



## TREATMENT OF CHRONIC HYPERTENSION DURING PREGNANCY

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Affecting 0.6–2.0% of women 18–29 years old and 4.6–22.3% of women 30–39 years old, chronic hypertension is a common disease in pregnancy.<sup>1</sup> Despite a long history of treating hypertension in pregnancy, few well designed studies exist to guide treatment. Instead, recommendations are derived from expert opinion and experience rather than standardized guidelines. Some trials have sought to compare antihypertensives in pregnancy. However, safe and effective treatment must be assessed on a case by case basis because many of these trials are not well designed or have unclear results. This article will review the roles and studies evaluating safety of selected antihypertensive therapies in the treatment of chronic hypertension in pregnancy.

### PREGNANCY CATEGORIES

All antihypertensive medications are listed as Pregnancy Categories B, C, or D (definitions in Table 1), meaning that none have clearly shown freedom from adverse events to the fetus. Although commonly regarded as safe in pregnancy, medications classified as Pregnancy Category B may still have risks to either the mother or fetus. Therefore, each therapeutic option must be evaluated based on the patient's comorbid conditions, risk factors, gestational age, and concomitant medications.

### ETIOLOGY OF HYPERTENSION IN PREGNANCY

Chronic hypertension in pregnancy is defined as systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg documented prior to pregnancy or diagnosed prior to week 20 of gestation. In contrast, pre-eclampsia is typically diagnosed after the 20<sup>th</sup> week and is associated with proteinuria and/or edema. Gestational hypertension, which is also diagnosed after the 20<sup>th</sup> week of gestation, is not accompanied by proteinuria. Pre-eclampsia and gestational hypertension are treated differently from chronic hypertension and will not be addressed in this article.

Women with mild pre-existent hypertension who become pregnant are at increased risk of several complications. First, pre-existent hypertension increases the absolute risk of superimposed preeclampsia by 10 to 25%. Secondly, the absolute risk of *abruptio placentae* is increased by 0.7 to 1.5%. Thirdly, a 12 to 34% increased risk of preterm birth, which is defined as delivery <37 weeks, is seen in pregnant mothers with pre-existing hypertension. Fourthly, fetal growth restriction increases 8 to 16% compared to mothers without pre-existing hypertension.<sup>3</sup> Finally, fetal mortality is also increased more than three-fold in women with chronic hypertension.<sup>4</sup>

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**Table 1. FDA Pregnancy Categories<sup>2</sup>**

CATEGORY	DEFINITION
<b>A</b>	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
<b>B</b>	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
<b>C</b>	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
<b>D</b>	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
<b>X</b>	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

### INDICATIONS FOR TREATMENT

The time frame for initiating treatment in the management of chronic hypertension of pregnancy is not agreed upon by all experts. Because of a natural decrease in blood pressure beginning at week 7 of gestation, many physicians are willing to wait until these physiologic changes begin and assess if this alone brings blood pressure within goal. In most pregnant patients with mild to moderate hypertension, defined as blood pressure of 140 to 160/90 to 100 mmHg, no clear evidence exists that initiation of treatment below this value improves fetal or maternal outcomes.<sup>5</sup> Consequently, clinicians should consider delaying treatment of mild to moderate hypertension.

A meta-analysis of seven randomized controlled trials studying a total of 623 pregnant women with mild chronic hypertension compared antihypertensive treatment with no treatment. The authors found a decrease in severe hypertension (defined as blood pressure > 160/100 mmHg) and need for additional antihypertensives, but found no difference in either maternal or fetal outcomes including mortality.<sup>6</sup> An upward trend in the incidence of fetal growth restriction was found, but failed to reach significance.

Several compelling indications may warrant antihypertensive therapy (Table 2), because they put the mother and fetus at high risk for adverse events. For these patients, blood pressure above 140/90 mmHg may be treated to a goal blood pressure of 120 to 140 mmHg/80 to 90 mmHg.

