Hypertension

AHA SCIENTIFIC STATEMENT

Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy: A Scientific Statement From the American Heart Association

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ABSTRACT: Hypertensive disorders of pregnancy (HDP) remain one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide. Affected women are also at increased risk for cardiovascular disease later in life, independently of traditional cardiovascular disease risks. Despite the immediate and long-term cardiovascular disease risks, recommendations for diagnosis and treatment of HDP in the United States have changed little, if at all, over past decades, unlike hypertension guidelines for the general population. The reasons for this approach include the question of benefit from normalization of blood pressure treatment for pregnant women, coupled with theoretical concerns for fetal well-being from a reduction in utero-placental perfusion and in utero exposure to antihypertensive medication. This report is based on a review of current literature and includes normal physiological changes in pregnancy that may affect clinical presentation of HDP; HDP epidemiology and the immediate and long-term sequelae of HDP; the pathophysiology of preeclampsia, an HDP commonly associated with proteinuria and increasingly recognized as a heterogeneous disease with different clinical phenotypes and likely distinct pathological mechanisms; a critical overview of current national and international HDP guidelines; emerging evidence that reducing blood pressure treatment goals in pregnancy may reduce maternal severe hypertension without increasing the risk of pregnancy loss, high-level neonatal care, or overall maternal complications; and the increasingly recognized morbidity associated with postpartum hypertension/preeclampsia. Finally, we discuss the future of research in the field and the pressing need to study socioeconomic and biological factors that may contribute to racial and ethnic maternal health care disparities.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ diagnosis ■ hypertension ■ pregnancy ■ therapeutics

Hypertensive disorders of pregnancy (HDP) encompass chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension.[1] The diagnostic criteria for HDP in the United States have evolved over the past 5 decades[1]; the most current definition of hypertension in pregnancy from the American College of Obstetricians and Gynecologists (ACOG) was published in 2013,[1] with updates and recommendations made in 2019 and 2020 (Table S1 and Table S2 in the Supplemental Material).[2,3] Most guidelines around the world are aligned in defining hypertension in pregnancy as blood pressure (BP) ≥140/90 mm Hg (see the Treatment of Hypertension in Pregnancy section). There is variability in the threshold for initiating antihypertensive treatment attributable to uncertainty about the maternal benefits of lowering BP and the potential fetal risks from medication-induced reductions in utero-placental circulation and in utero exposure to antihypertensive medications.[2] In contrast, diagnostic and treatment thresholds for the general population have evolved over the years[4,5]; in the 2017 American College of Cardiology/American Heart

Supplemental material is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYP.0000000000000208

Hypertension is available at www.ahajournals.org/journal/hyp

Table 1. Immediate Maternal and Fetal Complications of HDP

	Effect estimate (95% CI)
Maternal outcomes	
Mortality	
Chronic hypertension	aOR, 1.7 (1.2–2.4)[13]
Preeclampsia	OR, 2.7 (1.0–7.1)[14]* aOR, 2.6 (2.1–3.4)[13]
Preeclampsia superimposed on chronic hypertension	aOR, 2.3 (1.5–3.6)[13]
Myocardial infarction	
Chronic hypertension	aOR, 3.4 (2.2–5.1)[13]
Gestational hypertension	aOR, 1.0 (0.5–2.2)[13]
Preeclampsia	aOR, 3.0 (2.0–4.6)[13]
Preeclampsia superimposed on chronic hypertension	aOR, 5.2 (3.1–8.7)[13]
Stroke	
Chronic hypertension	aOR, 3.4 (2.8–4.1)[13]
Gestational hypertension	aOR, 1.4 (1.1–1.8)[13] aOR, 1.6 (1.1–2.3)[15]
Preeclampsia	aOR, 5.7 (5.0–6.5)[13] aOR, 7.1 (5.3–9.6)[15]
Preeclampsia superimposed on chronic hypertension	aOR, 7.8 (6.3–9.8)[13]
Eclampsia	aOR, 65.9 (43.6–99.6)[15]
Peripartum cardiomyopathy	
HDP	aOR, 3.2 (2.1–4.9), White women[16] aOR, 4.0 (2.3–7.1), Black women[16] aOR, 3.0 (1.3–7.0), Hispanic women[16]
Chronic hypertension	aOR, 3.8 (3.3–4.3)[13]
Gestational hypertension	aOR, 1.7 (1.5–2.1)[13]
Preeclampsia	aOR, 3.3 (2.9–3.7)[13]
Preeclampsia superimposed on chronic hypertension	aOR, 4.4 (3.6–5.3)[13]
SCAD	7.6% higher prevalence of preeclampsia in women with SCAD vs US women of childbearing age[17]
Fetal/neonatal outcomes	
SGA (birth weight <10th centile)	
HDP	RR, 1.6 (1.5–1.6)[18]
Severe hypertension	OR, 1.8 (1.2–2.6)[19]
Preeclampsia	OR, 1.5 (1.0–2.2)[19]
Stillbirth	
HDP	RR, 1.4 (1.1–1.8)[18]
Chronic hypertension	aOR, 1.7 (1.6–1.8)[13]
Preeclampsia	aOR, 1.3 (1.2–1.3)[13]
Preeclampsia superimposed on chronic hypertension	aOR, 1.8 (1.7–1.9)[13]
Preterm delivery (<37 wk)	
Chronic hypertension	aOR, 1.3 (1.2–1.3)[13]
Severe hypertension	OR, 2.6 (1.8–3.7)[19]
Preeclampsia	OR, 3.5 (2.5–4.9)[19] aOR, 3.1 (3.0–3.1)[13]
Preeclampsia superimposed on chronic hypertension	aOR, 4.7 (4.5–4.8)[13]
Preterm delivery (<34 wk)	
Severe hypertension	OR, 3.1 (2.0–4.8)[19]
Preeclampsia	OR, 2.6 (1.6–4.2)[19]
Placental abruption	
Chronic hypertension	aOR, 1.4 (1.4–1.5)[13]
Gestational hypertension	aOR, 1.1 (1.1–1.2)[13]
Preeclampsia	aOR, 2.3 (2.2–2.3)[13]
Preeclampsia superimposed on chronic hypertension	aOR, 2.2 (2.1–2.4)[13]
Postpartum hemorrhage	
Chronic hypertension	aOR, 1.3 (1.2–1.3)[13]
Gestational hypertension	aOR, 1.5 (1.4–1.5)[13]
Preeclampsia	aOR, 2.3 (2.2–2.4)[13]
Preeclampsia superimposed on chronic hypertension	aOR, 1.7 (1.6–1.7)[13]

Effect estimates are unadjusted unless specified as ARR/aOR. Different studies have adjusted for different variables; for specifics, please refer to the original references. Comparison groups are women who had normotensive pregnancies.

aOR indicates adjusted odds ratio; ARR, absolute risk reduction; HDP, hypertensive disorders of pregnancy; OR, odds ratio; RR, risk ratio; SCAD, spontaneous coronary artery dissection; and SGA, small for gestational age.

*The study end point was a composite of mortality and other serious complications.

Association (AHA) Hypertension Clinical Practice Guidelines, the threshold for the diagnosis of stage 1 hypertension was further lowered to 130/80 from 140/90 mm Hg[6] on the basis of observational studies and clinical trials demonstrating reduced cardiovascular disease (CVD) events with treatment to lower levels.[7,8]

This scientific statement presents a synthesis of the scientific evidence (from literature published until August 31, 2020) that is relevant to the current controversies concerning HDP diagnostic and treatment strategies. It is a timely statement given that current trends indicate that the incidence of HDP continues to increase[9,10] as a result of advanced age at first pregnancy and increased prevalence of obesity and other cardiometabolic risk factors. CVD, including cerebrovascular accidents and cardiomyopathy, now accounts for up to half of all maternal deaths.[11] Pregnancy-related stroke hospitalizations increased >60% from 1994 to 2011, and HDP-associated stroke rates increased 2-fold compared with non–HDP-related stroke.[10] Thus, in the discussion that follows, we emphasize the need for future research aimed at recognizing and appropriately treating HDP.

