Review Article

Management of hypertensive disorders in pregnancy: An updated review

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ABSTRACT

Hypertensive disorders in pregnancy (HDP) pose substantial risks to maternal and fetal health. Pre-eclampsia, a globally significant pregnancy complication associated with maternal mortality and adverse outcomes, is on the rise, driven by factors such as obesity, advanced maternal age, and the increasing prevalence of underlying medical conditions. This review explores recent advancements in managing these conditions, extending the scope to encompass cases of hypertension during pregnancy and up to 12 weeks postpartum. Notably, chronic hypertension is now incorporated within the HDP definition, with blood pressure (BP) assessment as a cornerstone in diagnosis. Emphasizing the importance of out-of-office BP measurements, including ambulatory and home-based monitoring, is underscored for pregnant and non-pregnant women. Recent insights into preeclampsia and other HDP have paved the way for enhanced preventive measures, screening protocols, and management strategies. With emerging early detection and intervention tools, there is significant potential for reshaping clinical practices.

Key words: Chronic hypertension, Classification of hypertensive disorders, Hypertensive disorders of pregnancy, Pre-eclampsia

Management of hypertensive disorders during pregnancy represents a significant challenge in maternal-fetal medicine. The understanding and management of these disorders have undergone a transformative journey over the years, reflecting the complexities involved in safeguarding maternal and fetal well-being. Historically, in Japan, the term "pregnancy toxemia" encompassed the triad of "hypertension," "proteinuria," and "edema" in its 1982 and 1984 definitions. However, the nomenclature shifted in 2005 to "pregnancy-induced hypertension." Subsequently, in 2018, Japan harmonized its classification with international standards, adopting the term "hypertensive disorders of pregnancy (HDP)." HDP encompasses hypertension during pregnancy and up to 12 weeks postpartum [1]. Chronic hypertension antedating pregnancy is now encompassed within this definition. The pathophysiology of HDP remains multifaceted, with several hypotheses proposed, including the two-stage theory and the concept of angiogenesis imbalance. In addition, investigating the levels of circulating angiogenic factors holds promise for preventing adverse outcomes in HDP [2].

Hypertension, the most prevalent medical complication during pregnancy, is a leading cause of maternal mortality in industrialized nations, with increasing prevalence [3]. Multiple factors, including maternal age, obesity, excessive gestational weight gain, and gestational diabetes, contribute to this rising trend. There are notable racial and ethnic disparities in HDP prevalence and associated mortality [4-6]. These disparities reflect broader systemic issues encompassing access to care and variations in social determinants of health rather than inherent physiological differences. This review provides a comprehensive update on the management of HDP, addressing evolving definitions, diagnostic criteria, and disparities that underscore the contemporary landscape of HDP management.

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EPIDEMIOLOGY

HDP represent a significant global health concern, contributing to a substantial burden of maternal and fetal morbidity and mortality [7]. These disorders are estimated to be responsible for 14% of maternal deaths worldwide, highlighting their profound impact on perinatal health. Despite variations in maternal mortality rates between high-income countries (HICs) and low- and middle-income countries (LMICs), HDP remains a leading cause of maternal death globally [8]. In HICs such as the UK and Ireland, HDP accounted for 2.8% of maternal deaths. At the same time, in the USA, they contributed to 7.4% of maternal deaths, emphasizing the widespread significance of these disorders. In LMICs, 10–15% of direct maternal deaths are associated with HDP, underscoring the need for comprehensive monitoring and intervention strategies [9]. The institute for health metrics and evaluation global burden of disease 2019 report provides a comprehensive overview of the global prevalence of

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HDP, revealing significant regional variations. Africa, Southeast Asia, and the Middle East exhibit higher mean prevalence, with Africa having the highest prevalence at 334.9/100,000 women of childbearing age [10].

In contrast, the Western Pacific region reports the lowest prevalence at 16.4/100,000 women of childbearing age. Notably, a considerable disparity exists in the disease burden of HDP between HICs and LMICs, with a lower sociodemographic index and human development index associated with a greater disease burden. These findings underscore the need for targeted efforts to address HDP, particularly in regions with higher disease burdens and lower socioeconomic indices. Epidemiological trends also suggest a positive impact of interventions, with decreasing death and incidence rates in many countries, indicating progress in managing this critical health issue [11].

