

Blood pressure control in hypertensive disorders of pregnancy

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Hypertension is a major cause of maternal morbidity and occurs as a complication in up to one in ten pregnancies. Hypertensive disorders of pregnancy encompass gestational hypertension, preeclampsia, chronic hypertension, and chronic hypertension with superimposed preeclampsia. However, the management of hypertensive disorders of pregnancy remains a matter of debate, particularly the blood pressure thresholds and targets for managing hypertension in pregnancy. Previously, there was no clear evidence of the effectiveness of aggressive blood pressure control in pregnancy due to the risk of fetal growth restriction. Recent clinical trials have shown that aggressive control of blood pressure in pregnant women is safe for both the mother and fetus. The purpose of this paper is to present a clinically oriented guide to the drugs of choice in patients with hypertension during pregnancy, present contrasts among different guidelines and recent clinical trials, and discuss the blood pressure thresholds and targets for hypertension during pregnancy based on recent studies.

Keywords: Pregnancy; Hypertension; Blood pressure

INTRODUCTION

Hypertension is the most common medical disorder and occurs as a complication in up to one in ten pregnancies [1,2]. The prevalence of hypertension in pregnancy is predicted to double in the future to reach one in five gestations [3]. High blood pressure during gestation increases the risk for cardiovascular disease later in life, independently of conventional cardiovascular disease risks [4,5]. However, the optimal threshold to start therapy and blood pressure targets remain a matter of debate. This review presents contrasts between different guidelines and outlines the blood pressure thresholds and targets for hypertension during pregnancy. Our purpose is to offer a clinically oriented

guide to the drugs of choice in patients with hypertensive disorders during pregnancy, present contrasts among different guidelines and recent clinical trials, and outline the blood pressure thresholds and targets for hypertension during gestation.

EPIDEMIOLOGICAL CHARACTERISTICS OF HYPERTENSION IN PREGNANCY

Hypertensive disorders are among the main contributors to pregnancy-related maternal and perinatal morbidity and mortality, implicated in 10% to 13% of United States maternal deaths [6]. According to the Korea National Health and Nutrition Examination Survey (KNHANES), hypertensive

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disorders during pregnancy have become more common over the past 10 years. In the KNHANES VIII, one-tenth of women had hypertension during gestation out of approximately 299,000 childbirths [7]. The prevalence of hypertensive disorders as a complication of pregnancy is 1.8% for preeclampsia or eclampsia, 3.1% for pregnancy-induced hypertension, and 5.4% for chronic hypertension [6,7].

Hypertensive disorders of pregnancy (HDPs) also cause maternal morbidity. A secondary analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Network Units Network cohort of women and neonates in 25 United States hospitals between 2008 and 2011, concluded that hypertensive complications (20.5%) were the second highest cause of severe maternal morbidity after postpartum hemorrhage (47.6%) [8]. Severe morbidity occurred in 2.9 per 1,000 women who gave birth. The composite of postpartum hemorrhage and HDPs accounted for more than two-thirds of the primary underlying causes of severe morbidity [8]. According to data from the National Center for Health Statistics, HDPs contribute to eight maternal deaths per one million live births in the United States [9]. Two recently published observational studies by Wu et al. [10] and Liu et al. [11] showed higher risks for incident stroke, myocardial infarction, peripartum cardiomyopathy, arrhythmia, and maternal death in mothers with chronic hypertension,

preeclampsia, and preeclampsia superimposed on chronic hypertension, as presented in Fig. 1.

DEFINITION AND SUBTYPES OF HYPERTENSION IN PREGNANCY

The terminology for hypertensive disorders in pregnant women has evolved through the years [12]; the most recent definition of hypertension in pregnancy is from the American College of Obstetricians and Gynecologists [12]. There are four categories of HDPs: gestational hypertension, preeclampsia, chronic hypertension, and chronic hypertension with superimposed preeclampsia [12]. In terms of the onset of hypertension, HDPs are classified as gestational or chronic hypertension. In terms of the presence of proteinuria and abnormal systemic findings, HDPs are classified as preeclampsia and chronic hypertension with superimposed preeclampsia. The classification of HDPs is presented in more detail below.