EPIDEMIOLOGY

HDP are the second leading cause of global maternal mortality behind maternal hemorrhage[12] and are a significant cause of short- and long-term maternal and fetal/offspring morbidity (Tables 1 and 2). Elevated systolic BPs throughout pregnancy, even below the diagnostic

Table 2. Long-Term Maternal and Offspring Complications of HDP

	Effect estimate (95% CI)
Maternal outcome	
Hypertension (≥140/90 mm Hg)	
HDP	HR, 2.3 (1.9–2.8)[20] OR, 11.6 (10.6–12.7)[21]
Preeclampsia	aHR, 4.5 (4.3–4.6)[22] aHR, 2.2 (2.1–2.3)[22] RR, 3.1 (2.5–3.9)[23] RR, 3.7 (2.7–5.1)[24] OR, 3.4 (3.1-5.0)[25]
Type 2 diabetes	
HDP	HR, 1.8 (1.5–2.1)[20] OR, 2.0 (1.7–2.4)[21] HR, 1.4 (1.3–1.7)[26]
Preeclampsia	aHR, 1.8 (1.6–1.9)[22] OR, 2.14 (1.5-3.0)[25]
Hyperlipidemia	
HDP	HR, 1.3 (1.4–1.5)[20] OR, 1.5 (1.3–1.7)[21]
Preeclampsia	aHR, 1.3 (1.3 to 1.4)[22]
Subclinical markers of vascular damage	
Augmentation index	Weighted mean difference, 5.5% (1.6%–9.4%)[27]
Carotid intima-media test	Weighted mean difference, 0.02 mm (0.00–0.04)[27] >0.77 mm; aOR, 3.2 (1.1–9.1)[28]
Carotid–femoral pulse wave velocity	Weighted mean difference, 0.6 m/s (0.2–1.1)[27]
Arterial stiffness index	Unadjusted difference, 0.32 m/s (0.13–0.51)[21]
CVD*	
Gestational hypertension	aHR, 1.4 (1.1–1.9)[29]† OR, 1.7 (1.3–2.2)[30]
Preeclampsia	aHR, 1.7 (1.3–2.1)[29] HR, 1.7 (1.6–1.8)[31] OR, 1.7 (2.5–3.0)[30]
Preeclampsia with severe features	OR, 2.7 (2.5–3.0)[30]
Early-onset preeclampsia (<34 wk of gestation)	aHR, 4.9 (3.0–7.8)[32] OR, 5.6 (1.5-21.4)[25]
Coronary heart disease	
HDP	aHR, 1.9 (1.4–2.5)[29] HR, 1.7 (1.3–2.3)[20] HR, 1.8 (1.3–2.6)[21]
Preeclampsia	aHR, 2.1 (1.5–3.0)[29] HR, 1.7 (1.5–1.8)[31] RR, 2.5 (1.4–4.4)[33]
Heart failure	
HDP	aHR, 1.5 (1.3–1.9)[31] HR, 2.7 (1.6–4.6)[20] HR, 1.7 (1.0–2.6)[21]
Preeclampsia	aHR, 2.1 (1.6–2.8)[31] aHR, 2.0 (1.1–3.7)[28] RR, 4.2 (2.1–8.4)[33]
Atrial fibrillation	
HDP	HR, 1.4 (1.1–1.6)[20]
Preeclampsia	aHR, 1.7 (1.4–2.2)[31]
All stroke	
HDP	aHR, 1.8 (1.6–2.1)[31] HR, 1.9 (1.3–2.6)[20]
Preeclampsia	aHR, 1.9 (1.5–2.4)[31] aHR, 1.5 (1.1–2.1)[29] RR, 1.8 (1.3–2.6)[33]
Ischemic hemorrhage	aHR, 1.7 (1.4–2.1)[31]
Intracerebral hemorrhage	aHR, 1.7 (1.2–2.4)[31]
Subarachnoid hemorrhage	aHR, 2.0 (1.6–2.5)[31]
Vascular dementia	
Gestational hypertension	aHR, 3.0 (2.1–4.3)[34]
Preeclampsia	aHR, 2.4 (1.8–3.2)[34] HR, 3.5 (2.0–6.1)[35]
Chronic kidney disease	
Gestational hypertension	RR, 1.5 (1.1–2.0)[36]
Preeclampsia	RR, 2.3 (1.5–3.5)[36]
End-stage kidney disease	
Gestational hypertension	RR, 3.6 (2.3–5.7)[36]
Preeclampsia	RR, 6.6 (2.7–14.8)[36]
Venous thromboembolism	
HDP	OR, 1.5 (1.2–1.9)[21]
Gestational hypertension	aHR, 1.4 (1.3–1.5)[37]
Preeclampsia	aHR, 1.6 (1.4–2.0)[37]
Offspring outcome	
CVD‡	
Severe preeclampsia, term delivery	aHR, 2.3 (1.1–4.7)[38]
Stroke	
Gestational hypertension	HR, 1.4 (1.0–1.8)[39]
Preeclampsia	HR, 1.9 (1.2–3.0)[39]
BMI	
Preeclampsia	Mean difference, 0.36 kg/m^2 (0.04–0.68)[40]
Hypertension (≥140/90 mm Hg)	
Gestational hypertension	SBP, 2.0 mm Hg (1.4–2.7)[41] DBP, 1.1 mm Hg (0.6–1.5)[41]
Preeclampsia	SBP, 5.2 mm Hg (1.6–8.7)[40] DBP, 4.1 mm Hg (0.7–7.4)[40]

All effect estimates are unadjusted unless specified as aHR. Different studies have adjusted for different variables; for specifics, please refer to the original references. Comparison groups are women who had normotensive pregnancies.

aHR indicates adjusted hazard ratio; aOR, adjusted odds ratio; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDP, hypertensive disorders of pregnancy; HR, hazard ratio; OR, odds ratio; RR, risk ratio; and SBP, systolic blood pressure.

*CVD included ischemic/hypertensive heart disease or stroke.

†Chronic hypertension was included as a CVD end point in this study.

‡CVD included cardiomyopathy, hypertension, pulmonary heart disease, arrhythmia, or heart failure.

