Hypertensive Disorders of Pregnancy

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KEYWORDS

• Gestational hypertension • Preeclampsia • Preeclampsia with severe features

KEY POINTS

- Hypertensive disorders of pregnancy (HDP) occur in up to 10% of all pregnancies and cause up to 16% of all maternal deaths.
- Neonatal complications include perinatal death and low birth weight.
- These syndromes include chronic hypertension, gestational hypertension, preeclampsia, superimposed preeclampsia, preeclampsia with severe features, eclampsia, and postpartum hypertension.
- Patients with a history of a hypertensive disorder are at significantly increased risk of developing cardiovascular disease later in life.

INTRODUCTION

Hippocrates of Kos is believed to have described eclampsia for the first time in fifth century BCE (εκλαμψια, translated as "a shining forth, exceeding brightness," probably from the older term, εκλαμπο, meaning "I burst forward violently"); in so doing, he wrote that "in pregnancy, drowsiness and headache accompanied by heaviness and convulsions is generally bad."[1] At present, the hypertensive disorders of pregnancy (HDPs) (chronic hypertension, gestational hypertension, preeclampsia, preeclampsia that is superimposed on chronic hypertension, preeclampsia with severe features, and postpartum hypertension) affect up to 10% of all pregnancies and are implicated in approximately 16% of maternal deaths.[2] Neonates delivered to patients with HDPs are at risk of perinatal death and low birth weight.[3] Between 1993 and 2014, these disorders increased in incidence in US women from 512 per 10,000 US women in 1993 to 912.4/10,000 in 2014.[4] Moreover, this entity results in death in non-Latinx black women at a rate 3 to 4 times that of non-Latinx white women.[5,6] In this article, the authors consider the 7 HDP-concerning risk factors, pathophysiology, definitions, symptoms, physical examination and laboratory findings, management, and prognosis.

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The HDPs include chronic hypertension, gestational hypertension, preeclampsia, superimposed preeclampsia, preeclampsia with severe features, eclampsia, and postpartum hypertension (Table 1).

PHYSIOLOGIC CHANGES OF PREGNANCY AFFECTING BLOOD PRESSURE

Some of the most dramatic changes in maternal physiology include those affecting the cardiovascular system, including an increase in blood volume of approximately 40% (and, of necessity, cardiac output). Primarily in the second trimester, peripheral vascular resistance is decreased due to effects from progesterone, nitric acid, prostaglandins, and arteriovenous shunting of blood to the uterus and placenta. This decreased resistance results in a relative reduction of mean arterial blood pressure (BP) until about 24 weeks' gestation. Despite an increase of renin and angiotensin II due to several factors, including placental production of estrogen,[8] most pregnant women are resistant to the increase in renin and angiotensin II.

PATHOPHYSIOLOGY OF HYPERTENSIVE DISORDERS

Numerous investigators have posited that preeclampsia can be divided into early- (occurring before 34 weeks gestational age) and late-onset preeclampsia (occurring at 34 weeks or thereafter) with placental abnormality noted more commonly in patients with early-onset preeclampsia, as was intrauterine growth restriction and stillbirth.[9,10] Maternal factors, such as obesity[7] and primiparity, were associated with late-onset preeclampsia.[11] Abnormal placentation is one cause of HDP.[12–15] Placentation involves in part the migration of cytotrophoblasts into the spiral arteries, causing changes within these vessels to increase blood flow. However, in patients who develop preeclampsia, pathologic changes that cause cytotrophoblasts to differentiate from a proliferative to an invasive type result in a narrowing of the spiral arterioles, placental ischemia, hypoxia,[16] and preeclampsia.[8,10] There is also an association between preeclampsia and third-trimester placental complications, including placenta accreta spectrum and retained placenta, suggesting a common pathway of these disorders.[9] The association between preeclampsia and autologous frozen embryo transfers or in donor oocyte recipient cycles in infertile patients may be due to in vitro fertilization,[17] increased serum estradiol levels, lack of relaxin production from the corpus luteum, ovarian hyperstimulation, or maternal immune response to paternally derived antigens.[18] Preeclampsia is also attributed to inhibition of vascular endothelial growth factor and placental growth factor by soluble fms-like tyrosine kinase 1 and thus causes an antiangiogenic effect.[19] Although preeclamptics have less circulating renin and angiotensin II compared with nonpreeclamptics, they have increased sensitivity to these hormones.[18]

Other risk factors for the HDPs are noted in Table 2.

