EDITORIAL

An epidemic of hypertensive disorders of pregnancy

The CDC recently reported that in 2019 hypertensive disorders of pregnancy (HDPs) were diagnosed in 15.9% of hospital deliveries. Does the increase in HDPs forecast a future rise in chronic hypertension, cardiovascular diseases, and stroke?

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Hypertension in pregnancy is a major challenge in current obstetric practice. Based on an analysis of the National Inpatient Sample, the Centers for Disease Control and Prevention (CDC) recently reported that from 2017 to 2019 the prevalence of hypertensive disorders in pregnancy increased from 13.3% to 15.9% of hospital deliveries.[1] During that same time period, the prevalence of pregnancy-associated hypertension, which includes preeclampsia, eclampsia, and gestational hypertension, increased from 10.8% to 13.0%.[1] The prevalence of chronic hypertension increased from 2.0% to 2.3%.[1] In 2017 and 2019, unspecified maternal hypertension was diagnosed in 0.5% and 0.6% of the sample, respectively.[1]

Bruno and colleagues reported a 3-fold increase in the prevalence of HDPs from 1989 to 2020, with an acceleration in the rate of increase from 2010 to 2020.[2] The increase in prevalence of HDPs may be caused by an increase in the prevalence of advanced maternal age, obesity, and diabetes. Black patients are disproportionately impacted by both pregnancy-associated hypertension and chronic hypertension.[1] In 2019, the prevalence of pregnancy-associated hypertension was greater among Black patients (15.6%), than White (12.1%), Hispanic (10.6%), or Asian or Pacific Islander patients (7.7%).[1] Similarly, the prevalence of chronic hypertension was greater among Black patients (4.3%) than among White (2.0%), Hispanic (1.5%), or Asian or Pacific Islander patients (1.2%).[1] Racial/ethnic differences in HDPs may be influenced by poverty; structural racism; or lack of access to care, diet, and obesity.[3,4]

HDPs are major contributors to maternal morbidity and mortality. The CDC reported that among maternal deaths occurring during the delivery hospitalization, 32% of the decedents had documented hypertension.[1] HDPs are associated with an approximately 2.5-fold increased risk of a severe morbidity, a composite measure that includes blood transfusion, acute kidney injury, disseminated intravascular coagulation, sepsis, shock, and pulmonary edema.[5] A history of HDPs is associated with an approximately 67% increase in the lifetime risk of cardiovascular disease, including coronary artery disease, stroke, peripheral vascular disease, and heart failure.[6,7]

What are the best antihypertensive medications for pregnancy?

All clinicians know that the use of angiotensin-converting-enzyme inhibitors (ACE-Is) and angiotensin-receptor-blockers (ARBs) are contraindicated in pregnancy because they cause major congenital anomalies, with an odds ratio of 1.8 (95% confidence interval [CI], 1.42-2.34), compared with no exposure.[8] In addition, ACE-Is and ARBs increase the risk of stillbirth, with an odds ratio of 1.75 (95% CI, 1.21-2.53).[8] No increase in congenital anomalies were detected