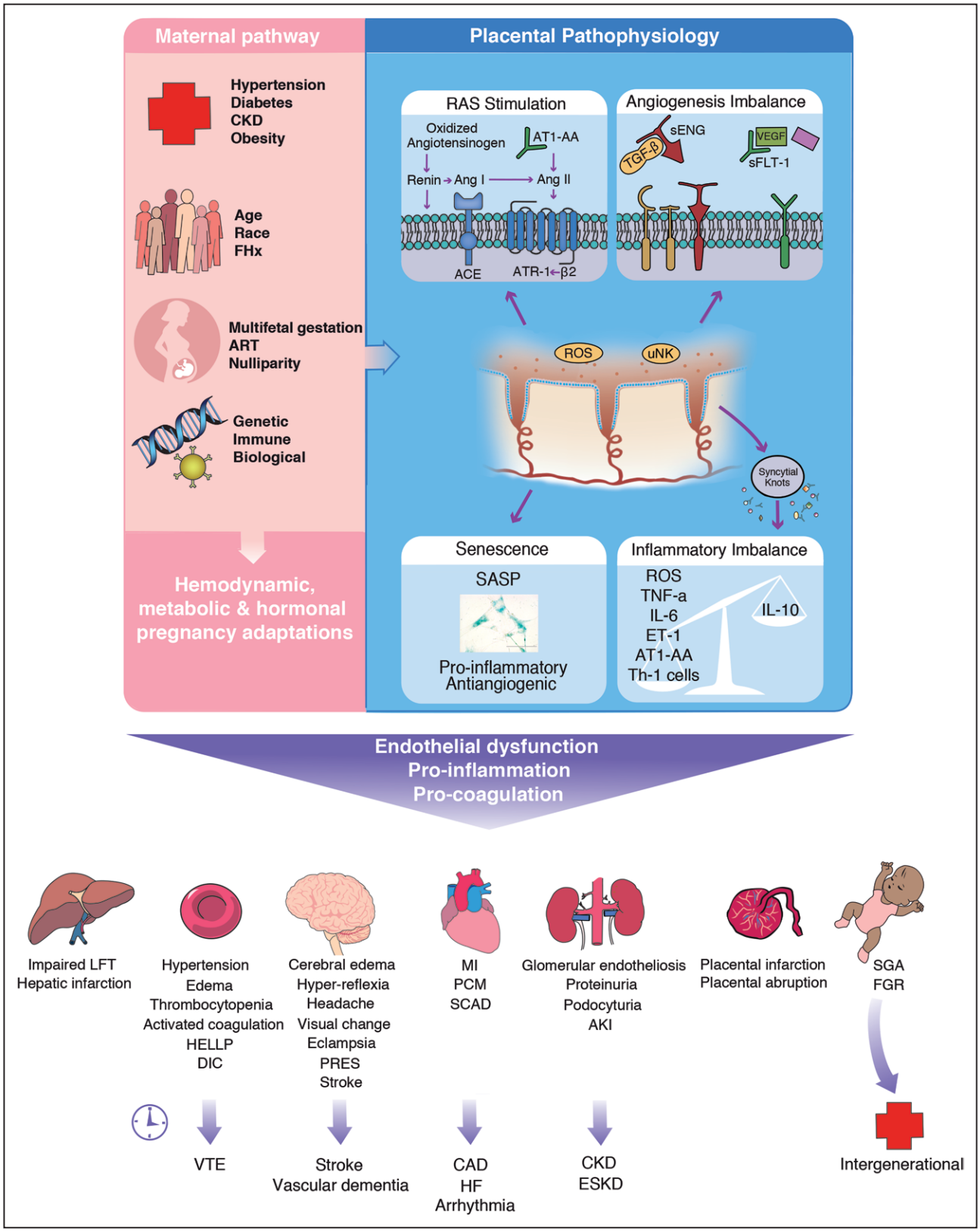

Figure. Pathogenesis of HDP.
Preexisting maternal comorbidities, nonmodifiable patient characteristics, reproductive history, and genetic and immune factors increase the risk of developing a hypertensive disorder of pregnancy (HDP). The molecular and pathophysiological mechanisms of preeclampsia are largely unknown, but the cause is likely a combination of, and interaction between, factors from both maternal and placental pathways.[61] Variable contributions of the underlying maternal and placental pathophysiological pathways result in the heterogeneous phenotypes of HDP. The associated widespread endovascular damage and dysfunction may be long-lasting with a possible intergenerational effect. (*Continued*)

threshold for hypertension, also are associated with increased risk of preterm delivery and infants who are small for gestational age and have low birth weight.[42,43]

Traditionally, the incidence of HDP was reported on a per-pregnancy basis to assist prediction of pregnancy-related complications (both maternal and fetal) in an obstetric clinical setting (Table 1). However, the HDP population-based incidence expressed per pregnancy (7.5%) underestimates the number of women affected by this condition during their reproductive years (15.3%).[20] Per-woman rather than per-pregnancy incidence provides better assessment of the number of women at risk for future CVD on the basis of their reproductive histories,[30] including development of diabetes and hypertension[20,21] (Table 2).

It is well accepted that hypertension develops significantly more frequently after HDP, but studies indicate that hypertension also develops faster in women with HDP and is diagnosed up to 10 years earlier compared with women with normotensive pregnancies,[20,26,44–46] although the precise timing requires further examination. Earlier onset of cardiometabolic risk factors and CVD events,[22,31,44] as well as higher rates of accumulated chronic conditions and multimorbidity,[20] supports the thesis of accelerated aging among women who have a history of HDP.[20,21,47]

PATHOPHYSIOLOGY OF HDP

Hemodynamic Changes in Normal Pregnancy and Preeclampsia

Systemic vascular resistance decreases while plasma volume and cardiac output increase during pregnancy. There is a physiological drop in BP, often detectable before the end of the first trimester,[48,49] attributable to vasodilation.[50] Meta-analyses and high-quality longitudinal studies found that compared with BP at 10 or 12 weeks, the BP drop during the second trimester was on average 1 to 2 mm Hg.[51–53] There is wide interindividual variability, and BP trajectories likely relate to preexisting maternal health factors[53] such as chronic hypertension and require further clarification. Renal blood flow and glomerular filtration rate increase by 50% in normal pregnancy but are ≈30% lower in women with preeclampsia as a result of both decreases in renal blood flow and the ultrafiltration coefficient, attributable to endotheliosis in the glomerular capillary bed.[54] Plasma volume increases in normal pregnancy, and earlier studies have suggested that it may be decreased in women with preeclampsia.[55] However, multiple longitudinal and cross-sectional studies in preeclamptic women have demonstrated that suppressed plasma renin activity, high BP, decreased glomerular filtration rate, and frequent development of edema are more consistent with an overfilled, vasoconstricted circulation rather than true hypovolemia and underfilling.[56] Cardiometabolic changes in normal pregnancy are more pronounced in women who develop preeclampsia and include increased insulin resistance, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.[57] Hypercoagulability, a feature of normal pregnancy, may be exaggerated in preeclampsia and is caused by increased thrombin generation, fibrinogen, and activated protein C resistance and reduced protein S and fibrinolysis.[58]

Abnormal Placentation and the Pathogenesis of the Maternal Preeclampsia Syndrome

The diameter of the uterine spiral arteries increases greatly during normal pregnancy as a result of remodeling of the endothelium and vascular smooth muscle, stimulated by release of proteases from endovascular trophoblast and uterine natural killer cells.[59] Failure of spiral artery remodeling (ie, retention of smooth muscle) is a feature of preeclampsia[60,61] and leads to decreased utero-placental perfusion, demonstrated by noninvasive blood flow and perfusion studies using Doppler ultrasound or magnetic resonance imaging (Figure).[61]

Placental pathology attributable to rheological consequences includes villous architectural changes caused by turbulent jets entering the intervillous space at rates of 1 to 2 m/s (10–20 times normal), causing the rupture of anchoring villi and the formation of echogenic cystic lesions that are visible by ultrasound.[64] In addition, retention of vascular smooth muscle preserves the ability of spontaneous vasoconstriction and ischemia-reperfusion injury, which may result in oxidative stress.

Alterations in angiogenic factors are recognized as a likely consequence of abnormal placentation occurring in early pregnancy. Increased circulating soluble fms-like tyrosine kinase 1, an antiangiogenic factor of placental origin, leads to neutralization and decrease of proangiogenic factors such as placental growth factor and vascular

Figure Continued. In podocyturia, the urinary loss of podocytes (glomerular epithelial cells) in preeclamptic women contributes to the development of proteinuria and has been documented both before and at the time of preeclampsia diagnosis.[62] Senescence is an irreversible cell-cycle arrest mechanism that leads to systematic metabolic and functional decline and may play a role in impaired angiogenesis in preeclampsia.[63] ACE indicates angiotensin-converting enzyme; AKI, acute kidney injury; Ang, angiotensin; AT1-AA, angiotensin II receptor 1 autoantibodies; ATR1, angiotensin II type 1 receptor; CAD, coronary artery disease; CKD, chronic kidney disease; CO, cardiac output; DIC, disseminated intravascular coagulation; ESKD, end-stage kidney disease; ET-1, endothelin-1; FGR, fetal growth restriction; GFR, glomerular filtration rate; HF, heart failure; IL, interleukin; MI, myocardial infarction; PCM, peripartum cardiomyopathy; PlGF, placental growth factor; PRES, posterior reversible encephalopathy syndrome; RAS, renin angiotensin system; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCAD, spontaneous coronary artery dissection; sENG, soluble endoglin; sFlt1, soluble fms-like tyrosine kinase 1; SGA, small for gestational age; Th-1, type 1 T helper cell; TNF-α, tumor necrosis factor-α; TPR, total peripheral resistance; uNK, uterine natural killer cell; VEGF, vascular endothelial growth factor; and VTE, venous thromboembolism.

