Long-Term Cardiovascular Disease Risk in Women After Hypertensive Disorders of Pregnancy: Recent Advances in Hypertension

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Abstract

Patients with a history of hypertensive disorders of pregnancy (HDP) suffer higher rates of long-term cardiovascular events including heart failure, coronary artery disease, and stroke. Cardiovascular changes during pregnancy can act as a natural stress test, subsequently unmasking latent cardiovascular disease in the form of HDP. Because HDP now affect 10% of pregnancies in the United States, the American Heart Association has called for physicians who provide peripartum care to promote early identification and cardiovascular risk reduction. In this review, we discuss the epidemiology, pathophysiology, and outcomes of HDP-associated cardiovascular disease. In addition, we propose a multi-pronged approach to support cardiovascular risk reduction for women with a history of HDP. Additional research is warranted to define appropriate blood pressure targets in the postpartum period, optimize the use of pregnancy history in risk stratification tools, and clarify the effectiveness of preventive interventions. The highest rates of HDP are in populations with poor access to resources and quality health care, making it a major risk for inequity of care. Interventions to decrease long-term cardiovascular disease risk in women following HDP must also target disparity reduction.

Keywords

cardiovascular disease; hypertension; preeclampsia; pregnancy; risk factors

One in 4 cardiovascular-related deaths in women are preventable. Nevertheless, cardiovascular disease (CVD) remains the leading cause of death among women.¹ Physiological changes during pregnancy may unmask asymptomatic CVD such as chronic

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Disclosures

None.
hypertension or prediabetes. Perinatal care may be the first time a woman interacts with a medical professional. Therefore, the peripartum period represents an important opportunity to identify women at risk for future CVD and deliver preventive health care.

Hypertensive disorders of pregnancy (HDP) include gestational hypertension, chronic hypertension (CHTN), preeclampsia, and superimposed preeclampsia, which affect ≈10% of all pregnancies in the United States. Gestational hypertension and preeclampsia are the most common, characterized by hypertension after 20 weeks of gestation. Preeclampsia is the leading cause of prematurity and ranks third among causes of maternal mortality worldwide. Additionally, in women with HDP cardiovascular events occur earlier and increase their risk of cardiac mortality. To mitigate this risk the American College of Cardiology and the American Heart Association guidelines were updated to include a history of HDP as a major risk factor for developing CVD. In 2017, they urgently called for collaboration between providers to promote early identification and modification of CVD in reproductive-aged women.

This review discusses the epidemiology, pathophysiology, and outcomes of CVD associated with HDP, with attention to new-onset hypertension in pregnancy (gestational hypertension and preeclampsia). We highlight ongoing health inequity, as the highest rates of HDP are among Black women with limited access to quality health care. Finally, we propose a model for leveraging postpartum care to address CVD risk factors and integrating a history of HDP into long-term CVD risk management.

**HDP CLINICAL DEFINITIONS**

Hypertension during pregnancy is defined as systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg on 2 occasions at least 4 hours apart. For further description of the HDP subtypes, please see Table.

**HDP PATHOPHYSIOLOGY**

Although the pathogenesis of HDP is incompletely understood, disordered inflammatory responses and/or imbalanced angiogenic profiles play a role. Preeclampsia, a syndrome of multi-factorial causes, is characterized by a dysfunctional placenta that releases antiangiogenic and inflammatory factors into the maternal circulation. These soluble factors are associated with endothelial dysfunction, hypertension, and organ damage. Risk factors for preeclampsia include >35 years of age, nulliparity, history of preeclampsia, use of assisted reproductive technologies, and several chronic medical conditions (eg, CHTN, kidney disease, and diabetes). Increased maternal levels of TNF-α (tumor necrosis factor-alpha) and angiotensin II type 1 receptor autoantibodies support inflammation in preeclampsia. Male fetal sex is associated with an increased risk of preeclampsia in non-Asian mothers. Genetic variations in the fetal genome near FLT1 (fms-related tyrosine kinase 1), a gene involved in angiogenesis, as well as maternal polymorphisms in ACVR2a, the receptor for activin A may also play a role in preeclampsia pathogenesis.