Gestational hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg that develops in pregnancy after 20 weeks of gestation and resolves before 12 weeks postpartum in the absence of proteinuria or systemic findings [12]. Chronic hypertension is systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg diagnosed before pregnancy or 20 weeks

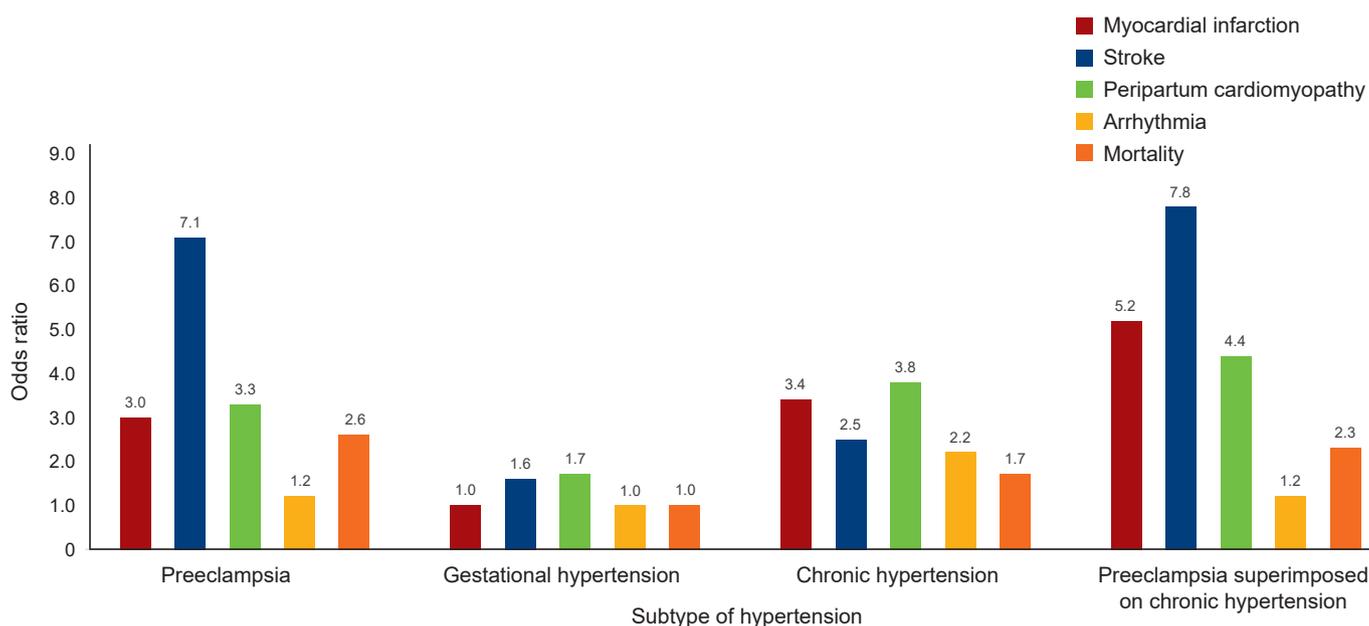


Fig. 1. Odds ratios for maternal complications according to the subtype of hypertension in pregnancy.

of gestation. Hypertension first diagnosed after 20 weeks of gestation that persists for greater than 12 weeks postpartum is also considered chronic hypertension [12]. Preeclampsia is hypertension after 20 weeks of gestation in a previously normotensive patient with the finding of proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/ μ L), impaired liver function (elevated blood levels of liver transaminases to twice the normal threshold concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal diseases), pulmonary edema, or new-onset cerebral or visual disturbances [12]. Severe preeclampsia involves a systolic blood pressure of at least 160 mmHg or diastolic blood pressure of at least 110 mmHg on two occasions at least 4 hours apart with systemic findings [12]. Chronic hypertension with superimposed preeclampsia is chronic hypertension in the setting of new-onset worsening blood pressures, proteinuria (≥ 0.3 g of protein in 24 hours), thrombocytopenia, or any other systemic features of the preeclampsia syndrome [12].

According to blood pressure values, there are three levels of hypertension in gestation: mild, moderate, and severe. The definition of mild hypertension is diastolic blood pressure 90 to 99 mmHg or systolic blood pressure of 140 to 149 mmHg. Moderate hypertension is defined as a diastolic blood pressure of 100 to 109 mmHg or systolic blood pressure of 150 to 159 mmHg. Severe hypertension occurs when the diastolic blood pressure is 110 mmHg or higher or the systolic blood pressure is 160 mmHg or higher [13].