endothelial growth factor, which then contribute to the hypertension and glomerulopathy characteristic of the maternal syndrome.[61] Measurements of angiogenic biomarkers have been incorporated into risk stratification in several innovative therapeutic trials for preeclampsia prevention[65,66] but are not routinely used to guide clinical care in most countries, including the United States. An increased soluble fms-like tyrosine kinase 1/placental growth factor ratio may be particularly pronounced in women with early (<34 gestational weeks), severe preeclampsia, which has been designated by some as placental preeclampsia[67] because of the association between placental ischemia and adverse fetal outcomes (fetal growth restriction in particular). Preeclampsia occurring later in pregnancy, labeled maternal preeclampsia by some, has been associated with more pronounced maternal vascular dysfunction before pregnancy (secondary to hypertension, diabetes, or obesity), less pronounced placental pathology, and fewer fetal complications. In maternal preeclampsia, pregnancy acts as a physiological stress test that exacerbates preexisting endothelial dysfunction. This underscores the heterogeneity of HDP, whereby the extremes of clinical subtypes (early versus late, mild versus severe, and presence or absence of fetal growth restriction) may reflect distinct underlying mechanisms.[67] Sharp discrimination between maternal and placental preeclampsia is overly simplistic and artificial because both processes likely play a role but with varying contributions. Regardless of the clinical subtype, diagnosis and treatment of hypertension remain a mainstay of the prevention of immediate maternal complications and permanent cardiovascular injury, together with seizure prevention with magnesium sulfate.

PREVENTION OF PREECLAMPSIA AND ADVERSE MATERNAL AND FETAL OUTCOMES

Preconception health and its impact on both pregnancy outcomes and future health have gained attention.[68] Lifestyle changes before and during pregnancy may ameliorate both maternal and fetal risks. A meta-analysis of 44 randomized controlled trials reported that dietary interventions reduce maternal gestational weight gain and improve pregnancy outcomes.[69] Exercise may reduce gestational hypertension and preeclampsia risk by ≈30 and 40%, respectively.[70,71] The first Canadian guideline for physical activity throughout pregnancy published in 2019 recommends that all women without contraindication should be physically active during pregnancy.[72] Low-dose aspirin, starting between 12 and 16 weeks of gestation, reduces the risk of preeclampsia and related adverse outcomes by 10% to 20% in women at increased risk (Table 3).[97,99–101] The ACOG recommends daily low-dose aspirin for women with a history of early-onset preeclampsia and preterm delivery or for women with >1 pregnancy complicated by preeclampsia.[97]

The optimal dose of aspirin has not been formally tested, with most trials using 81 to 150 mg daily.[100] Promising results from experimental studies and a pilot trial of pravastatin[102,103] need to be critically viewed because of concerns related to fetal safety. Experimental evidence suggests that metformin may prevent preeclampsia by reducing soluble fms-like tyrosine kinase 1 and soluble endoglin secretion from primary endothelial tissue and through senomorphic mechanisms.[63,104,105] Clinical studies have indicated that metformin may reduce the odds of gestational hypertension in women with gestational diabetes and that it may prevent preeclampsia.[106]

BP MEASUREMENT IN PREGNANCY

Accurate BP measurement is crucial for classifying hypertension and initiating treatment, regardless of pregnancy status. Because mercury sphygmomanometers are less available, aneroid devices are commonly used, although they require calibration and are less accurate. Several oscillometric automated devices have been validated in pregnant women, including those with gestational hypertension and preeclampsia.[107]

Although most current guidelines recommend hypertension management based on office BP in pregnancy, for the general population, out-of-office BP measurements are widely endorsed as more accurate and better predictors of cardiovascular morbidity and mortality.[6,108] Although several studies report BP levels during pregnancy using self-measured BP or ambulatory BP monitoring, current data describing appropriate out-of-office cutoffs for HDP diagnosis are limited.[109] The ACOG and the International Society for the Study of Hypertension in Pregnancy recommend the use of self-measured BP in women with chronic or gestational hypertension, particularly when uncontrolled.[1,110] Available information does not demonstrate a systematic difference between self-measurements and office BP measurements in pregnancy, which suggests that appropriate treatment and diagnostic thresholds for self-monitoring during pregnancy may be equivalent to standard clinic thresholds; however, additional information on appropriate methodology and validation of devices is needed.

Nonsustained Hypertension

White coat hypertension is reported in 25% of the nonpregnant adult population. Its prevalence in pregnancy is less certain, ranging from 4% to 30%.[2] According to 24-hour BP measurements, 32% of women with hypertension had white coat hypertension, but just 8% were diagnosed as such.[111] A meta-analysis of studies addressing white coat hypertension reported increased risks of preeclampsia and adverse fetal outcomes compared with women with normotension. Risks were lower compared with women with sustained chronic or gestational hypertension.[81] The frequency and clinical significance of

Table 3. Risk Factors for Preeclampsia

Risk factors	Effect estimate (95% CI)
High*	
Prior preeclampsia	RR, 8.4 (7.1–9.9)[73]
Chronic stage 2 hypertension† (≥140/90 mm Hg)	RR, 5.1 (4.0–6.5)[73]
Pregestational diabetes	RR, 3.7 (3.1–4.3)[73]
Multifetal pregnancy	RR, 2.9 (2.6–3.1)[73]
Antiphospholipid syndrome	RR, 2.8 (1.8–4.3)[73]
Systemic lupus erythematosus	RR, 2.5 (1.0–6.3)[73]
Chronic kidney disease	OR, 10.4 (6.3–17.1)[74]
Moderate*	
Maternal age >35 y	RR, 1.2 (1.1–1.3)[73]
Prepregnancy BMI >30 kg/m^2	aOR, 3.7 (3.5–3.9)[75] RR, 2.8 (2.6–3.1)[73]
Family history (first-degree relative)	RR, 2.9 (1.7–4.9)[76]
Race (Black)	aHR, 1.6 (1.5–1.6)[77] HR, 2.2 (1.9–2.6), early onset[78] HR, 1.3 (1.2–1.4), late onset[78]
Low socioeconomic status	aOR, 4.91 (1.9–12.5)[79]
Nulliparity	RR, 2.1 (1.9–2.4)[73]
History of adverse pregnancy outcome:	
Stillbirth	RR, 2.4 (1.7–3.4)[73]
Placental abruption	RR, 2.0 (1.4–2.7)[73]
Other	
Chronic hypertension (130–134/80–84 mm Hg)	aOR, 2.2 (1.9–2.5), mild[80] aOR, 2.7 (2.0–3.5), severe[80]
Chronic hypertension (135–139/85–90 mm Hg)	aOR, 2.7 (2.3–3.2), mild[80] aOR, 3.8 (2.8–5.1), severe[80]
Severe hypertension	OR, 6.1 (4.4–8.5)[19]
White coat hypertension	RR, 2.4 (1.2–4.8)[81]
Prepregnancy BMI >25 kg/m^2	RR, 2.1 (2.0–2.2)[73]
Insulin resistance >75th centile	aOR, 1.9 (1.1–3.2)[82]
Gestational diabetes	aOR, 1.6 (1.4–1.9)[83]
Recovered acute kidney injury	aOR, 2.9 (1.9–4.4)[84]
Hyperthyroidism	aOR, 1.8 (1.1–2.9)[85]
Hydatidiform mole	OR, 10.1 (3.4–30.0)[86]
Fetus with trisomy 13	Incidence with 24%–44% vs without 2%–8%[87]
Genetic susceptibility[88,89]	
Assisted reproductive technology	RR, 1.8 (1.6–2.1)[73]
Oocyte donation	OR, 4.3 (3.1–6.1)[90]
New paternity	OR, 2.3 (1.2–4.4)[91]
Pregnancy interval >4 y	OR, 1.1 (1.0–1.2), recurrent preeclampsia[92] OR, 2.1 (1.3–3.3)[91]
Migraine	OR, 2.1 (1.5–2.9)[93]

ACOG indicates American College of Obstetricians and Gynecologists; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; BMI, body mass index; HR, hazard ratio; OR, odds ratio; and RR, relative risk.

Other risk factors are based on an emerging number of factors that may increase risk of preeclampsia. Cohabitation of >12 months[94] and smoking[95,96] have an inverse association with preeclampsia risk. All estimates are unadjusted unless specified as aHR/aOR. Different studies have adjusted for different variables; for specifics, please refer to the original references. Comparison groups are women without the risk factor of interest.