CHRONIC HYPERTENSION

Approximately 10% of women of reproductive age are hypertensive.[20] In the context of pregnancy, chronic hypertension occurs before conception, to midpregnancy (20 weeks' gestation), or persists past 12 weeks after delivery. Chronic hypertension is defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as the presence of systolic blood pressure (SBP) of at least 140 mm Hg and a diastolic BP (DBP) of at least 90 mm Hg on 2 separate occasions at least 4 hours apart.[21] However, although no changes in the definition are proposed at this time, Duffy and colleagues[22] have reported that a single elevated BP in gestation was

Table 1
Classification of hypertensive disorders of pregnancy[7]

	Time of Diagnosis	Diagnostic Feature
Chronic hypertension	<20 wk	Hypertension ≥ 140/90 mm Hg present before conception or diagnosed <20 wk
Gestational hypertension	>20 wk	New-onset hypertension with the absence of proteinuria
Preeclampsia	>20 wk	New-onset hypertension and proteinuria (≥ 300 mg/24 h) or new-onset hypertension with end-organ dysfunction in the absence of proteinuria
Preeclampsia superimposed on chronic hypertension	>20 wk	Worsening hypertension with new onset of proteinuria or features of end-organ dysfunction

associated with the development of an HDP, abruptio placentae, cerebrovascular accident, and preterm delivery in a study of more than 300,000 gravid patients. Chronic hypertension in pregnancy is associated with superimposed preeclampsia, cesarean delivery, preterm delivery, low birth weight, and neonatal intensive care unit (NICU) admission.[23] The Fetal Medicine Foundation offers an online calculator to determine an individual patient's risk (https://www.fetalmedicine.org/research/assess/preeclampsia/first-trimester) **Box 1**.[24]

The management of chronic hypertension requires that the clinician be mindful of the benefit of lowered complications of pregnancy and of the risk of hypotensive episodes that could lead to other complications. The Control of Hypertension in Pregnancy Study (CHIPS) Trial defined "tight" BP control as a target DBP of 85 mm Hg and "less tight" control as a target DBP of 100 mm Hg. There was no difference in perinatal outcomes (perinatal death or admission to the NICU for >48 hours) between patients in the "tight" BP control group versus those in the "less tight" group; however, there was more severe hypertension seen in gravid patients in the "less tight" group.[25] Moreover, the ISSHP recommends "tight" BP control in patients with chronic hypertension.[26] **Table 3** lists the agents that may be used to control BP in nonurgent circumstances in patients with chronic hypertension.

GESTATIONAL HYPERTENSION

This condition that affects 5% to 10% of all pregnancies[27] is distinguished from chronic hypertension by the time during pregnancy when it presents, namely, at or after 20 weeks of gestation. Patients with gestational hypertension do not have a history of antecedent chronic hypertension. As with chronic hypertension, it is defined by the presence of SBP of at least 140 mm Hg and DBP of at least 90 mm Hg on 2 separate occasions at least 4 hours apart. Furthermore, none of the other conditions that define preeclampsia are present. Approximately 25% of patients with gestational hypertension will develop preeclampsia in the pregnancy; the earlier that the gestational hypertension presents, the higher the risk of preeclampsia.[21] As with preeclampsia, gestational hypertension confers on the patient an increased risk of cardiovascular disease later in life. Patients with gestational hypertension will require laboratory data listed in **Box 2** to rule out preeclampsia as well as close monitoring, including

Table 2
Risk factors for hypertensive disorders of pregnancy[2]

High-Risk Factors	Moderate-Risk Factors
History of preeclampsia, especially associated with adverse outcome	Nulliparity
Multifetal gestation	Obesity
Chronic hypertension	Family history of preeclampsia (mother or sister)
Pregestational diabetes	Demographic characteristics (African American or low socioeconomic status)
Renal disease	Age $\geq$ 35 y
Autoimmune disease	Personal history factors (ie, low-birth-weight infants, previous adverse pregnancy outcome, >10 y pregnancy interval)

BP at home and in the office. Medication is not indicated in the management of gestational hypertension alone.