HDP – Definition and Classification

HDP is categorized into four types based on specific clinical criteria. Pre-eclampsia, occurring after 20 gestational weeks, involves hypertension, along with proteinuria, organ damage, or uteroplacental dysfunction. Gestational hypertension, similar to preeclampsia, is characterized by hypertension alone after 20 gestational weeks. Superimposed preeclampsia, according to the Japan society for the study of hypertension in pregnancy, entails hypertension accompanied by organ damage or proteinuria. Chronic hypertension encompasses cases where elevated blood pressure (BP) exists before conception, arises before 20 weeks gestation, or persists beyond 12-week post-delivery. This classification aids in precise diagnosis and targeted management, facilitating tailored interventions for improved maternal and fetal outcomes (Fig. 1).

Chronic Hypertension

Chronic hypertension in pregnancy is a multifaceted condition characterized by elevated BP that either pre-dates conception, emerges before 20-week gestational age, or persists beyond 12-week post-delivery. As per the 2017 guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), elevated BP is defined as a systolic BP ranging from 120 to 129 mmHg, with a diastolic BP below 80 mmHg. Diagnosis of hypertension is established when the systolic BP reaches 130 mmHg or higher or the diastolic BP is 80 mmHg or higher, based on the average of two or more readings on two or more occasions [12]. Notably, the diagnostic criteria for hypertension by the ACC/AHA differ from those used in defining HDP.

Chronic hypertension significantly impacts 1%–5% of pregnancies, with this percentage expected to rise, attributed in part to an increase in the age of pregnant women and the growing prevalence of obesity [13]. The condition can be categorized into two types based on underlying pathophysiology: Essential hypertension (primary hypertension) and secondary hypertension. Essential hypertension lacks an obvious cause, while secondary hypertension, constituting 10–15% of chronic hypertension cases, is associated with underlying processes such as renal disease, aortic disease, collagen or vascular disease, and endocrinopathies [14].

Distinguishing chronic hypertension from gestational hypertension is crucial, especially concerning the time of elevated BP detection. In chronic hypertension, elevated pressure is identified before 20 weeks gestation or persists postpartum, whereas gestational hypertension manifests after 20 weeks in a woman without pre-existing hypertension [15]. Physiological changes during pregnancy, such as reduced vascular tone, can mask chronic hypertension, making recognition challenging. Chronic hypertension is linked to an increased risk of maternal and fetal complications, with the severity of BP elevation correlating with the risk. Mild-to-moderate hypertension during pregnancy is typically considered when systolic BP ranges from 140 to 159 mmHg, diastolic BP from 90 to 109 mmHg, or both. Severe hypertension is defined as systolic pressure of 160 mmHg or higher or diastolic pressure of 110 mmHg or higher [16]. Notably, chronic hypertension without superimposed preeclampsia independently poses risks for perinatal death and small-for-gestational-age births.

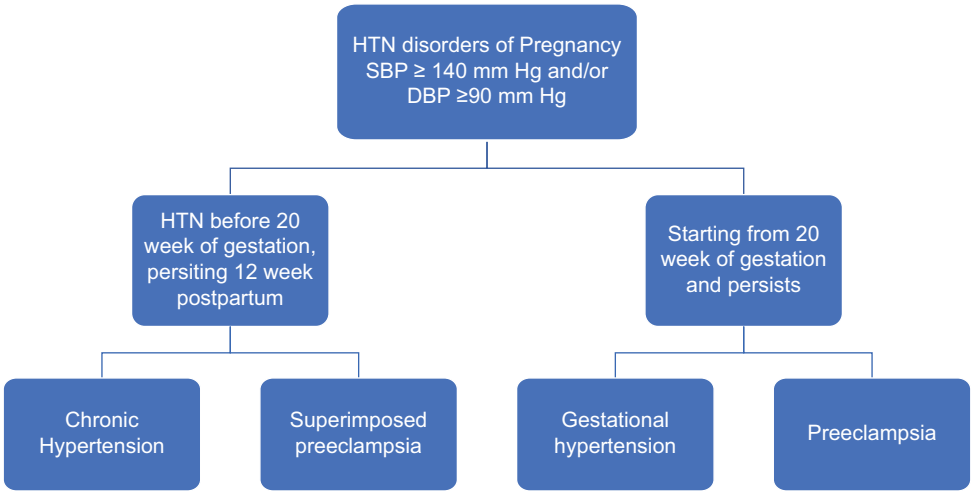

Figure 1: Classification of hypertensive disorders of pregnancy. HTN=Hypertension