*Classification of risk factors as high or moderate is based on the ACOG recommendations for aspirin therapy to prevent preeclampsia. Therapy is indicated when ≥1 high or ≥2 moderate risk factors are present.[97,98]

†Based on the 2017 Hypertension Clinical Practice Guidelines.[6]

masked hypertension in pregnancy have not been extensively studied. Any category of nonsustained BP elevation in pregnancy can progress to sustained hypertension and requires follow-up. Self-measured BP is important for diagnosing nonsustained BP elevations, including masked hypertension and white coat hypertension, that occur before 20 weeks of gestation. For clinical purposes, the definition of hypertension in pregnancy requires 2 elevated BP measurements 4 hours apart (Table S1).

BP Variation

In the nonpregnant population, the association between BP variation, independent of baseline BP, and CVD risk is mixed, although greater variability is more convincingly associated with increased stroke risk.[112–118] Limited small studies of gestational short-term and visit-to-visit BP variation suggest that greater variation is associated with adverse maternal and perinatal outcomes,[119,120] but evidence is currently inconclusive, and there is need for consensus on the methodology for the measurement of BP variability in pregnancy.

Standard gestational age–specific BPs and centiles can assist in clinical interpretation of BP changes from expected levels.[53,120] Nationally representative, population-specific gestational BP references have been reported from China and the United Kingdom.[49,51] Studies addressing the association of BP changes in relation to healthy BP standards with maternal and perinatal outcomes are needed.

Secondary Hypertension

Most (≈90%) women with chronic hypertension have primary hypertension. Secondary hypertension may occur in a small proportion of women and is associated with worse maternal and fetal outcomes. It should be considered if maternal age is <35 years, hypertension is severe or resistant, there is no family history of hypertension, or there are suggestive laboratory features such as hypokalemia, elevated creatinine, or albuminuria early in pregnancy (Table S3).[121,122] Last, the prevalence of obesity in women of reproductive age has increased in recent years, and obstructive sleep apnea may play an increasing role in secondary hypertension among pregnant women.[123,124] Because there are no pregnancy-specific guidelines for obstructive sleep apnea treatment, pregnant women with sleep apnea should be managed concurrently with a sleep medicine specialist for application of available diagnostic and therapeutic methods, depending on the stage of pregnancy.

Postpartum Hypertension and Postpartum Preeclampsia

Postpartum hypertension and postpartum preeclampsia are not specifically included in the classification of HDP, but there is increasing awareness of their significance,

as documented in the 2013 ACOG executive summary that implemented changes in clinical practice through closer postpartum monitoring and visits.[125] These entities are particularly important for 2 reasons. First, ≈60% of all maternal deaths occur within the first year postpartum, and HDP remain one of the leading causes of maternal mortality.[126] Second, postpartum hypertension offers an opportunity to use medications and to achieve BP goals without limitations related to their potential negative impacts on the fetus. The prevalence of postpartum hypertension may be as high as 8% in women without antepartum hypertension (followed up 48 hours after delivery and up to 6 weeks postpartum) and up to 50% in women with a history of preeclampsia 6 to 12 weeks after delivery.[127,128] The distinction between postpartum aggravation of antepartum HDP and de novo postpartum preeclampsia (also called delayed-onset postpartum preeclampsia) is unclear. Further research addressing underlying mechanisms is needed to clarify appropriate treatment and the need for magnesium sulfate for seizure prevention. The duration ranges from days to 3 months, contributing to serious short-term maternal complications such as stroke, seizures, and cardiomyopathy and metabolic dysregulation such as insulin resistance and weight gain.[127,128] Patient education is an important tool for early recognition of symptoms and signs. Novel approaches such as remote hypertension monitoring programs have potential to improve compliance and early diagnosis of postpartum hypertension and preeclampsia.[129]

The rate of elevation in the antepartum soluble fms-like tyrosine kinase 1/placental growth factor ratio is an independent predictor of hypertension that persists postpartum.[130] Furthermore, preeclampsia-associated endothelial dysfunction and altered cerebrovascular autoregulation have been shown to persist postpartum[131] and may amplify postpartum hypertension risk. Intravenous fluids, mobilization of extravascular fluid, and use of nonsteroidal anti-inflammatory drugs for postpartum analgesia may contribute to its occurrence. A recent randomized controlled clinical trial has shown that postpartum use of furosemide in women with HDP was associated with a 60% reduction in persistent hypertension at day 7 after delivery (adjusted relative risk, 0.40).[132] If these findings can be implemented in the clinic, there is significant opportunity to reduce maternal morbidity in the postpartum period and to avoid unnecessary hospitalization. In nonpregnant individuals, there is abundant evidence that nonsteroidal anti-inflammatory drugs are associated with clinically significant increases in BP.[133–135] A recent systematic review and meta-analysis that included 5 randomized controlled trials and 5 retrospective cohorts concluded that compared with acetaminophen, nonsteroidal anti-inflammatory drugs were not associated with increased BPs up to discharge (2–4 days postpartum).[136] The authors considered the quality of evidence to be low because of the small sample sizes, imprecise results, and short duration of follow-up. Additional investigation is needed to address the impact of longer duration of postpartum nonsteroidal anti-inflammatory drug use in older women with chronic hypertension and additional renal and cardiovascular risk factors.[137,138]

TREATMENT OF HYPERTENSION IN PREGNANCY

Current BP Goals for Pregnant Patients

The recent American College of Cardiology/AHA task force guidelines lowered the threshold for the diagnosis of hypertension in nonpregnant patients to 130/80 mm Hg for stage 1 hypertension and to 140/90 mm Hg for stage 2 hypertension, resulting in larger numbers of individuals being diagnosed and treated.[6] There is robust evidence in the general population demonstrating reduced CVD risk with treatment to lower levels.[7] Indeed, most cardiovascular events occur in individuals with BP levels of 140 to 159/90 to 109 mm Hg.[139] Even younger individuals with hypertension demonstrate early vascular remodeling and endothelial dysfunction, particularly in smaller arteries and arterioles, which leads to progressive stiffening of larger blood vessels and organ damage if hypertension is untreated.[140,141] For all HDP, hypertension is defined internationally as a BP ≥140/90 mm Hg, although treatment thresholds and targets vary (Table 4).

The recommendations of published guidelines addressing diagnosis and treatment of HDP are summarized in Table 4. Differences among societies further demonstrate confusion in the field, which likely contributes to a failure to move forward. The ACOG recommends antihypertensive therapy for women with preeclampsia and a sustained systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg and with chronic hypertension at a systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg, with a treatment goal of 120 to 160/80 to 110 mm Hg.[2] Internationally, the majority of hypertension societies endorse a more aggressive approach for antihypertensive treatment, recommending therapy when BP is ≥140/90 mm Hg.[110,142–144,149,151] Therapeutic targets similar to the American College of Cardiology/AHA target of 130/80 mm Hg[6] are recommended by the International Society for the Study of Hypertension in Pregnancy,[110] Hypertension Canada Guidelines,[146,149] National Institute for Health and Care Excellence,[144] and World Health Organization.[143] The following question arises: Why are the diagnostic and treatment BP thresholds higher in the United States compared with those recommended for nonpregnant individuals and compared with the majority of international guidelines addressing HDP?