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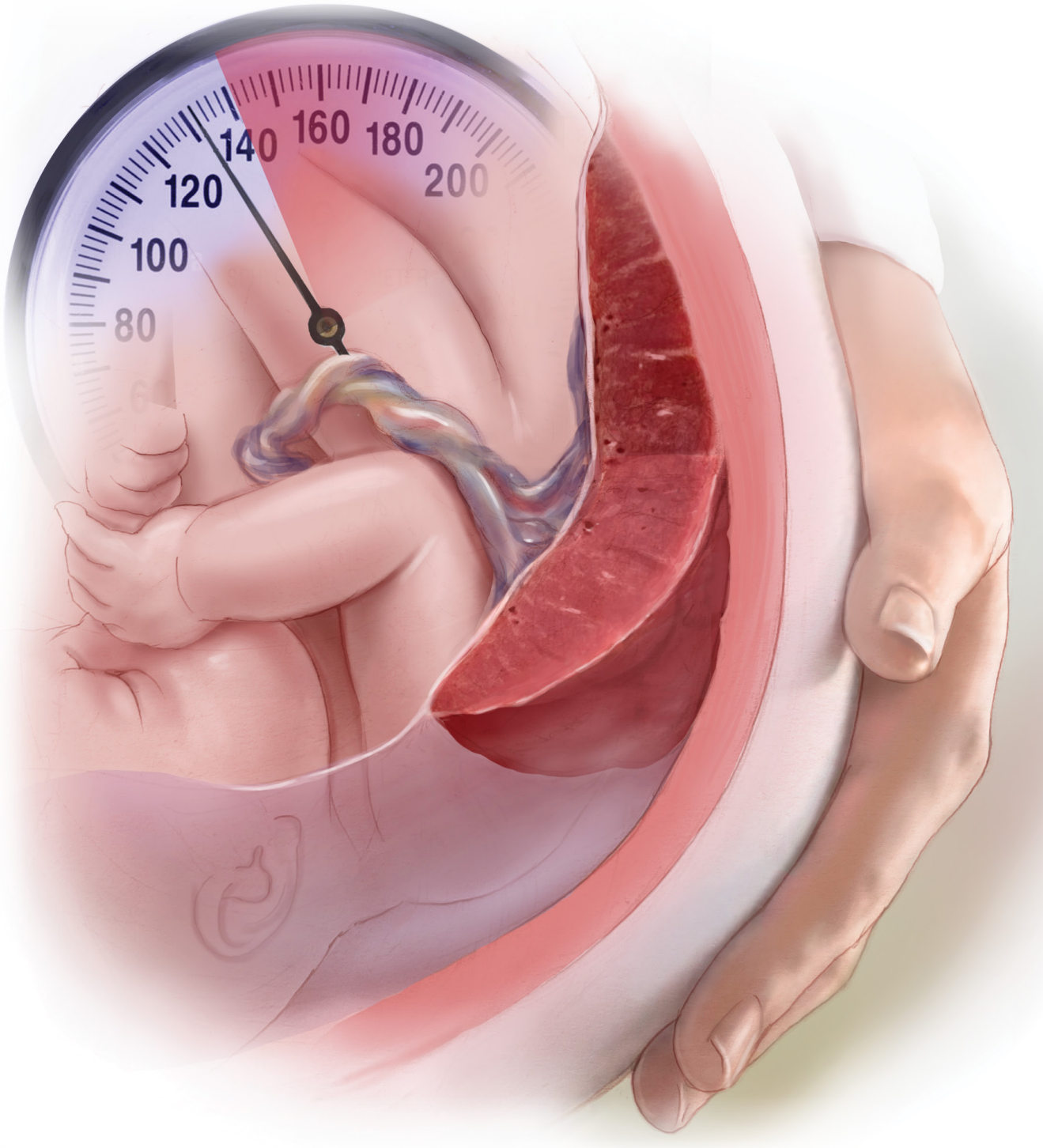

for patients exposed to other antihypertensive medications.[8] Prior to attempting conception, patients with chronic hypertension should discontinue ACE-Is and ARBs and initiate an alternative medication.

The most commonly used antihypertensive medications in pregnancy are labetalol, nifedipine, and methyldopa.[9] Labetalol blocks the beta-1, beta-2, and alpha-1 adrenergic receptors.[10] Nifedipine blocks calcium entry into cells through the L-type calcium channel.[11] Methyldopa is a central nervous system alpha-2 adrenergic agonist.[12] The dose range for these commonly used medications are labetalol 400 mg to 2,400 mg daily in divided doses every 8 to 12 hours, nifedipine extended-release 30 mg to 120 mg daily, and methyldopa 500 mg to 2 g daily in 2 to 4 divided doses. Some clinicians recommend prescribing divided doses of nifedipine extended release at doses ≥ 60 mg for patients who have bothersome adverse effects, hypotension following a single daily

dose, or hypertension between single daily doses. The nifedipine extended release tablets should not be divided. If monotherapy with the maximal daily dose of labetalol does not achieve the blood pressure (BP) target, adding nifedipine as a second agent is an option.[9] Similarly, if monotherapy with the maximal daily dose of nifedipine extended release does not achieve the BP target, adding labetalol as a second agent is an option.[9]

In a network meta-analysis of antihypertensive medications used in pregnancy, that included 61 trials and 6,923 participants, all the medications studied reduced the risk of developing severe hypertension by 30% to 70%.[13] Sufficient data was available to also report that labetalol used to treat hypertension in pregnancy reduced the risk of developing proteinuria.[13] Given similar efficacy among antihypertensive medications, patient comorbidities may influence the medication choice. For example, labetalol may not be the optimal medication for a patient with poorly controlled asthma due to its ability to cause bronchospasm.[14,15] Methyldopa may not be the optimal medication for a patient with depression.[16] **Based on the available data, labetalol, nifedipine, and methyldopa are the best antihypertensive medications for pregnant patients.**

What is an optimal BP target when treating chronic hypertension in pregnancy?

When treating chronic hypertension in pregnant patients, a concern is that reducing maternal BP may decrease uteroplacental perfusion and result in fetal growth restriction. However, a recent trial reported that a BP treatment target < 140/90 mm Hg is associated with better outcomes for both mother and newborn than withholding antihypertension medications. In the trial, 2,408 women with chronic hypertension diagnosed before 20 weeks of gestation were randomly assigned to an active treatment group with prescription of antihypertension medicines to achieve a BP target of < 140/90 mm Hg; or to a control group where no antihypertension or no additional antihypertension treatment was prescribed unless BP was ≥ 160 mm Hg systolic or ≥ 105 mm Hg diastolic.[9] The hypertension medications prescribed to the patients in the active treatment group were labetalol (63.2%), nifedipine (33.4%), amlodipine (1.7%), methyldopa (0.5%), hydrochlorothiazide (0.3%), metoprolol (0.2%), and missing/unknown/other (0.7%).[9]