Preeclampsia

Preeclampsia is a syndrome presenting at or after 20 weeks gestational age that includes hypertension accompanied by evidence of end-organ dysfunction affecting at least one of the following systems: renal, hepatic, hematologic, and/or the central nervous system. Symptoms may include severe headache, The BP parameters of preeclampsia are the same as that of chronic hypertension or gestational hypertension, for example, SBP greater than or equal to 140 mm Hg and/or DBP greater than or

Box 1
Suggested workup of women with chronic hypertension[18]

Explore lifestyle factors that could increase BP
- Assess excessive salt intake
- Assess excessive alcohol intake
- Sedentary lifestyle
- Medications or illicit substances that can increase BP (eg, decongestants, NSAIDs, immunosuppressants, antidepressants, cocaine)

Rule out obvious secondary causes of hypertension
- Serum electrolyte levels (including serum potassium and calcium levels)
- Serum creatinine level
- Thyroid-stimulating hormone
- Urinalysis

Evaluate baseline cardiovascular risk
- Fasting blood glucose level
- Lipid profile
- Electrocardiography

Establish results of baseline blood work critical to the evaluation of superimposed preeclampsia
- Complete blood cell count (particularly for platelet count)
- Serum creatinine levels
- Liver enzyme levels (AST or ALT)

AST, alanine aminotransferase; AST, aspartate aminotransferase; NSAID, nonsteroidal anti-inflammatory drug.

equal to 90 mm Hg. In 2013, the American College of Obstetricians and Gynecologists Task Force on Hypertension and Pregnancy issued a report that updated definitions and management guidelines[28]; in 2018, the ISSHP updated its definitions and management guidelines. The criteria for evidence of end-organ dysfunction are given in **Table 4**.

Presentation of Preeclampsia

The patient may be asymptomatic or may present with a bilateral frontal or occipital headache that is often worse with an elevation of BP or with activity, and that does not improve with over-the-counter medications; indeed, headache due to preeclampsia is the most common cause of headache (other than tension headache or migraine headache) in pregnancy.[13] Patients may also present with dyspnea, visual changes, scotomata, and right upper quadrant and/or epigastric pain.[29] Although lower extremity edema is often seen in preeclamptic patients, it is no longer a diagnostic criterion.

Preeclampsia can be further subdivided between preeclampsia and preeclampsia with severe features. The difference between the 2 is that preeclampsia with severe features is defined by the presence of SBP of greater than or equal to 160 mm Hg and/or by DBP of greater than or equal to 110 mm Hg measured on 2 separate occasions 4 hours apart while the patient is at bed rest.[31] **Table 5** identifies the severe features of preeclampsia. The clinician should not be lulled into a false sense of security when managing the care of a patient with preeclampsia without severe features, as many acute syndromes in medicine, including the HDPs, can be unpredictable in their course and can worsen rapidly, with little warning.

HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELETS

Although this life-threatening syndrome has been considered a complication of preeclampsia, up to 20% of patients with HELLP syndrome do not have a history of hypertension or other defining characteristics of preeclampsia at the time of the presentation of HELLP.[32] However, up to a fifth of preeclamptic patients will develop HELLP, and all patients with HELLP should be assumed to have preeclampsia.[25] Approximately 0.2% to 0.6% of all pregnancies will be associated with HELLP syndrome.[33]

Although patients may present with epigastric or right upper quadrant pain, headache, visual changes, and nausea and vomiting, this syndrome is diagnosed by the presence of hemolysis, elevated levels of transaminases, and thrombocytopenia and usually presents between 27 and 37 weeks of gestation.[34] Although **Table 6** notes the major diagnostic criteria for the 2 major classifications of HELLP syndrome, the reader should note that hemolysis is identified by schistocytes seen on peripheral smear, low serum haptoglobin levels, elevated indirect bilirubin levels, and elevated levels of lactate dehydrogenase.[32] Differential diagnosis of HELLP includes acute fatty liver of pregnancy as well as other thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome[34]; it is also associated with the potential for disseminated intravascular coagulation (DIC)[32] and hematoma of the liver capsule.[35]

Management of HELLP syndrome is supportive. In pregnancies less than 24 weeks of gestation, termination is often recommended[36]; otherwise, antenatal steroids should be administered for pregnancies less than 34 weeks and magnesium sulfate for gestations less than 32 weeks to reduce neonatal morbidity.[32] Delivery is curative for HELLP syndrome, but the timing of delivery must be individualized. However, expeditious delivery should be undertaken in patients with severe, uncontrolled

Table 3
Suggested dose titration of antihypertensive therapy for nonurgent control of hypertension in pregnancy[18]