Determining the optimal BP threshold in pregnancy for antihypertensive treatment and therapeutic targets requires a balance between the prevention of maternal hypertensive complications and the avoidance of fetal

Table 4. Summary and Key Features of Published Guidelines for the Diagnosis and Treatment of HDP

Guideline		Hypertension in pregnancy diagnosis*	Treatment threshold, mm Hg	Treatment target, mm Hg	Continuation of antihypertensive therapy
ACOG	2013[1] 2019[2] 2020[3]		≥160/105 with diagnosis of chronic hypertension[1] ≥160/110 if acute[3]/chronic hypertension[2]†	120–159/80–105[1] 120–159/80–109 if chronic[2]†	Guided by informed discussion with women
World Health Organization	2018[142] 2020[143]	Not defined	Not specified‡	Above lower limits of normal[143]	Not specified
National Institute for Health and Care Excellence	2019[144]		≥140/90	≤135/85	Continue treatment unless <110/70 mm Hg or symptomatic hypotension
Society of Obstetricians and Gynaecologists, Canada	2018[145] 2020[146]		≥140/90[145,146]	DBP, 85[145,146] <140/90+comorbidities[145]	Not specified
International Society for the Study of Hypertension in Pregnancy	2018[110]	Plus the absence of preeclampsia features	≥140/90 in office ≥135/85 at home	110–140/85	Not specified
European Society of Cardiology	2018[147]	"Antenatally unclassified" if first BP measure >20 wk of gestation	≥150/95 ≥140/90+end-organ damage/gestational hypertension	Not specified	Consider discontinuation if BP 140–159/90–109 mm Hg+normal renal function
Society of Obstetric Medicine of Australia and New Zealand	2014[148]		≥160/100 ≥140/90, optional	Based on clinician assessment	Consider discontinuation if BP fall <20 wk of gestation

Guideline		Preeclampsia diagnosis§	Superimposed preeclampsia on chronic hypertension diagnosis§	Treatment threshold, mm Hg	Treatment target, mm Hg
ACOG	2019[2]		Chronic hypertension+sudden change in preeclampsia diagnostic parameters	≥160/110[2]	Not specified
National Institute for Health and Care Excellence	2019[144]	Symptoms include utero-placental dysfunction‖	Not specified	≥140/90	≤135/85
Society of Obstetricians and Gynaecologists, Canada	2014[145] 2018[149]	Symptoms include ≥1 severe complications	≥20 wk of gestation+resistant hypertension+new or worsening proteinuria or ≥1 adverse conditions or severe complications of preeclampsia	≥140/90[149]	DBP, 85[149]
International Society for the Study of Hypertension in Pregnancy	2018[110]	Symptoms include utero-placental dysfunction‡	Chronic essential hypertension+≥1 sign of maternal organ dysfunction consistent with preeclampsia, or new-onset proteinuria in the setting of a rise in BP	≥140/90	110–140/85
European Society of Cardiology	2018[147]	Proteinuria necessary, only high suspicion if hypertension+abnormal biochemistry/symptomatic	Hypertension <20 wk of gestation+superimposed gestational hypertension+proteinuria	≥140/90	Not specified
Society of Obstetric Medicine of Australia and New Zealand	2014[148]	Symptoms include fetal growth restriction	Preexisting hypertension with proteinuria or ≥1 systemic features of preeclampsia	160/100 140–160/90–100, optional	Individual assessment

(*Continued*)

Table 4. Continued

Guideline		Future CVD risk management
ACOG	2019[150]	Postpartum follow-up visit (early postpartum visit) with either the primary care professional or cardiologist is recommended within 7–10 d of delivery for women with hypertensive disorders
National Institute for Health and Care Excellence	2019[144]	Referral to family care doctor for CVD risk prevention
Society of Obstetricians and Gynaecologists, Canada	2014[145]	All women who have had HDP should pursue a healthy diet and lifestyle
International Society for the Study of Hypertension in Pregnancy	2018[110]	Regular general practitioner follow-up to monitor BP+periodic measurement of fasting lipids and blood sugar. Adopt healthy lifestyle with maintenance of ideal weight and regular aerobic exercise
European Society of Cardiology	2018[147]	Annual primary care physician CVD risk screen
Society of Obstetric Medicine of Australia and New Zealand	2014[148]	Advise optimization of CVD risk factors

ACOG indicates American College of Obstetricians and Gynecologists; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; and HDP, hypertensive disorders of pregnancy.

*Systolic BP ≥140 mm Hg+DBP ≥90 mm Hg; gestational hypertension, >20 weeks of gestation+previously normal BP; chronic/preexisting hypertension, <20 weeks of gestation.

†ACOG guidelines state to consider a lower treatment threshold for chronic hypertension if comorbidities or renal failure is present and to consult with other subspecialties about antihypertensive treatment BP targets, although this is not specified in the recommendations.[2]

‡World Health Organization recommendations state that "women with nonsevere hypertension during pregnancy should be offered antihypertensive drug treatment in the context of good quality antenatal care follow-up"[143] and that "women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs."[142]

§All guidelines require systolic BP ≥140 mm Hg+DBP ≥90 mm Hg >20 weeks of gestation+previously normal BP+≥1 proteinuria/abnormal renal or liver function tests or platelet count/symptoms and signs consistent with end-organ damage of preeclampsia.

‖Utero-placental dysfunction: fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth.

risks. The US (ACOG) guidelines are influenced by at least 3 debated issues. First is the prevailing perspective, based on small studies, that there are no measurable immediate or long-term health benefits of stricter BP treatment for the relatively short duration of pregnancy (4–9 months, depending on type of HDP) in young women without other CVD risks. Second, there are concerns that lowering maternal BP may compromise utero-placental circulation and negatively affect fetal well-being and growth. Third, therapeutic options are limited because of concerns about potential adverse fetal effects, particularly malformations from intrauterine exposure to antihypertensive medications. Furthermore, discrepancies among international guidelines are a reflection of the country-specific context within which they were developed. Such debate and subsequent inconsistencies in recommendations hinder progression toward consensus for optimal management of HDP internationally. For example, differences in BP thresholds for initiating antihypertensive therapy make combining results from observational studies of antihypertensive therapy for meta-analysis more challenging.

BP Goals for Pregnant Patients: Emerging Data, Limitations, and Current Controversies

There are several compelling reasons to consider lower BP thresholds. First, more aggressive treatment of hypertension in pregnancy prevents the development of severe hypertension, as demonstrated by both a systematic review of randomized trials[152] and CHIPS (Control of Hypertension in Pregnancy Study), in which the average BP achieved by tight control was 133/85 mm Hg.[14] Although comparison of less tight versus tight control showed no effect on rates of preeclampsia, the former group demonstrated a higher risk of thrombocytopenia and elevated liver enzyme levels, markers of disease severity. In addition, in this trial and elsewhere, tight control may have decreased the risk of preterm birth.[153] The importance of severe hypertension as an outcome has been questioned,[19] although exploratory analyses of the CHIPS data (adjusted for allocated group and prognostic factors) showed that severe hypertension is a surrogate marker for adverse maternal and perinatal outcomes, independently of and similar in magnitude to preeclampsia.[14,19] This is especially relevant in high-risk populations such as Black women for whom the risk of hypertension-related adverse outcomes is high.[154] A study of Black women with chronic hypertension showed that using antihypertensives before 20 weeks of gestation and achieving a BP <140/90 mm Hg were associated with lower incidences of superimposed preeclampsia and preterm delivery <35 weeks compared with women with BP ≥140/90 mm Hg.[155] Furthermore, lower (<140/90 mm Hg) versus higher (≥140/90 mm Hg) BP levels during pregnancy have been associated with lower rates of preeclampsia, including preeclampsia with severe features, and lower rates of preterm delivery.[153] Lower rates of

preeclampsia with treatment of hypertension reported by these most recent studies are in sharp contrast to the majority of previous studies indicating that treatment of hypertension does not prevent preeclampsia. Whether there is a difference between women with chronic hypertension (who were preferentially recruited in these 2 studies indicating benefit) and those with gestational hypertension remains unknown; the answer will require prospective, adequately powered studies. On the basis of results of retrospective studies, including one showing benefit of tighter BP control[156] and another indicating that malignant/uncontrolled hypertension in the nonpregnant state has changes in the brain similar to those from eclampsia,[157] a large randomized controlled trial, the CHAP Project (Chronic Hypertension and Pregnancy), is nearing completion in the United States (ClinicalTrials.gov identifier: NCT02299414). The CHAP project is comparing outcomes between pregnant women with chronic hypertension who are given antihypertensive treatment to maintain BP <140/90 mm Hg with women given no treatment unless BP is ≥160/105 mm Hg.