### SELECTED THERAPEUTIC OPTIONS

#### *Methyldopa*

Methyldopa is a centrally acting  $\alpha$ -adrenergic antagonist used in the treatment of hypertension. Methyldopa is Pregnancy Category B (Table 3) and has a long, established track record in the treatment of hypertension in pregnancy. Many studies have been conducted in both humans and animals with no incidence of serious adverse events to the fetus.<sup>7,8</sup> While no congenital abnormalities have been observed, the use of methyldopa is limited by its adverse events to the mother, including somnolence, lethargy, and orthostatic hypotension. Methyldopa has been used safely as an antihypertensive in pregnancy and is frequently used by physicians based on its lack of documented fetal adverse effects.<sup>8</sup>

#### *Labetalol*

Labetalol has combined  $\alpha$ - and  $\beta$ -adrenergic antagonist activity and is one of the most frequently used  $\beta$ -antagonists in the treatment of hypertension in pregnancy. Labetalol is Pregnancy Category B. Unlike other nonspecific  $\beta$ -antagonists such as propranolol, labetalol has not been found to increase respiratory depression, fetal growth restriction, bradycardia, or hypoglycemia.<sup>7</sup> Possibly because of its combination of  $\alpha$ - and  $\beta$ -antagonism, labetalol is not associated with decreased placental perfusion that can occur with pure  $\beta$ -antagonists. Consequently, labetalol is a regularly prescribed antihypertensive and may be a good option if the mother cannot tolerate methyldopa.<sup>9</sup> Because of

**Table 2. Risk Factors Associated with Antihypertensive Drug Use in Pregnancy<sup>3</sup>**

- Secondary, rather than essential, hypertension (e.g., renal disease, collagen vascular disease, coarctation of the aorta)
- End-organ damage (e.g., ventricular dysfunction, retinopathy)
- Dyslipidemia
- Maternal age over 40 years old
- Microvascular disease
- History of stroke
- Previous perinatal loss
- Diabetes

potential adverse events, newborns of all mothers taking  $\beta$ -blockers should be screened for lung function and hypoglycemia postpartum.

#### *$\beta$ -antagonists with Intrinsic Sympathomimetic Activity*

$\beta$ -antagonists with intrinsic sympathomimetic activity (ISA) such as pindolol (Pregnancy Category B) may have advantages in pregnant women compared to non-ISA agents. Pindolol has been found superior to  $\beta$ -antagonists without ISA in pregnant patients. Head to head studies with other  $\beta$ -antagonists, including atenolol, found pindolol superior regarding fetal hemodynamics<sup>10</sup> and birth weight.<sup>11</sup>  $\beta$ -antagonists with ISA are associated with fewer adverse events than agents without ISA and therefore may be a better choice for the treatment of hypertension.

#### *$\beta$ -antagonists: Other Considerations*

Unlike labetalol and pindolol which have data documenting safety in pregnancy, some  $\beta$ -antagonists are likely harmful to the fetus based on available evidence. Atenolol and propranolol are two agents that increase the risk of adverse events to the fetus and should not be used as antihypertensive therapy unless the benefit clearly outweighs the risk to the fetus.

Atenolol decreases fetal birth weight compared to placebo,<sup>12</sup> labetalol,<sup>13</sup> and  $\beta$ -antagonists with ISA.<sup>11</sup> Atenolol is also associated with neonatal bradycardia. One study found a 39% incidence of bradycardia in newborns of mothers treated with atenolol versus 10% with newborns of placebo-exposed mothers.<sup>14</sup> In addition to fetal risks while in the womb, atenolol may cause harm in newborns. A case study found persistent concentrations of atenolol in a newborn which the authors associated with various adverse reactions including bradycardia and hypotension.<sup>15</sup> The increased proportion of body water and the renal insufficiency of newborns combined with the water-soluble nature of atenolol put the fetus at risk for accumulation after delivery. The long term effects of atenolol are largely unknown, but with the availability of antihypertensive

agents with better safety data in pregnancy, atenolol should be avoided.<sup>12</sup>

Propranolol is a non-specific  $\beta$ -antagonist classified as Pregnancy Category C. Because of a number of reports showing increased risk to the fetus, propranolol is best avoided during pregnancy. A pooled analysis of 167 case reports of live-born infants born to patients taking propranolol during pregnancy showed a high number of newborns with intrauterine growth restriction (14%), hypoglycemia (10%), bradycardia (7%), respiratory depression (6%), and other adverse events post delivery.<sup>7</sup> However, the actual incidence of adverse events may be less than reported since this analysis was not a representative sample. Nonetheless, patients should be carefully evaluated for risk and benefit before initiating propranolol as a first line agent.<sup>7</sup>

#### *Hydralazine*

Hydralazine is a peripheral arterial vasodilator that is Pregnancy Category C. No reports of congenital defects have been associated with hydralazine, and it is a commonly prescribed antihypertensive for pregnant women outside the United States.<sup>7</sup> Adverse events for the fetus, however, have been documented. One case report describes a fetus that developed an atrial arrhythmia in the womb while the mother was taking hydralazine.<sup>16</sup> The arrhythmia resolved 24 hours after discontinuing the medication. Aside from risk of fetal harm, hydralazine therapy has the potential to cause adverse reactions in the mother including orthostatic hypotension, peripheral edema, drowsiness, and more serious adverse events such as blood dyscrasias and a lupus-like syndrome. Practitioners should carefully consider the potential risk of fetal and maternal harm before a pregnant patient is treated with hydralazine.