Gestational Hypertension

Gestational hypertension, previously known as pregnancy-induced hypertension, is characterized by the onset of new hypertension after 20 weeks of gestation without meeting the diagnostic criteria for preeclampsia. This diagnosis is provisional and may transition to chronic hypertension if elevated BP persists beyond 12-week postpartum. However, if BP normalizes after this period, the diagnosis may be changed to transient hypertension of pregnancy. Gestational hypertension is observed in 6%–17% of healthy nulliparous women and 2%–4% of multiparous women. Of those initially diagnosed, 15%–46% may progress to preeclampsia, with the risk inversely related to the gestational age at diagnosis [17].

Similar to chronic hypertension, gestational hypertension is categorized as mild or severe. Mild gestational hypertension is defined by a systolic BP of 140–159 mmHg and a diastolic BP of 90–109 mmHg on two separate occasions, at least 4 h apart and within 1 week. In severe gestational hypertension, the systolic BP exceeds 160 mmHg, and the diastolic BP is >110 mmHg. The lack of prenatal care can complicate the diagnosis, as factors such as pain, anxiety, acute illness, and "white coat" hypertension in the emergency department can contribute to elevated BP readings.

Outcomes differ significantly between non-severe and severe gestational hypertension. Non-severe cases are generally associated with favorable outcomes, while severe gestational hypertension carries a worse prognosis for both the mother and fetus. Monitoring and screening for preeclampsia and signs of end-organ dysfunction are crucial in pregnant women with suspected gestational hypertension. This includes a comprehensive assessment involving a review of systems, physical examination, ultrasound for fetal growth assessment, urinalysis, blood analysis, and tocodynamometry monitoring for fetal distress if necessary. The American College of Obstetrics and Gynecology (ACOG) task force on hypertension in pregnancy recommends close monitoring of BP twice weekly, along with weekly assessments of platelet count and liver enzymes in women diagnosed with gestational hypertension. Routine prescription of bed rest, a low-salt diet, or weight loss is not recommended, as these interventions have limited effects on end-organ dysfunction and the progression to preeclampsia.

Pre-eclampsia

Pre-eclampsia is characterized by the onset of new-onset hypertension after 20 weeks of gestation, accompanied by proteinuria or evidence of end-organ dysfunction. The features of end-organ dysfunction include thrombocytopenia, liver or renal impairment, pulmonary edema, and neurologic or visual dysfunction. Preeclampsia can be classified as early-onset (before 34 weeks) or late-onset (at 34 weeks or later). Severe features include BP >160/100 mmHg, acute kidney injury, liver function test abnormalities, central nervous system symptoms, platelet count $<100\times10^9$/L, and pulmonary edema.

The mechanism behind preeclampsia involves abnormal placentation and a dysfunctional maternal immune response. Abnormal invasion of fetal cytotrophoblasts leads to insufficient remodeling of spiral arteries, reducing placental perfusion. A systemic inflammatory response is initiated due to placental ischemia, resulting in endothelial dysfunction and systemic disturbances seen in preeclampsia. Risk factors for pre-eclampsia include a history of the condition, antiphospholipid antibody syndrome, chronic hypertension, pre-gestational diabetes mellitus, high pre-pregnancy BMI, and assisted reproductive technology. Racial disparities exist, with African American women having a higher incidence and severity of preeclampsia [18,19].

HELLP syndrome considered a variant of severe preeclampsia, is characterized by hemolysis, elevated liver enzymes, and low platelets. It is associated with a greater degree of hepatic inflammation and activation of the complement and coagulation cascades. Eclampsia, defined as seizures in a pregnant woman with pre-eclampsia and no other identifiable cause, can occur during the antepartum, intrapartum, or postpartum periods. Signs and symptoms preceding seizures include elevated BP, headache, visual changes, and right upper quadrant and epigastric pain. More than 90% of eclampsia cases occur after 28 weeks gestation, with up to 44% in the postpartum period. Up to 25% of women with eclampsia report no preceding symptoms [20-22].