If a patient in the control group developed severe hypertension, they were started on an antihypertension medicine and the BP treatment target was < 140/90 mm Hg. Compared with the control regimen, active treatment resulted in a significant decrease in the development of preeclampsia (24.4% vs 31.1%; risk ratio [RR], 0.79; 95% CI, 0.69-0.89), severe hypertension (36.1% vs 44.3%; RR, 0.82; 95% CI, 0.74-0.90), preterm birth < 37 weeks' gestation (27.5% vs 31.4%; RR, 0.87; 95% CI, 0.77-0.99), preterm birth < 35 weeks' gestation (12.2% vs 16.7%; odds ratio [OR], 0.69; 95% CI, 0.55-0.88), and low birth-weight (< 2,500 g) newborns (19.2% vs 23.1%; RR, 0.83; 95% CI, 0.71-0.97).[9] The percentage of small for gestational age birth weight below the 10th percentile was similar in the treatment and control groups, 11.2% and 10.4%, respectively (adjusted RR, 1.04; 95% CI, 0.82-1.31).[9] The number of patients who would need to be treated to prevent one primary-outcome event was 15.[9] **The investigators concluded that for pregnant patients with chronic hypertension, the optimal BP target is < 140/90 mm Hg**.[9]

When does BP reach a postpartum peak?

In pregnant patients with hypertension, BP may decrease immediately after birth. **Following birth, BP tends to increase, reaching a peak 3 to 6 days postpartum.**[17,18] This pattern was observed in patients with and without preeclampsia in the index pregnancy. Among 136 patients without antepartum preeclampsia, the prevalence of a diastolic BP > 89 mm Hg was 5% and 15% on postpartum days 1 and 3, respectively.[17] The postpartum rise in BP may be due to mobilization of water from the extravascular to the intravascular space and excretion of total body sodium that accumulated during pregnancy.[19] In one study of 998 consecutive singleton cesarean births, 7.7% of the patients with no recorded elevated BP before delivery developed de novo hypertension postpartum.[20] Compared with patients without antepartum or new onset postpartum hypertension, the patients who developed postpartum hypertension had a higher body mass index, were more likely to be Black and to have a history of type 2 diabetes. Compared with patients without antepartum or postpartum hypertension, the patients who developed de novo postpartum hypertension, had significantly elevated soluble fms-like tyrosine kinase-1 and significantly decreased placental growth factor, a pattern seen with preeclampsia.[20] These results suggest that de novo postpartum hypertension may have molecular causes similar to preeclampsia.[20]

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Postpartum hypertension should be treated with a medication that is thought to be safe for breastfeeding patients, including labetalol, nifedipine, or enalapril.[21-23] The relative infant dose of labetalol, nifedipine, and enalapril is approximately 3.6%, ≤ 3.2%, and 1.1%, respectively.[24] If the relative infant dose of a medication is < 10% it is generally considered to be compatible with breastfeeding.[25]

Many obstetricians have seldom prescribed enalapril, an ACE-I. The initial dose of enalapril is 5 mg or 10 mg daily. After initiation of treatment, the dose can be adjusted based on BP measurement. The maximal daily dose is 40 mg daily in one dose or two divided doses. Similar to other hypertension medicines, enalapril therapy may cause hypotension and dizziness. Enalapril should not be used by pregnant patients because it is associated with an increased risk of congenital anomalies and fetal demise.

Does a HDP increase the risk of developing chronic hypertension?

All obstetricians know that a patient with a history of a HDP is at an increased risk for developing chronic hypertension treated with a medication, but the magnitude of the risk is less well known. In a nationwide study in Denmark, the prevalence of chronic hypertension treated with medication 10 years after delivery among patients with a history of a HDP in their first pregnancy, was 14%, 21%, and 32%, if the first pregnancy occurred in the patient's 20s, 30s, or 40s, respectively.[26] The corresponding prevalence of chronic hypertension in patients without a history of a HDP was 4%, 6%, and 11%, if the first pregnancy occurred in the 20s, 30s, or 40s, respectively.[26] Maternal age is an important predictor of who will develop chronic hypertension within 10 years following a pregnancy with a HDP.

In modern obstetric practice, the hypertensive disorders of pregnancy are prevalent and associated with increased maternal and newborn morbidity. Appropriate treatment of hypertension with labetalol, nifedipine, or methyldopa improves maternal and newborn health. Available evidence suggests that maintaining BP < 140/90 mm Hg during pregnancy for most patients is a practical goal with significant benefit. A significant public-health concern is that an increase in the prevalence of HDPs will eventually translate into an increase in chronic hypertension and the attendant complications of heart attack, heart failure, stroke, and renal insufficiency. Recognizing the increased prevalence of HDPs, ObGyns will need to alert patients to their long-term health risks and coordinate appropriate follow-up and treatment to optimize the future health of their patients. ●

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