#### *Calcium Channel Antagonists*

Dihydropyridine calcium channel antagonists such as nifedipine have been used to treat hypertension in

pregnant women; however all dihydropyridines are Pregnancy Category C. Animal studies in rats and rabbits have shown teratogenicity at doses well above the maximum human dose, but these findings have not been substantiated in humans. In a study of 23 women receiving slow release nifedipine, the authors found no evidence of fetal harm.<sup>17</sup> However, almost all babies born were “small-for-dates.” The authors attributed this finding to the complicated patients enrolled in the study and their respective disease states. Given the limited data, nifedipine is considered a second line agent to be used only when the benefit outweighs the potential risks.<sup>3</sup>

The non-dihydropyridine calcium channel antagonists diltiazem and verapamil are rarely used in pregnancy as antihypertensives and are Pregnancy Category C. Diltiazem causes teratogenic effects on the skeletal system in high dose animal studies,<sup>18</sup> but teratogenicity has not been found in humans.<sup>7,19</sup> A chart review of 229,101 completed pregnancies showed 27

newborns exposed to diltiazem.<sup>7</sup> Of these, four (14.8%) had major birth defects, of which two were cardiovascular defects (7.4%). Based on the small sample size, the significance of these findings is unclear, but it is possible that fetuses exposed to diltiazem may be at increased risk of cardiovascular abnormalities. This possible association is reason enough to be wary of the use of diltiazem for treating hypertension during pregnancy.

Verapamil is not often used as an antihypertensive due to its relatively weak action on the vasculature. One case study has demonstrated efficacy in the treatment of fetal tachycardia in combination with digoxin.<sup>20</sup> However, the authors of this case study could not conclude that the resolution of tachycardia was due to digoxin, verapamil, or the combination of the two. Despite documented safety in some pregnancies, one case report has shown a possible association with fetal AV block and death (in combination with digoxin).<sup>21</sup> No reports have demonstrated teratogenicity,

**Table 3. Antihypertensive Therapeutic Options in Pregnancy**

MEDICATION	PREGNANCY CATEGORY	STARTING DOSE	MAXIMUM DOSE	COMPATIBLE W/ BREASTFEEDING?
<b>Methyldopa</b> (Aldomet®)	B	250mg PO BID	3g/day PO	Yes*
<b>Labetalol</b> (Trandate®, Normodyne®)	C	100mg PO BID	2400 mg/day PO	Yes*
<b>Pindolol</b> (Visken®)	B	5mg PO TID	40mg/day PO	No <sup>†</sup>
<b>Propranolol</b> (Inderal®)	C	40mg PO BID	640mg/day PO	Yes*
<b>Hydralazine</b> (Apresoline®)	C	10mg 2-4 times daily	300mg/day PO	Yes*
<b>Nifedipine</b> (Procardia®)	C	30mg XL PO daily	90mg/day PO (XL)	Yes*
<b>Diltiazem (CD)</b> (Cardizem®, Tiazac®, Dilacor®)	C	120-240mg PO daily	480mg/day PO	Yes*
<b>Verapamil</b> (Calan® IR, Isoptin®, Verelan® SR)	C	80mg PO TID (IR) 240mg daily (Verelan)	480mg/day PO (IR) 480mg/day PO (Verelan)	Yes*
<b>Hydrochlorothiazide</b> (Hydrodiuril®, Microzide®, others)	B	12.5-25mg PO daily	50mg/day PO	Yes*
<b>Clonidine</b> (Catapres®)	C	0.1mg BID	2.4mg/day PO	Weigh Risk/Benefit <sup>†</sup>

**XL** = extended release; **CD** = Controlled dose (once daily); **IR** = Immediate Release; **PO** = By mouth.

\* According to American Association of Pediatrics Committee on Drugs 2001

<sup>†</sup> According to manufacturer’s recommendations

but because of verapamil's inferior blood pressure control, other options may be more beneficial in treating hypertension uncomplicated by arrhythmias or tachycardia during pregnancy.