Chronic Hypertension with Superimposed Pre-eclampsia

It is a hypertensive disorder occurring in pregnant patients with preexisting chronic hypertension after 20 weeks gestation. This condition poses a higher risk of maternal and fetal complications compared to either chronic hypertension or pre-eclampsia alone. Diagnosis can be challenging as the patient's BP is already elevated due to chronic hypertension, and the preexisting condition might have induced proteinuria. Suspicion for superimposed pre-eclampsia arises if there is an increase in BP if the BP becomes resistant to treatment, or if there is an escalation in the level of proteinuria. This hypertensive disorder underscores the complexity of managing pregnant individuals with chronic hypertension, requiring careful monitoring and timely interventions to mitigate risks. The overlap of chronic hypertension and preeclampsia necessitates vigilant attention to evolving symptoms and signs, emphasizing the importance of regular prenatal care and close collaboration between obstetricians and other health-care providers. The management of chronic hypertension with superimposed preeclampsia typically involves a multidisciplinary approach to ensure optimal outcomes for both the mother and the fetus [15].

MANAGEMENT OF HDP

Fig. 2 summarizes the management plan of HDP.

Chronic Hypertension in Pregnancy

The management of chronic hypertension in pregnancy requires careful consideration, especially for women who may be taking antihypertensive drugs before conception or continue them during

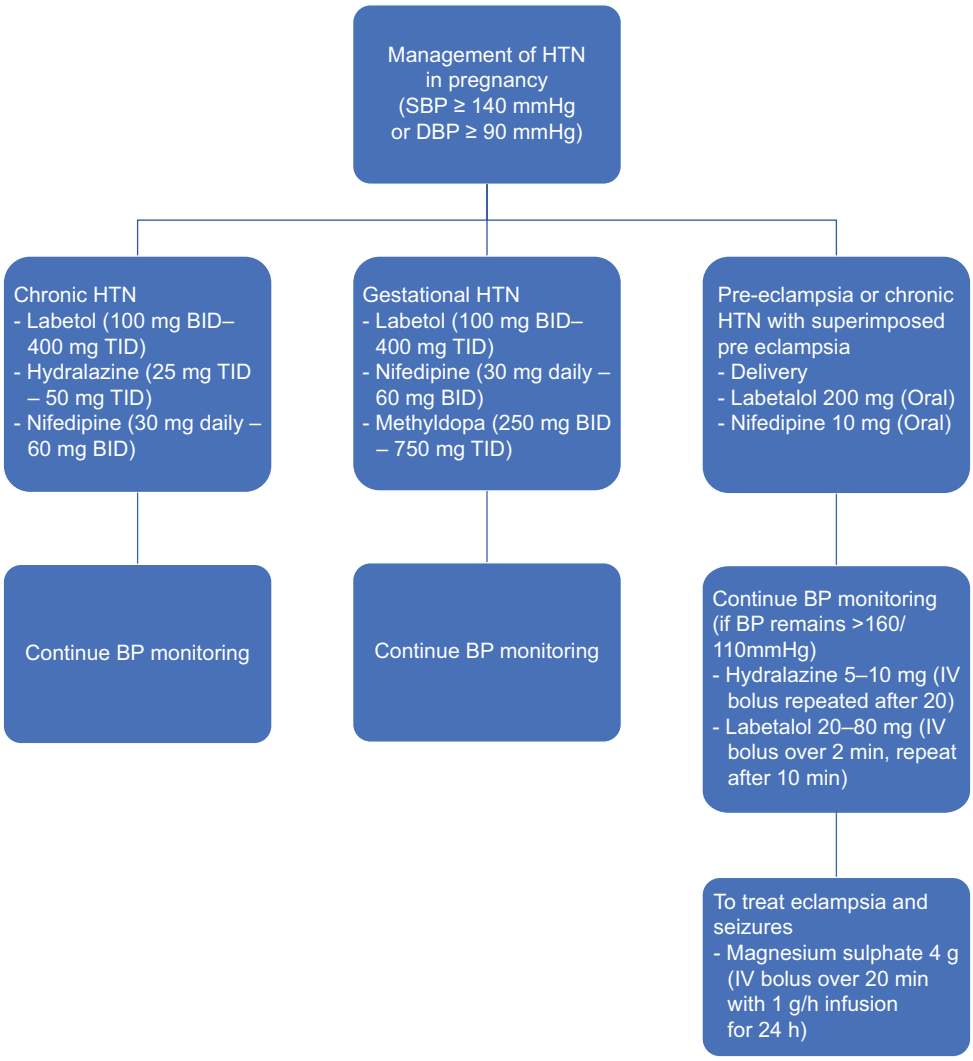

Figure 2: Algorithm for management of hypertensive disorders in pregnancy. HTN=Hypertension, BID=Twice a day, TID=3 times a day, IV=Intravenous; BP=Blood pressure; 160/110 mmHg or above – severe HTN