MANAGEMENT OF HYPERTENSION IN PREGNANCY

The management of hypertension aims to reduce maternal risk and ensure safety for the fetus. The guidelines from the European Society of Cardiology and the European Society of Hypertension and the International Society for the Study of Hypertension in Pregnancy recommend the initiation of antihypertensive medication for all subtypes of hypertension in pregnancy when the blood pressure exceeds 140/90 mmHg [14,15], which is in line with the recommendations of the National Institute for Health and Care Excellence guidelines [3]. Jung et al. [16] recently reported that maternal and fetal morbidity was more likely in women with

stage I hypertension than in the normotensive group (systolic blood pressure: odds ratio [OR] 1.68, 95% confidence interval [CI] 1.59–1.78; diastolic blood pressure: OR 1.56, 95% CI 1.42–1.72). A linear association was found between prepregnancy blood pressure and the primary outcome. Even worse, women with HDP in their first pregnancy had a 63% higher likelihood of cardiovascular disease (95% CI, 1.37–1.94) than women with normotensive pregnancies [5]. Established cardiovascular disease risk factors arising after pregnancy explained most of the increased risk of cardiovascular disease. Therefore, most hypertension guidelines recommend vigorous blood pressure control even in pregnancy.

According to the American College of Obstetricians and Gynecologists and the Korean Society of Hypertension, the threshold for initiating pharmacological treatment is when the blood pressure exceeds 160/90 mmHg [12,17]. While there is little dissent about the need for pharmacological treatment in patients with a blood pressure of 160/110 mmHg or higher, there is no clear evidence for the effectiveness of aggressive blood pressure treatment. The Korean guideline recommends controlling the blood pressure to less than 150/100 mmHg and avoiding a reduction of the diastolic blood pressure to less than 80 mmHg [17]. Patients with severe hypertension should receive treatment to avoid maternal morbidity (eclampsia or stroke) [10–12,15,17]. The European guidelines recommend a blood pressure target of <140/90 mmHg, which is also suggested for pregnant women receiving antihypertensive therapy [14]. The blood pressure thresholds and targets from several guidelines are depicted in Fig. 2 [3,7,12,14,15,17].

The Control of Hypertension in Pregnancy Study (CHIPS) compared a tight diastolic blood pressure target of less than 85 mmHg as opposed to a less tight target of less than 100 mmHg in pregnant women with nonsevere, nonproteinuric preexisting or gestational high blood pressure, with regard to maternal and perinatal events. The primary outcome was composite pregnancy loss or neonatal intensive care unit admission for longer than 48 hours. The secondary outcomes were serious maternal complications until hospital discharge or puerperium mortality. The study reported a significantly higher incidence of severe hypertension in the less tight control group (40.6% vs. 27.5%, $P < 0.001$), and the primary outcome of pregnancy loss or high-level neonatal care rates was similar between the two groups (OR, 1.02;

