afterload making it an excellent drug for acute severe hypertension. Its prolonged administration should be, however, avoided because of the risk of fetal cyanide toxicity (Baker 1990).

Nitroglycerin (C) is a rapidly acting antihypertensive drug with a short half-life. It relaxes mainly venous vascular smooth muscle, decreasing preload at low doses and afterload at high doses. It has been used to treat acute myocardial infarction during pregnancy (Kulka et al. 2001) or pulmonary edema complicating severe preeclempsia although overall there are limited data on its use in pregnancy (Cotton et al. 1986).

Intravenous diazoxide (C) was one of the first agents to be used; however, even in small doses it can lead to significant maternal hypotension, uterine atony, maternal, and neonatal hyperglycemia (Morris et al. 1977).

Conclusions

Drug therapy to lower arterial pressure in pregnancy should be used mainly for maternal safety due to lack of data to support an improvement in fetal outcome. Drug therapy is usually indicated if arterial pressures exceeds 150 to 160 mmHg systolic or 100 to 110 mmHg diastolic or in the presence of target organ damage. Multiple drug classes have demonstrated efficacy as well as maternal and fetal safety in the treatment of hypertension in pregnancy with overall insufficient first-trimester data. Methyldopa remains the first drug of choice in the treatment of chronic hypertension. β-Adrenoceptor antagonists, especially those with vasodilating properties (labetalol, pindolol), are gradually becoming a standard therapy. ACE inhibitors, ARBs, and direct renin inhibitors should not be used in pregnancy or in females planning to conceive. Diuretic therapy is inappropriate in preeclempsia because plasma volume is reduced. In severe

uncontrolled hypertension, intravenous labetalol or oral nifedipine can be used. Due to excessive adverse perinatal effects, intravenous hydralazine is less frequently used. During lactation no adverse effects have been reported from exposure to methyldopa or hydralazine. Among β-adrenoceptor antagonists propranolol and labetalol are preferred.. ACEIs, ARBs, and renin inhibitors should be avoided. Diuretics may suppress lactation and should be used with caution.

Conflict of Interest

The authors have no conflict of interest.

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