Second, there is evidence that the pathophysiology of the neurological manifestations (headaches, visual disturbances, seizures) of preeclampsia is similar to that of the posterior reversible leukoencephalopathy syndrome.[158] Women with preeclampsia may be more susceptible to severe neurological outcomes such as intracerebral hemorrhage at lower systolic BPs (eg, 150–170 mm Hg)[157] compared with nonpregnant subjects, thus raising the possibility that lowering BP below current targets (eg, <150/90 mm Hg) may prevent these rare but devastating outcomes.[157]

Third, treatment of nonsevere hypertension in pregnancy (eg, BPs 140–155/90–109 mm Hg) may permit prolongation of pregnancy in women without other severe features of preeclampsia who would require delivery.

Fourth, ACOG guidelines recommend withholding antihypertensive therapy for patients with preeclampsia unless BP approaches 160/110 mm Hg. They also recommend urgent delivery for women with severe features of preeclampsia, which include uncontrollable hypertension with BP ≥160/110 mm Hg, even for pregnancies <34 gestational weeks, unless high-level care is available in facilities with adequate maternal and neonatal intensive care resources.[3,110,159] Lowering thresholds for treatment may allow timely BP control and avoidance of rushed deliveries that commonly lead to prematurity and related complications.

Fifth, the classic view that young women with hypertension without other CVD risk factors are at low short-term CVD risk from untreated hypertension during the duration of pregnancy is challenged by current epidemiological and demographic trends toward advanced age at first pregnancy and higher CVD risk (subclinical or diagnosed).[9,160–162] This could also be relevant among women with multiple pregnancies, who may spend several years of their lives either pregnant or breastfeeding with uncontrolled hypertension. In addition, modern fertility techniques facilitate pregnancy in women with preexisting conditions associated with elevated CVD risk (eg, diabetes, chronic kidney disease, and polycystic ovary syndrome). Preexisting chronic kidney disease and heart disease are present in 3% and 1% to 4% of pregnancies in high-income countries, respectively.[163] Several guidelines consequently endorse more aggressive treatment in these women.[147,148]

Finally, there is abundant evidence that HDP are associated with increased risk of both immediate and postpartum complications (such as acute cardiovascular and cerebrovascular disease)[164] and future maternal vascular disease (Table 2). Whether better management of BP during pregnancy will lead to lower rates of morbidity related to hypertension in the immediate postpartum period is not known. Traditional CVD risk factors (eg, obesity, hypertension, diabetes, hyperlipidemia) are associated with increased risk of HDP,[73] but the associations between HDP and future CVD, renal disease, and vascular dementia persist, even after adjustment for such factors.[31,34,36] It is estimated that approximately two-thirds of HDP-associated CVD risk is mediated by established risk factors, and the remainder is likely explained by an HDP-specific pathogenesis.[21,29] Whether treatment of nonsevere hypertension is beneficial for preventing long-term morbidity beyond pregnancy and the puerperium remains to be demonstrated. Furthermore, evidence is needed to clarify concerns about the observed, albeit nonstatistically significant, trend toward increased small-for-gestational-age risk and decreased preterm birth in women with tight versus less tight BP control in CHIPS.[165] The possible risk of drug-associated fetal malformations, long-term neurodevelopmental effects on offspring,[166] and suggested differential effects on these outcomes by antihypertensive class[152,167] are all areas that require further investigation.

Given new developments in the field of hypertension outside of pregnancy that support lower BP treatment targets, together with emerging data from larger clinical trials in pregnancy, this working group supports continued investigation to determine whether BP levels similar to those recommended outside of pregnancy for the initiation of therapy and as therapeutic targets are beneficial for the mother and safe and beneficial for the fetus. While awaiting more conclusive data and trials nearing completion, we endorse informed decision-making in partnership with the patient as to whether to treat nonsevere hypertension during pregnancy to targets similar to those recommended in nonpregnant individuals. Personalization of therapy, by giving special attention to other risk factors related to hypertension-related adverse outcomes (such as preexisting heart or kidney disease, obesity, and Black race), is a rational approach.

Antihypertensive Medications

Initial antihypertensive therapy is widely established to be monotherapy with an accepted first-line drug: labetalol or methyldopa. Some,[1,110,142–144,147,149] but not all,[148] societies

support the use of nifedipine as an initial therapy. In countries where labetalol is unavailable (eg, Germany), alternative β-blockers such as metoprolol or oxprenolol can be considered. These therapeutic options are based on small individual trials and are advocated by national and international clinical practice guidelines. There is no clear evidence that one drug is preferable to another according to a systematic review of randomized trials for all types of pregnancy hypertension considered together, for all antihypertensives considered together, or for β-blockers (including labetalol) considered separately.[152] However, in a separate network meta-analysis, specifically for treatment of chronic hypertension, atenolol was associated with fetal growth restriction,[168] especially when given for a longer duration.[169] These data conflict with some observational studies that have associated β-blocker treatment (including labetalol) with an excess of small-for-gestational-age infants, although the authors did not necessarily adjust for treatment indication and severity of maternal disease.[170] These conflicting data underscore a need for more fetal and newborn data on the safety of currently used antihypertensive agents in pregnancy.

Numerous clinical trials have compared various short-acting antihypertensives in the setting of acute, severe hypertension in pregnancy. The drugs most commonly examined are parenteral hydralazine, parenteral labetalol, and oral nifedipine (short, intermediate, or long acting). A Cochrane review concluded that these drugs were comparable with respect to safety and efficacy and recommended that professionals choose on the basis of experience and familiarity with a particular drug.[171] Most cases of severe hypertension can be successfully controlled with these drugs using doses and protocols recommended by professional societies.[172] In resource-poor countries, a report documented successful treatment of acute severe hypertension with oral preparations of labetalol, intermediate-acting nifedipine, and methyldopa.[173] Additional agents that may be considered for resistant hypertension, although not extensively studied, include nicardipine, clonidine, and furosemide.[174–176] Notably, diuretics, the mainstay of hypertension treatment in nonpregnant individuals, are not used often in pregnant women. This position is informed mainly by earlier studies suggesting that women with preeclampsia have lower plasma volume, suggesting that diuretics may further aggravate volume depletion and promote reactive vasoconstriction. However, older studies demonstrated their favorable safety profile in pregnancy,[177] and more recent guidelines have acknowledged that in women with salt-sensitive chronic hypertension or chronic kidney disease and reduced glomerular filtration rate, diuretics may be used safely, although perhaps at lower doses.[2] Recent studies demonstrate that they may be particularly effective in postpartum hypertension.[132]

The limitations of existing data on the safety of antihypertensives in pregnancy are highlighted by a systematic review of studies addressing in utero exposure to antihypertensive medications and adverse fetal outcomes. Only 5 of 47 studies were considered high quality, and few studies reported increased odds of adverse effects in treated compared with normotensive untreated women, including congenital malformations, and effects were not uniformly observed across different studies using the same medications.[166] Furthermore, similar adverse events have been reported in untreated women with hypertension, leading to the conclusion that the evidence for teratogenicity of most antihypertensive agents is weak.[178,179]

Although first-trimester exposure to medication raises concern about structural malformations (other than those attributable to physical or vascular disruption), the fetal central nervous system develops throughout gestation and may be affected by exposures at any time point. However, no firm conclusions can be drawn about long-term child outcomes given the paucity of relevant high-quality studies.[166] No adverse neurodevelopmental effects have been observed for methyldopa,[180] nifedipine,[181] or atenolol,[182] although atenolol should be used with caution (see above). Registry data adjusted for important covariates were reassuring about the effects of preeclampsia itself; only a minimal effect was seen on standardized mathematics test scores in children from affected pregnancies at 9, 12, and 15 years of age.[183] In addition, when control subjects with untreated or treated hypertension have been used, children from labetalol- and methyldopa-treated women had similar IQ scores.[2,14,158,184,185] Small clinical trials and observational studies suggest that amlodipine, clonidine, and thiazide diuretics are probably safe in pregnancy as well.[177,186,187] It is also widely accepted that all renin-angiotensin system blockers should be avoided during pregnancy,[188] especially during the second and third trimesters when blockade of the fetal renin-angiotensin system clearly interferes with kidney development and function. Given suboptimal and frequently contradicting data on fetal safety after exposure to antihypertensive medications in utero, well-designed, carefully controlled trials are needed, with attention given to short- and long-term fetal and maternal outcomes. Last, the professionals in the field should be familiar with services offered by the Organization of Teratology Information Specialists.[189] The organization was founded in 1987 as a way of connecting experts in the field of birth defects research to the general public. It provides up-to-date information about the risks of medications during pregnancy and breastfeeding to patients, health care professionals, and researchers in the field of teratology.

