

# Safety of Antihypertensive Medications in Pregnancy: Living With Uncertainty

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**H**ypertension is one of the most common medical complications of pregnancy. Clinical management is challenging; strategies that are standard of care in nonpregnant individuals, such as lowering blood pressure (BP) to 120/80 mm Hg, may be beneficial for maternal health<sup>1</sup> but must be considered carefully in the context of possible teratogenicity of medications if taken in early pregnancy. As pregnancy progresses, the impact of drugs on blood flow and placental perfusion must be addressed. Even if medications are not teratogenic, less easily detected effects on placental and fetal growth and metabolism are important. That said, and regardless of etiology, severe hypertension—defined as 160/110 mm Hg—is associated with serious maternal morbidity and mortality, and treatment with antihypertensive drugs is almost always indicated.<sup>2,3</sup> What remains unclear, although currently under investigation, is whether the treatment is worse than the disease in pregnancies complicated by “mild to moderate” hypertension (140–159/90–109 mm Hg). Lowering BP in women with less severe, so-called mild to moderate hypertension is not routine practice in the United States, although it may be appropriate in some women with chronic hypertension, depending on maternal symptoms, acuity of the BP increase, comorbidities, and gestational age.<sup>2</sup> At present, some evidence suggests that antihypertensive treatment in women with mild to moderate chronic or gestational hypertension may prevent the development of severe hypertension,<sup>4</sup> and retrospective data suggest that lower BP is associated with better pregnancy outcomes.<sup>5</sup> The existing data have not demonstrated an

association of treatment to lower BP targets with fetal benefit, although published trials were underpowered to detect changes in fetal death. Consequently, we are left with uncertainty regarding the impact of antihypertensive therapy on fetal growth and long-term health. Guidelines for treatment of hypertension in pregnancy vary among geographic regions of the world except all agree that treatment of severe hypertension is indicated.<sup>2,3</sup>

The practitioner is faced with the challenge of prescribing (or continuing) antihypertensive medications, which may be beneficial for the mother but are of unclear benefit for the fetus. The drugs most commonly used—methyldopa, labetalol, and nifedipine—are widely accepted as safe in pregnancy, based on many years of experience, observational data from large databases, and meta-analyses of multiple small clinical trials. A recent comprehensive systematic review of published studies addressing adverse outcomes in children with in utero exposure to antihypertensive medications<sup>6</sup> found 47 studies eligible for inclusion, and only 5 were considered of excellent quality. Although several studies reported increased odds of preterm birth, low birth weight, and congenital malformations in treated patients compared with normotensive untreated reference groups, these adverse effects were not uniformly observed in different studies within the same class of medication. Similar adverse events were also observed in untreated hypertensive women. The conclusions of the authors were that although there is no compelling evidence for teratogenicity of most antihypertensive agents, the methodological weakness of the evidence prevents definitive answers about the safety of these drugs, even when including studies with hundreds of thousands of participants.<sup>6</sup>

In this issue of the *Journal of the American Heart Association (JAHA)*, Mito and colleagues report important new information about amlodipine exposure in the first trimester of pregnancy.<sup>7</sup> Amlodipine is among the most widely prescribed antihypertensive medications for nonpregnant individuals; however, before the study by Mito and colleagues, only limited data (<50 cases) regarding safety in pregnancy were available.<sup>8,9</sup> Mito and colleagues retrospectively examined birth outcomes of 231 pregnant women with chronic hypertension who delivered at the National Center for Child Health and Development, Osaka Women’s and

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Children's Hospital, and the National Cerebral and Cardiovascular Center from 2008 to 2016 in Japan. In total, 48 participants had first-trimester exposure to amlodipine, 54 were exposed to other antihypertensives, and 129 had no drug exposure. Rates of fetal morphologic abnormalities were similar in all 3 groups: 4.2%, 5.6%, and 4.7%, respectively. The 5 women with malformations in the 2 groups with antihypertensive medication exposure in the first trimester included 3 cases of heart malformations (pulmonary valve stenosis, ventricular septal defect) and 2 with hypospadias. Among women without antihypertensive exposure, there were 6 malformations including heart malformations (ventricular septal defect, patent foramen ovale), Potter syndrome, low-lying conus medullaris, and hypospadias. The association of hypertension itself with specific birth defects has been observed previously. Anomalies in the kidney, limbs, lips, and palate; heart malformations; hypospadias; and esophageal atresia have been reported.<sup>10,11</sup> Mito and colleagues concluded that, based on this admittedly small sample, amlodipine exposure in early pregnancy does not appear to be associated with an increased rate of fetal malformations compared with other antihypertensive medications or maternal hypertension without treatment.