First Line	Low	If BP Not Controlled	Medium	If BP is Not Controlled on Medium Dosage	High	Maximum
Labetalol	100 mg tid–qid	Proceed to medium-dose of same low-dose medication	200 mg tid–qid	Consider adding another low-dose medication rather than going to a high dose of the same medication, for a maximum of 3 medications	300 mg tid–qid	1200 mg/d
Nifedipine (PA or MR)	10 mg po bid–tid		20 mg bid-tid		30 mg bid–tid	120 mg/d
Nifedipine (XL or LA)	30 mg qd		30 mg bid or 60 mg qd		30 mg qam and 60 mg qpm	120 mg/d
Methyldopa	250 mg tid–qid		500 mg tid-qid		750 mg tid	2500 mg/d

Abbreviations: bid, twice a day; LA, long acting; MR, modified release; PA, prolonged action; po, by mouth; qam; qd, every day; qid, 4 times a day; qpm; tid; 3 times a day; XL, extended release.

Box 2
Laboratory studies used in the diagnosis of preeclampsia

Complete blood cell count
Blood urea nitrogen
Creatinine
Transaminases
24-hour urine, or urine protein:creatinine ratio
Lactate dehydrogenase level
Uric acid level

hypertension, eclampsia, pulmonary edema, DIC, abnormal electronic fetal monitoring, abruptio placentae, or fetal demise.[37]

SUPERIMPOSED PREECLAMPSIA

This condition is defined as the development of preeclampsia in patients with an antecedent history of chronic hypertension. Approximately 26% of women with chronic hypertension will develop preeclampsia.[38]

PREECLAMPSIA WITH SEVERE FEATURES

This entity is distinguished from preeclampsia only by the presence of severe range BPs (SBP $\geq$ 160 mm Hg and/or DBP $\geq$ 110 mm Hg).

MANAGEMENT OF PREECLAMPSIA

All patients diagnosed with preeclampsia should be admitted to an antepartum unit.[24,39] If a patient is sufficiently stable for discharge, the patient should be seen by the clinician in the office twice a week for evaluation of repeat laboratory studies, physical examination, and review of BP readings. Ultrasound evaluation of the fetus (umbilical artery Doppler, measurement of amniotic fluid volume, and fetal measurements of biparietal diameter, head circumference, femur length, and abdominal circumference) should be evaluated weekly.[24] BPs should be maintained under "tight"

Table 4
International Society for the Study of Hypertension in Pregnancy 2018 definitions for preeclampsia[30]

Blood pressure	$\geq$ 140 mm Hg systolic and/or $\geq$ 90 mm Hg diastolic
Renal insufficiency	Creatinine >90 μmol/L, 1 mg/dL
Liver involvement	Elevated transaminases with or without right upper quadrant or epigastric abdominal pain
Neurologic complications	Eclampsia, altered mental status, blindness, stroke, hyperreflexia with clonus, severe headache with hyperreflexia, persistent visual scotomata
Hematologic complications	Thrombocytopenia with platelet count <150,000/dL, DIC, hemolysis
Uteroplacental dysfunction	Fetal growth restriction, abnormal umbilical artery Doppler wave

Abbreviation: DIC, disseminated intravascular coagulation.

Table 5
Severe features of preeclampsia[28]

Severe hypertension	SBP $\geq$ 160 mm Hg, DBP $\geq$ 110 mm Hg 2 Measurements 4 h apart at rest
CNS symptoms	Persistent headache Visual changes
Thrombocytopenia	Platelet count <100,000/mL
Renal insufficiency	Elevated creatinine level >1.1 mg/dL Doubling of baseline creatinine
Liver dysfunction	Levels of transaminases $\geq$ 2$\times$ upper limit of normal Persistent severe RUQ or epigastric tenderness
Pulmonary edema	Diagnosed on physical examination

Abbreviations: CNS, central nervous system; RUQ, right upper quadrant.

control as identified earlier with agents such as nifedipine, methyldopa, labetalol, oxprenolol, diltiazem, hydralazine, or prazosin.[24] When the patient is at 37 weeks' gestation, or if the clinical course worsens, the patient should be delivered.[26] Patients who are less than 34 weeks' gestation should be cared for under the supervision of a perinatologist. Indications for delivery for such patients include the inability to control BP; hypoxemia (oxygen saturation <90%); worsened transaminase values, hemolysis, creatinine values, and/or thrombocytopenia; continued or worsened neurologic symptoms or signs; eclampsia; evidence of abruptio placentae; reversed end-diastolic flow seen on umbilical artery Doppler; category 2 or 3 electronic fetal monitoring; or fetal demise.[24] Termination of pregnancy should be recommended at or before 24 weeks' gestation.[26]