pregnancy. Certain antihypertensive medications such as labetalol and methyldopa can be used safely in pregnancy. Nifedipine is safe if used after 20 weeks of pregnancy, while ACE inhibitors and angiotensin receptor blockers are contraindicated or not recommended during pregnancy. This emphasizes the need for a thorough understanding of the drug regimen (Table 1) [23,24]. It is crucial to assess the safety of the medications in use and make adjustments as necessary. For pregnant individuals with chronic hypertension, regular maternal reviews and strict BP control form the cornerstone of management. During the first trimester, the physiological decrease in BP may allow for a reduction or discontinuation of antihypertensive drug therapy. The goal is to maintain BP within the range of 110–140/85 mmHg [25]. This optimal management approach not only focuses on controlling maternal BP but also includes vigilant monitoring for the development of preeclampsia. This condition can complicate chronic hypertension in pregnancy [26].

Close surveillance of fetal growth and well-being is essential, with attention to signs and symptoms that may indicate pre-eclampsia, such as headache, visual changes, epigastric or right upper quadrant pain, and edema. Regular BP measurements, ideally using automated office or liquid crystal sphygmomanometers, are a key component of assessment [25]. In addition, testing for proteinuria is crucial, and various methods, including dipstick urinalysis and spot urine protein: Creatinine (P/C) ratio, are employed. Dipstick urinalysis, while commonly used for screening, may require further evaluation with spot urine P/Cratio if results indicate "1+" or more, as it is sensitive but less specific [25]. Incorporating home BP monitoring into the assessment can enhance overall management strategies.

Gestational Hypertension

The management of gestational hypertension requires vigilant monitoring and a tailored approach to ensure the well-being of both the mother and the fetus. Regular BP monitoring is essential, with the goal of maintaining BP within the range of 110–140/80–90 mmHg [25]. This ongoing assessment is crucial for detecting any deviations from the target range and enables timely intervention if needed. Regular evaluation for the development of preeclampsia is a key component of the management strategy. Close surveillance of fetal growth and

well-being further enhances the comprehensive care provided to pregnant individuals with gestational hypertension. Once BP is under control, outpatient care can be continued, with regular reviews to monitor the patient's condition closely.

For pregnant women with gestational hypertension, especially those without evidence of severe hypertension or progression to preeclampsia, outpatient management is deemed safe. The ACOG recommends regular in-office BP monitoring, urine protein excretion assessments, and twice-weekly home BP measurements. These measures, coupled with non-pharmacologic interventions, form a comprehensive approach to managing gestational hypertension. Non-pharmacologic interventions involve lifestyle modifications, including monitoring activity levels and adhering to a balanced diet. However, it is crucial to note that despite these interventions, up to 50% of women with gestational hypertension may progress to preeclampsia. In cases where gestational hypertension reaches severe-range BPs, initiation of antihypertensive therapy is recommended. Women in this category should be managed similarly to those with severe preeclampsia, emphasizing the importance of proactive and individualized care based on the severity of the condition [26-31].

Pre-eclampsia and Preeclampsia Superimposed on Chronic Hypertension

The management of pre-eclampsia, whether it is new onset or superimposed on chronic hypertension, demands a multidisciplinary approach to optimize outcomes for both the mother and the fetus, recognizing that delivery remains the only definitive cure. Striking a balance between the welfare of the growing fetus and the ongoing risk of maternal complications is crucial in this complex scenario. Specialized care at a center equipped with the necessary protocols and expertise is imperative, given that inpatient care is typically warranted.