The study by Mito et al<sup>7</sup> is small—a weakness acknowledged by the authors; however, its importance is that it adds incrementally to the evidence regarding the safety of amlodipine. In addition, it confirms previous reports of comparable rates of malformations associated with both treated and untreated hypertension that are slightly higher than the baseline of 1% to 3% in women without exposure to hypertension with or without medication use. In their retrospective cohort, the authors leveraged information obtained from electronic medical records and excluded patients who did not meet established guidelines criteria for chronic (preexisting) hypertension.<sup>3</sup> There was a higher prevalence of fetal growth restriction in a prior pregnancy in women who were exposed to amlodipine compared with other antihypertensive or no therapy (10/48 versus 5/54 or 7/129); however, no evidence showed lower birth weight in the index pregnancy. The rates of preeclampsia were similar across treatment groups (17/60 with amlodipine versus 14/57 with other medications versus 43/129 without medication). As reported previously,<sup>12</sup> preeclampsia was common in pregnancies complicated by fetal malformations (5/11).

Calcium channel blockers (CCBs) have been used to treat hypertension in pregnancy for ≈30 years, with most of the published literature and guidelines focusing on extended-release nifedipine (nifedipine XL). The experience with nifedipine has been favorable; although not licensed specifically for pregnancy, most guidelines recommend it, along with labetalol and methyldopa for pregnant women with

hypertension.<sup>2</sup> Given the difficulties establishing drug safety in pregnancy, what would be the incentive for a practitioner to use amlodipine, given the limited published data? Amlodipine is widely used in nonpregnant patients. It is estimated that a significant number of pregnancies are unplanned and undiagnosed until the late first trimester, making it likely that unplanned first-trimester exposure to amlodipine occurs more frequently than reported. Any available safety data can potentially provide invaluable reassurance to patients and their physicians in these circumstances.

Would there be any reasons to preferentially use amlodipine rather than nifedipine XL in pregnancy, provided sufficient safety data were available? Both are dihydropyridine CCBs, and lower BP similarly by preventing the entry of calcium through L-type calcium channels in the vasculature.<sup>13,14</sup> The half-lives of the various dihydropyridines differ, which may affect BP control over a 24-hour period. Amlodipine is one of the longest acting dihydropyridine CCBs. Nifedipine XL is designed to provide BP control at a constant rate over 24 hours and has a shorter half-life than amlodipine (≥44 hours),<sup>13</sup> but in most patients it provides adequate BP control over a 24-hour period, provided the dose is adjusted appropriately. A Cochrane review addressed the 24-hour BP variability of different dihydropyridine CCBs (including amlodipine and nifedipine XL) in studies that utilized 24-hour ambulatory BP monitoring. The authors concluded that in 16 studies, with >2700 participants, the BP-lowering effects of all dihydropyridine CCBs were stable over time and not significantly different.<sup>14</sup> Differences in BP levels between different drugs could not be compared because dosing was not controlled.

Nifedipine is also available in a short/immediate-acting capsule and a prolonged-acting tablet that is usually prescribed 2 to 3 times daily. Nifedipine is a vasodilator, and the shorter acting preparations are more likely to be associated with more rapid acute decreases in BP and reflex activation of the sympathetic nervous system, causing increases in heart rate and headaches, especially when used at higher doses (>60 mg/d).<sup>15,16</sup> Moreover, abrupt decreases in BP associated with nifedipine capsules are potentially more problematic for placental perfusion.<sup>17</sup> Dose-related maternal adverse effects attributable to nifedipine such as headache, tachycardia, hypotension flushing, and nausea have been well documented,<sup>15</sup> although no comparative data exist for amlodipine in pregnancy. Amlodipine, which has a gradual onset of action,<sup>16</sup> is less likely to be associated with vasodilator symptoms and thus may be associated with better compliance and possibly smoother 24-hour BP control compared with twice-daily nifedipine tablets.<sup>18</sup> However, if the extended-release preparation of nifedipine is used, the differences may not be significant in terms of 24-hour BP control or side effects.<sup>19</sup> The slow onset of amlodipine also

implies that antihypertensive effects are delayed ( $\approx 8$  hours).<sup>16</sup> Limited information suggests that both nifedipine and amlodipine get into breast milk but are unlikely to be associated with adverse fetal effects.<sup>20</sup> Additional questions, not addressed by most studies, assess the impact of drug safety for different maternal diagnoses (eg, preeclampsia versus chronic hypertension) and pregnancy-related changes in drug pharmacokinetics.

We are left with a situation in which some uncertainty remains regarding important safety issues when prescribing most antihypertensive drugs in pregnancy, despite documentation of use in hundreds of thousands of women. These drugs are not major teratogens, but more subtle and long-term adverse consequences cannot be ruled out by available studies. The practitioner must carefully consider the risks versus the benefits of antihypertensive use in pregnancy, and clinical trials are needed to compare treatment of hypertension in pregnancy with and without antihypertensive drugs. The CHAP (Chronic Hypertension Associated With Pregnancy) study addresses this question and is nearing completion. In the meantime, although not the last word, Mito and colleagues<sup>7</sup> have contributed to our comfort with respect to amlodipine, but at present there is little reason to preferentially prescribe it over nifedipine XL in pregnant women. The uncertainties surrounding therapeutic interventions in pregnancy are a fact of life and one that is not likely to be easily resolved.

## Disclosures

Dr August is a member of adjudication committees for Bayer and Janssen. Dr Malha has no disclosures to report.

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