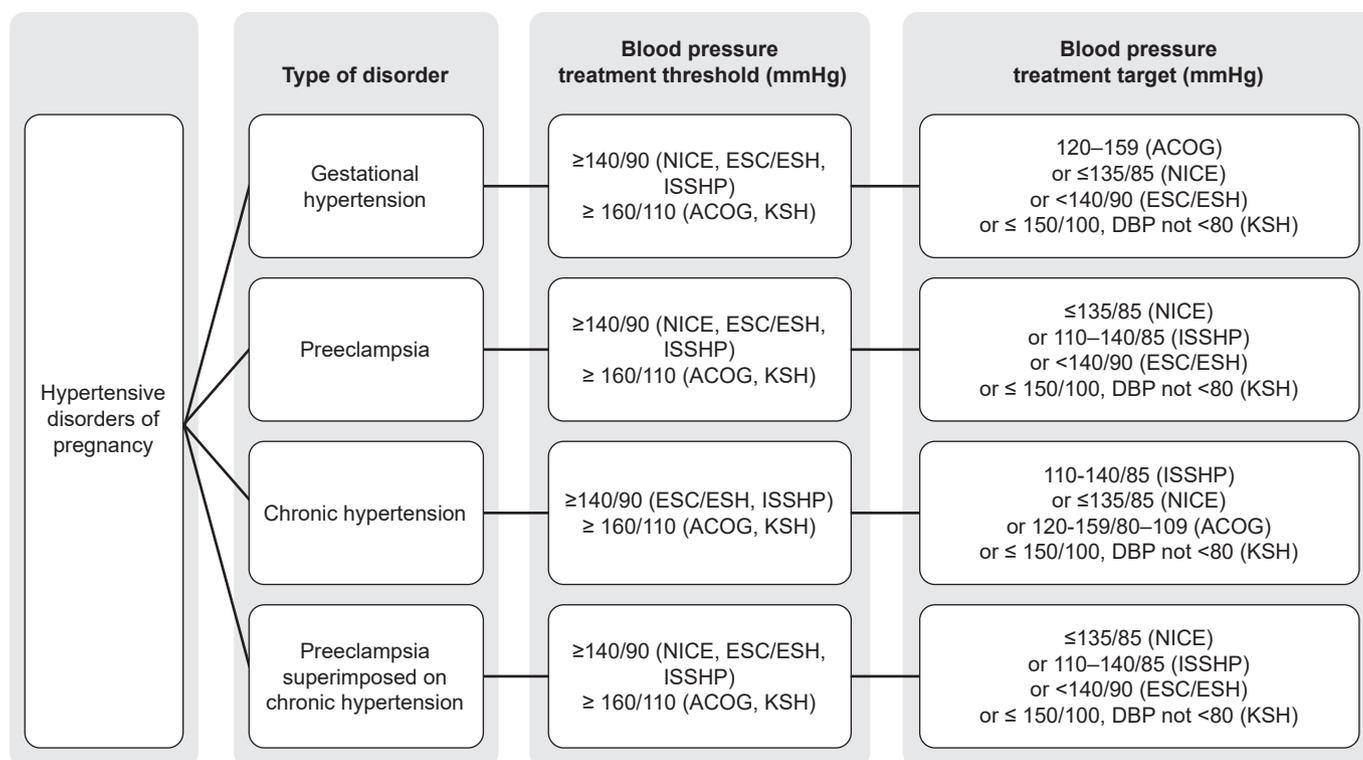


Fig. 2. Hypertensive disorders of pregnancy: blood pressure thresholds and targets. NICE, National Institute for Health and Care Excellence; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ISSHP, International Society for the Study of Hypertension in Pregnancy; ACOG, American College of Obstetricians and Gynecologists; KSH, Korean Society of Hypertension; DBP, diastolic blood pressure.

95% CI, 0.77–1.35). The CHIPS study concluded that although tighter versus much less tight control showed comparable results in the risk of adverse events and composite severe maternal complications, stricter blood pressure control may diminish the risk of developing more severe hypertension and preeclampsia [18].

A recent randomized, open-label, and multicenter clinical trial in the United States—namely, the Chronic Hypertension and Pregnancy trial—compared the outcomes of two interventions at different blood pressure target thresholds: either receiving antihypertensive medications recommended for use in pregnancy (active-treatment group) or receiving no such treatment unless severe hypertension (systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 105 mm Hg) developed (control group) [19]. This trial included 2,408 pregnant women with mild hypertension. This study's primary endpoint was a composite of severe preeclampsia, placental abruption, preterm birth < 35 weeks of gestation due to a medical indication, or perinatal death [19]. The

active-treatment group had a lower incidence of the primary endpoint than the control group (30.2% vs. 37.0%; adjusted risk ratio, 0.82; 95% CI, 0.74–0.92; $P < 0.001$) [19]. In terms of infant safety, babies whose sizes fell below the 10th percentile or below the 5th percentile for gestational age did not differ significantly between the groups [19]. Further assurance of the safety of active treatment was provided by virtually identical placental weights in the two treatment groups [19]. The results of the Chronic Hypertension and Pregnancy trial were supported by the findings of the CHIPS trial that there was no evidence of decreased fetal growth in patients with maternal hypertension who received more aggressive treatments [18,19].

The preference for antihypertensive therapy in most guidelines is methyldopa, labetalol, or long-acting nifedipine. In Korea, methyldopa is not readily available, long-acting nifedipine is easily available in clinics, and labetalol is available through the Korea Orphan and Essential Drug Center. Therefore, pregnancy-associated hypertension is

Table 1. Common pharmacological therapies for hypertensive disorders of pregnancy