POSTPARTUM SCREENING

International guidelines, including those of the ACOG, the International Society for the Study of Hypertension in Pregnancy, the European Society of Cardiology, and the AHA, emphasize the need for appropriate postpartum screening and control of cardiovascular risk factors for women with a history of preeclampsia. However, the lack of studies

demonstrating efficacy and effectiveness of counseling and interventions in formerly preeclamptic women impedes the development of evidence-based guidelines. The recommendations given by different guidelines are vague and imprecise (Table 4). Randomized trials are needed to evaluate potential long-term cardiovascular benefits of early initiation of statins, aspirin, or renin-angiotensin system blockers in women with only a history of HDP as a risk factor. Lifestyle interventions addressing obesity, hypertension, and dyslipidemia are good clinical practices. Studies demonstrating the efficacy of these interventions in women of reproductive age are also needed.

MULTIDISCIPLINARY TEAM APPROACH

Management of hypertension in pregnancy requires multidisciplinary collaborations among obstetricians, maternal fetal medicine specialists, neonatologists, nephrologists and hypertension specialists, cardiologists, anesthesiologists, pharmacists, nurses, and midwives, all of whom contribute to providing cohesive and safe preconception, antepartum, peripartum, and postpartum care. In particular, nurses and midwives in case management roles coordinate care and facilitate access to resources and services that improve health outcomes such as group prenatal care,[190] economic vulnerability and chronic stress risk assessments, medication adjustments, lifestyle advice, and patient education. During hospital admission, nursing recognition of maternal compromise through the use of early warning scores,[191] hypertension bundles, and toolkits ensures timely communication with a physician or advanced practice nurse and has been shown to reduce maternal mortality from hypertensive disorders.[192]

HYPERTENSION IN PREGNANCY AND RACIAL DISPARITIES

Maternal mortality within the United States is among the highest of high-income countries, with a maternal mortality ratio of 18 per 100 000 live births.[193] Within the United States, racial maternal health disparities are unacceptably large. The estimated maternal mortality ratio in 2016 for White women was 13 per 100 000 live births, 30 for American Indian and Alaska Native women, and 41 for Black American women, similar to that of an upper-middle–income country.[194] In addition to Black, American Indian, and Alaska Native women having poorer social determinants of health, implicit racial bias is present within the US health care system, and management of severe maternal morbidity is consistently worse for these women.[195] HDP disproportionally affect Black, American Indian, and Alaska Native women,[194,196,197] predominantly because of the overall higher prevalence of CVD risk factors,[198] but there is also evidence to suggest that biological factors (eg, specific genetic variants) may increase the risk of preeclampsia for Black women.[199,200] Furthermore, preeclampsia-related severe morbidity and mortality are higher for Black women, whereas for Hispanic women, pregnancy outcomes tend to be better than those of Black or White women of similar risk.[201,202]

Studies must include sufficient numbers of participants from all racial groups, especially Black women, to address maternal health disparities and to inform policy and clinical practice. We endorse studies addressing the prevention of shared risk factors for HDP and CVD and those aiming to improve antenatal and postnatal outcomes.

CONCLUSION AND FUTURE DIRECTIVES

Evidence suggests that antihypertensive therapy for pregnancy hypertension of any type halves the incidence of severe hypertension. To some, if not many, this is sufficiently compelling to dictate a change in practice toward more aggressive treatment. This may be of particular importance in underresourced communities with less experience and low capacity to respond to hypertensive urgencies and emergencies. Of high-income countries, the United States has one of the highest hypertension-related maternal mortality rates[12] and increasing maternal morbidity and mortality from cardiovascular conditions and cerebrovascular accidents.[10,11] A lower treatment threshold than currently proposed by the ACOG has the potential to decrease serious hypertensive end-organ complications. The view that mild to moderate hypertension of short duration during pregnancy is not harmful to the mother may be further addressed by CHAP, a trial that will extend observations made in earlier trials of women with chronic hypertension that demonstrated that normalization of BP with antihypertensive treatment did not adversely affect fetal growth or neurodevelopmental outcomes. From existing data, physicians are encouraged to individualize treatment decisions, taking other risk factors into account. Future clinical trials should address questions on the optimal BP treatment thresholds and should be adequately powered to assess the effects of different BP targets on maternal and fetal/neonatal outcomes. Of note, when HDP were reclassified using the lower American College of Cardiology/AHA diagnostic threshold (systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg), results indicated that using the lower diagnostic threshold for hypertension in pregnancy may better identify women at risk for developing preeclampsia and pregnancies at risk for adverse fetal/neonatal outcomes.[203]

Studies are also needed to determine adequate levels of BP control in the postpartum period given that there are no longer reservations about the impact of BP treatment on the fetus, that significant maternal morbidity and mortality occur during this time period, and that

prolonged postpartum in-hospital stay and readmissions have a significant impact on health care resources and birth experiences.

Treatment of hypertension, prevention of seizures, and timed birth with close fetal monitoring are currently the main therapeutic options for women with preeclampsia. The superiority of any of the widely used antihypertensive(s) has not been demonstrated, and combination therapies have not been tested. Although a "same drug for all" approach is practical in many settings, a more personalized approach based on patient preferences, age, race, heart rate, BP variations measured at home or in clinic, or more detailed hemodynamic assessments may be more effective in protecting women from complications of hypertensive pregnancies and possible postpregnancy CVD consequences. As timely and optimal cardiovascular risk identification and reduction cross specialties, with women of reproductive age being seen primarily by obstetrics and gynecology specialists and only later in life by internists and cardiologists, a close collaboration among these specialties should be encouraged, as advised by the AHA/ACOG presidential advisory.[204] Ongoing research addressing causative pathways has the potential to identify new biomarkers and novel therapeutics that target fundamental mechanisms of preeclampsia.

Last, on a global level, evidence-based consensus on diagnostic and treatment thresholds (such as ≥140/90 mm Hg), targets (keeping it <140/90 mm Hg), long-term CVD risk assessment, and HDP terminology is needed to facilitate progression in the field and to ensure that all women worldwide receive optimal care before, during, and after pregnancy. Future guidelines should avoid integration of historical, unsubstantiated perspectives that impede improvements in women's health during pregnancy and throughout women's reproductive lives.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 13, 2021, and the American Heart Association Executive Committee on October 14, 2021. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Garovic VD, Dechend R, Easterling T, Karumanchi SA, McMurtry Baird S, Magee LA, Rana S, Vermunt JV, August P; on behalf of the American Heart Association Council on Hypertension; Council on the Kidney in Cardiovascular Disease, Kidney in Heart Disease Science Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Hypertension in pregnancy: diagnosis, blood pressure goals, and pharmacotherapy: a scientific statement from the American Heart Association. *Hypertension*. 2022;79:e•••–e•••. doi: 10.1161/HYP.0000000000000208

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Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
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(*Continued*)

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Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
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Jane V. Vermunt	Mayo Clinic	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
George Bakris	University of Chicago Medicine	None	None	None	None	None	None	None
Laxmi S. Mehta	The Ohio State University	None	None	None	None	None	None	None
Laurence Shields	Dignity Health	None	None	None	None	None	None	None
Ravi Thadhani	Harvard Medical School	Thermo Fisher (grant to Cedars-Sinai to perform diagnostics study)†; Beckman Coulter(Grant to Cedars-Sinai to perform diagnostics study)†; Siemens (grant to Cedars-Sinai to perform diagnostics study)†	None	Thermo Fisher*; Roche*	None	Mass General Brigham (patent royalties paid to my hospital based on patents on diagnostics for preeclampsia)*	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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