In cases of severe hypertension associated with preeclampsia, urgent management is essential, necessitating the use of antihypertensive drugs for the rapid reduction of BP (Table 2) [31]. In addition, the consideration of an infusion of magnesium sulfate

Table 1: Safe and unsafe antihypertensive drugs in pregnancy

Antihypertensive class/drug	Advice on safety	Dose/recommendation	Adverse effects
Labetalol (beta blocker)	Safe	100 mg BID–400 mg TID	Hypotension, bradycardia, bronchospasm, neonatal hypoglycemia
Nifedipine (Calcium channel antagonist)	Safe	30 mg Q day–60 mg TID	Headache, tachycardia, and peripheral edema
Methyldopa (Central action)	Safe	250 mg BID–750 mg TID	Depression, hypotension, dry mouth, anxiety, sedation
Hydralazine (Vasodilator)	Safe	10mg QID, 25 mg TID–50 mg TID	Flushing, tachycardia, headache, fetal distress, lupus-like syndrome
Prazosin (Alpha Blocker)	Safe	0.5 mg BID–5 mg TID	Orthostatic hypotension
Diuretics (e.g., Hydrochlorothiazide)	Avoid	Use an alternative medication	Fetal hypoglycemia, hypokalemia, hyponatremia, thrombocytopenia, and maternal hypovolemia.
Beta-blockers other than labetalol (e.g., atenolol)	Avoid	Use an alternative medication	Intrauterine growth restriction and fetal bradycardia.
ACE inhibitors (captopril, enalapril, ramipril)	Contraindicated	Ideally, the drug use must be stopped before conception	Teratogenic in the 2nd and 3rd trimester, intrauterine growth restriction.
Angiotensin receptor blockers (Losartan)	Contraindicated	Ideally, the drug use must be stopped before conception	Teratogenic in the 2nd and 3rd trimester.
Calcium channel antagonists (other than nifedipine, e.g., Diltiazem)	Avoid	Use an alternative antihypertensive	Maternal hypotension and fetal hypoxia.

BID=Twice a day; TID=3 times a day; QID=Every day

Table 2: Safe antihypertensive drugs for urgent management of preeclampsia

Antihypertensive drug	Recommended dose	Side effects
Labetalol	20–80 mg, IV bolus over 2 min, repeat after 10 min in case BP remains >160/110mmHg	Bradycardia and hypotension
Labetalol	200 mg, Oral	Headache, Bradycardia, and bronchospasm
Hydralazine	5–10 mg, IV bolus repeat after 20 min if BP remains >160/110 mmHg	Tachycardia, hypotension, nausea, and headache
Nifedipine	10 mg, Oral	Headache and flushing
Treatment of eclampsia and seizures		
Magnesium sulfate	4 g Intravenous bolus over 20 min, followed by 1 g/h infusion, typically continued for 24 h	Flushing, respiratory depression caution in renal impairment as magnesium is excreted renally and toxicity may occur

IV: Intravenous; BP: Blood pressure

is warranted, as it has been shown to reduce the rate of seizures by 50% [32]. This comprehensive and specialized approach ensures that the complexities of pre-eclampsia, particularly when occurring in conjunction with chronic hypertension, are addressed with precision and urgency to safeguard the well-being of both the mother and the fetus.

Future Health Risks

Mothers who have encountered HDPs confront an increased likelihood of future health complications, including maternal myocardial infarction, heart failure, chronic hypertension, and stroke. Notably, the severity of preeclampsia, one of the common HDPs, demonstrates a positive correlation between the seriousness of cardiovascular diseases and an earlier onset of these conditions. This significant observation has led various professional organizations, such as the American Heart Association, American College of Cardiology, American Stroke Association, and American College of Obstetrics and Gynecology, to recognize preeclampsia as a clinical risk factor requiring screening during comprehensive cardiovascular risk assessments. Identifying HDPs early and delivering timely intervention is imperative, as a longer duration between diagnosis and treatment is associated with an escalated risk of maternal cardiovascular complications [33].

CONCLUSION

The management of HDP presents a multifaceted challenge, requiring a nuanced and comprehensive approach. Advances in diagnostic criteria, surveillance protocols, and intervention strategies have contributed to enhanced outcomes for both mothers and fetuses. The recognition of the long-term health implications for mothers who have experienced hypertensive disorders emphasizes the importance of early identification and intervention. The integration of out-of-office BP monitoring, individualized care for different hypertensive conditions, and a multidisciplinary approach in severe cases underscore the strides made in reshaping clinical practices. Continuous research and collaborative efforts remain imperative to refine management strategies further and mitigate the global burden of HDP.

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