### *Clonidine*

Clonidine (Pregnancy Category C) is a centrally acting  $\alpha_2$ -adrenergic agonist used as adjunct therapy to treat hypertension in the general population. Data in pregnancy, however, is limited. No congenital defects have been reported with clonidine although one retrospective analysis found a possible association with sleep disturbances and hyperactivity with children whose mothers had taken clonidine during pregnancy.<sup>22</sup> Clonidine therapy is often limited by an increased incidence of somnolence, dizziness, and lethargy which may be intolerable for the mother. Because of a lack of data, clonidine should not be used as first line therapy, but may be appropriate for adjunct therapy in severe hypertension if other antihypertensive options are limited.

### *Thiazide and Thiazide-like Diuretics*

Thiazides and thiazide-like diuretics include chlorothiazide, hydrochlorothiazide (HCTZ), chlorthalidone, indapamide, and metolazone. All are FDA Pregnancy Category B except chlorothiazide which is Category C, though all have very similar pharmacologic profiles. Thiazide diuretics create imbalances in serum electrolytes, especially potassium. Electrolyte disturbances caused by thiazide diuretics have not been linked to fetal harm, but the true risk is unknown. Thiazide diuretics also decrease plasma volume expansion that occurs naturally as pregnancy progresses. One study found that patients treated with diuretics had only an 18% increase in plasma volume versus 52% in those receiving placebo.<sup>23</sup> However, no differences were observed in fetal or maternal adverse outcomes.

Since thiazide diuretics contract volume early in therapy, pregnant mothers should be evaluated for indications to continue a thiazide if she has been on this medicine for a long period of time. Unfortunately, no well designed trials have evaluated the feasibility of this option. Most practitioners consider thiazide diuretics as Pregnancy Category D and avoid their use due to theoretical complications from limited plasma volume expansion and electrolyte disturbances. Prospective trials evaluating the safety of thiazide diuretics should be performed since they have been shown to possess mortality benefit to non-pregnant patients<sup>24</sup> and are well tolerated in the treatment of hypertension in the general population.

### *ACE-Inhibitors and ARBs*

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs), while widely used in the general population, are Pregnancy Category D and should not be used in pregnancy. A review of Tennessee Medicaid patients found that infants exposed to ACE inhibitors in the first trimester were at increased risk for malformations of the cardiovascular system (RR, 3.72; 95% CI, 1.89 to 7.30) and the central nervous system (RR, 4.39; 95% CI, 1.37 to 14.02).<sup>25</sup> Fetal complications of oligohydramnios, renal failure, and in-utero death are associated with ACE-I and ARB exposure in the second and third trimester.<sup>26</sup>

While the fetal harm caused by ACE-Is and ARBs is well documented, a 2008 retrospective cohort study of Tennessee Medicaid patients found an alarming trend of increased usage of ACE-Is and ARBs in pregnant females from 1986 to 2003.<sup>27</sup> The incidence rose from 11.2 per 10,000 pregnancies during 1986-1988 to 58.9 per 10,000 pregnancies in 2003. Disturbingly, the rates of usage in the second and third trimester nearly tripled despite a black box warning issued by the FDA in 1992, warning of the fetal harm caused by these medications. The application of this study to all pregnancies may be questioned, but it shows that prescribers should be more vigilant in discontinuing ACE-Is and ARBs as soon as pregnancy is discovered to avoid the potential for fetal adverse events.

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## SUMMARY

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Antihypertensive therapy is best initiated when blood pressure exceeds 160/100 mmHg in pregnant women with chronic hypertension without additional risk factors of fetal harm. Women with secondary hypertension, end organ damage, dyslipidemia, greater than 40 years old, microvascular disease, previous stroke, previous perinatal loss, and/or diabetes mellitus should be treated for any blood pressure above 140/90 mmHg with a goal systolic pressure of 120 to 140 mmHg and goal diastolic pressure of 80-90 mmHg. Methyldopa, labetalol, and pindolol are the best choices for first line therapy whereas  $\beta$ -antagonists without ISA, hydralazine, calcium channel antagonists, thiazide diuretics, and clonidine are best reserved for second line or adjunct therapy. ACE-Is and ARBs have no place in the treatment of hypertension in pregnancy as they lead to congenital defects and are no more effective than other classes of antihypertensives. Ultimately, the choice of antihypertensive therapy should be individualized regarding each patient's risk factors.

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