Prophylaxis for eclampsia with magnesium sulfate ($MgSO_4$) should be used in patients with severe range BPs and neurologic symptoms[24]; any patient less than 32 weeks gestational age should also be given $MgSO_4$ for fetal neuroprotection, for example, to reduce the risk of cerebral palsy.[40] In either case, a loading dose of 4 to 6 g is given intravenously (IV), followed by 1 to 2 g/h via IV infusion. Fluid intake should be managed carefully to reduce the risk of pulmonary edema.

Table 6
Main diagnostic criteria for the Mississippi and Tennessee classifications of hemolysis, elevated liver enzymes, and low platelets syndrome[32]

	HELLP Class	Platelets (L)	AST[a] or ALT (IU/L)	LDH (IU/L)
Mississippi	1	$\leq$ 50 $\times 10^6$	$\geq$ 70	$\geq$ 600
	2	$\leq$ 100 $\times 10^6$– $\geq$ 50 $\times 10^6$	$\geq$ 70	$\geq$ 600
	3	$\leq$ 150$\times 10^6$– $\geq$ 10 0$\times 10^6$	$\geq$ 40	$\geq$ 600
	Partial HELLP	Presence of 2 of the 3 aforementioned laboratory abnormalities along with evidence of severe preeclampsia or eclampsia		
Tennessee		$\leq$ 100 x10^6	$\geq$ 70	$\geq$ 600

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.
[a] The Tennessee classification uses only AST readings.

Prevention of Preeclampsia

Through its effects on platelet aggregation and its effects on thromboxane A2, low-dose (80–100 mg daily) aspirin has been found to be of benefit in the prevention of preeclampsia, especially in patients who have a history significant for the disease.[41] Several meta-analyses of folic acid supplementation and reduction of the risk of preeclampsia[42–44] have not found a sufficient benefit to warrant its use at this time; further studies are needed. Several meta-analyses have reported a potential risk reduction of preeclampsia in patients taking calcium supplements during pregnancy.[45–47]

ECLAMPSIA

The most severe form of hypertensive disorders presents with tonic-clonic, focal, or multifocal seizures, often with a prodrome of severe frontal or occipital headache, visual changes, scotomata, or photophobia. Approximately 25% of cases do not present with hypertension or proteinuria and most cases occur during the antepartum course after 28 weeks' gestation.[48] Patients with eclampsia should be given magnesium sulfate 6 g IV over 15 to 20 minutes.[48] Delivery should be accomplished expeditiously. Maternal mortality may be as high as 7%, and the risk of perinatal mortality is as high as 11.8%.[48]

POSTPARTUM HYPERTENSION

Although usually preeclampsia is ultimately treated by delivery, up to 10% of recent parturients may present with an HDP during the puerperium.[49] The diagnostic criteria for this condition are an SBP of 150 mm Hg and a DBP of 100 mm Hg. Patients may also present with severe headache, blurred vision, scotomata, right upper quadrant or epigastric pain, dyspnea, and altered mental status in addition to the BP parameters noted earlier. BP normally decreases in the first 48 to 72 hours postpartum, so it is possible that this syndrome may not be recognized before discharge from the hospital. Most patients with HDPs will have clinical improvement within a week after delivery.[49] As part of its Safe Mother Initiative, the American College of Obstetricians and Gynecologists District II (New York State) has developed recommendations for patients with a history of preeclampsia that recommends BP measurement 72 hours after delivery with an outpatient evaluation within 3 to 5 days postpartum, repeated in 7 to 10 days postpartum or earlier if symptoms are present.[50] If SBP is persistently at or greater than 150 mm Hg or if DBP is persistently at or greater than 100 mm Hg, antihypertensive therapy is indicated with nifedipine, labetalol, captopril, or enalapril, all of which are considered to be safe in lactating patients.[49]

SUMMARY

The HDPs are common and can cause significant maternal and neonatal morbidity and mortality. With careful attention and management, complications can be reduced.

DISCLOSURE

The author has nothing to disclose.

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