Drug class	Drug (daily dose)	Safety and efficacy	Side effect	Study
First-line drugs of choice				
Central alpha-2 adrenergic agonists	Methyldopa (0.5–3 g/day in 2 divided doses)	Fetal and neonatal safety with FDA class B, class I level B Drug choice for severe hypertension	Particular concern for hemolytic anemia and hepatic disturbance May aggravate depressive disorder	ACOG report [12] Williams et al. [14] Brown et al. [20] Easterling et al. [22]
Beta-blockers	Labetalol (200–1,200 mg/day PO in 2–3 divided doses)	Safe and FDA class C, class I level Drug choice for severe hypertension	May be associated with fetal growth restriction Neonatal hypoglycemia with larger doses	ACOG report [12] Williams et al. [14] Easterling et al. [22]
Second-line drugs of choice				
Calcium channel blockers	Nifedipine (slow-release tablet, 10–30 mg PO)	Safe and FDA class C, class I level C, avoid sublingual capsule use (risk of fetal distress) Drug of choice for severe hypertension	Tocolytic effect may inhibit birth delivery Concern that using a short-acting agent in combination with magnesium may induce profound hypotension	Williams et al. [14] Brown et al. [20] Easterling et al. [22]
Central alpha-2 adrenergic agonists	Clonidine (0.1–0.6 mg/day in 2 divided doses)	Limited data in pregnancy, FDA class C	Similar to methyldopa	Brown et al. [20]
Alternative option				
Diuretics	Hydrochlorothiazide (12.5–25 mg/day)	FDA class B, and few studies in patients with hypertension	Should not be used for preeclampsia prevention because it may aggravate volume depletion and electrolyte abnormalities	Brown et al. [20]
Direct vasodilators	Hydralazine (50–300 mg/day in 2–4 divided doses)	FDA class D May be orally used as a third choice or used intravenously for hypertensive crisis	Drug-induced symptoms: nausea, headache, light-headedness, flushing, and palpitation Drug-induced lupus, neonatal lupus, maternal polyneuropathy, tachyphylaxis, and thrombocytopenia	Brown et al. [20]
Alpha-1 adrenergic-blockers	Prazosin (0.5–5 mg three times a day)	No fetal adverse effects reported Considered a second-line agent	Associated with palpitations and postural hypotension	Brown et al. [20]
Proscribed or not recommended				
Renin-angiotensin system inhibitors	Angiotensin 2 converting enzyme inhibitors Angiotensin 2 receptor antagonists	FDA class C in first trimester FDA class D second and third semester Teratogenic effect on fetus, class III level C Teratogenic effect on fetus, class III level C	Associated with adverse fetal effects	Williams et al. [14] Brown et al. [20]
Aldosterone receptor antagonists	Spiro-lactone	Not recommended in pregnancy due to antiandrogenic effects	Feminization of male infants	Williams et al. [14] Bortolotto et al. [21] Brown et al. [20] Bortolotto et al. [21]

FDA, Food and Drug Administration; ACOG, American College of Obstetricians and Gynecologists; PO, per oral.

usually controlled by long-acting nifedipine and labetalol. The benefits of drug treatment for the mother and fetus in pregnancies complicated by hypertension have not been extensively studied; the best data were obtained from a single trial using methyldopa, performed 40 years ago. Pharmacological treatment includes oral methyldopa, labetalol, and nifedipine, and alternative agents include hydralazine and prazosin [14,15]. Intravenous hydralazine is not the drug of choice, as it is associated with more significant perinatal adverse effects than other antihypertensive drugs. Nonetheless, hydralazine is still used when other treatment regimens fail to achieve adequate blood pressure control [14,20]. The use of renin-angiotensin system inhibitors may cause congenital malformations in pregnancy, so these medications should be substituted before pregnancy or during pregnancy planning [14,15,21]. Diuretics should be prescribed cautiously because they may aggravate electrolyte abnormalities and volume depletion [20]. The pharmacological treatment options based on the latest guidelines and evidence are listed in Table 1 [12,14,20–22].

There is no agreed-upon definition of severe hypertension, with values ranging between 160 and 180 mmHg for systolic blood pressure and >110 mmHg for diastolic blood pressure. The 2018 European Society of Cardiology Task Force on cardiovascular disease during pregnancy considers a systolic blood pressure \geq 170 mmHg or diastolic blood pressure \geq 110 mmHg an emergency in a pregnant woman, who should be immediately admitted to the hospital for treatment [14]. The administration of intravenous labetalol has been recommended for emergency situations, although nitroglycerin or nitroprusside might be used as alternative medications [17].

CONCLUSIONS

The management of HDPs is important to minimize maternal mortality and morbidity. Antihypertensive drugs safe for pregnant women are methyldopa, labetalol, and nifedipine. Although the blood pressure reduction targets vary among guidelines, setting more aggressive blood pressure reduction targets (below 140/90 mmHg, with diastolic blood pressure not below 80 mmHg) may be useful for reducing maternal complications. The preferred medications for antihypertensive therapy are labetalol, long-acting nifedipine, and methyldopa (not readily available in Korea). Research

on the active management of maternal hypertension is needed that involves various races so that it can be generalized to a wide range of populations.

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Ethical statements

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

Conceptualization: all authors; Data curation: all authors; Investigation: HR; Methodology: HYL; Validation: HYL; Writing–original draft: all authors; Writing–review & editing: all authors.

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