Delivery (of the placenta) leads to resolution of several preeclampsia symptoms, highlighting the placental role in preeclampsia pathogenesis. During pregnancy in a patient...
with preeclampsia, dysregulated remodeling of the uteroplacental spiral arteries\textsuperscript{15,16} causes placental oxidative stress and ischemia with excessive release of inflammatory and anti-angiogenic factors such as sFlt1 (soluble fms-like tyrosine kinase 1).\textsuperscript{17,18} sFlt1 interferes with PlGF (placental growth factor) and vascular endothelial growth factor binding.\textsuperscript{19} Circulating sFlt1 levels are increased both during active disease and several weeks before symptom onset.\textsuperscript{20} An elevated sFlt1-to-PIGF ratio or depressed PlGF alone are increasingly used to predict risk of preeclampsia and guide management.\textsuperscript{21–24} Evidence suggests that sFlt1 levels can predict adverse pregnancy outcomes and cardiovascular dysfunction during preeclampsia and postpartum.\textsuperscript{25,26}

Preeclampsia is also considered a cardiovascular system maladaptation to pregnancy.\textsuperscript{27} Preexisting cardiovascular dysfunction may lead to placental dysfunction and preeclampsia.\textsuperscript{28} Bolstering this theory, vascular lesions found in placentas of preeclamptic patients resemble early atherosclerotic plaques.\textsuperscript{16,29}

**CVD MECHANISMS AMONG WOMEN WITH HDP**

The association between HDP and CVD is well established, especially among patients with preeclampsia.\textsuperscript{4,30,31} The increased cardiovascular demands during pregnancy (eg, increased cardiac output) may unmask latent hypertension, making pregnancy a cardiovascular stress test.\textsuperscript{32,33} However, evidence suggests that preeclampsia and other HDP also contribute independently to postpartum CVD risk.\textsuperscript{34} For example, increased levels of preeclampsia-associated inflammatory cells\textsuperscript{35} and angiotensin II type 1 receptor autoantibodies are found in preeclamptic patients several years postpartum,\textsuperscript{10,36} which may explain the independent association between preeclampsia and subsequent CVD risk. Another possible factor linking preeclampsia and myocardial dysfunction is dysregulated activin A signaling. Activin A, a marker of myocardial inflammation and fibrosis, may contribute to the pathogenesis of preeclampsia and be predictive of heart failure development.\textsuperscript{37,38} In women with HDP, elevated activin A levels correlated strongly with myocardial dysfunction and increased left ventricular mass 1-year postpartum\textsuperscript{39} and 8 to 10 years after preeclamptic pregnancy.\textsuperscript{40}

It is likely that both preexisting risk factors and HDP-induced dysfunction leads to elevated CVD risk.\textsuperscript{41} Indeed, a 2010 review of \(\approx 25000\) women found that prepregnancy obesity, dyslipidemias, and BP contributed as much as HDP to future CVD risk.\textsuperscript{42} Without intervention, each HDP occurrence compounds a woman’s vascular susceptibility increasing rates of vascular dysfunction by middle age, relative to women without HDP.

**LONG-TERM CARDIOVASCULAR RISK**

**HDP and Risk of CHTN**

Patients with HDP are at higher risk for developing chronic conditions that predispose them to CVD (eg, diabetes).\textsuperscript{43–45} The risk of CHTN is 4-fold higher 1-year postpartum, and remains 2-fold higher 10 and 20 years postpartum, relative to those with normotensive pregnancies.\textsuperscript{46,47} Emerging evidence suggests that smoking, obesity, and preterm delivery may help identify HDP patients at risk of developing CHTN.\textsuperscript{48,49}
HDP and Risk of Cardiovascular Events and Mortality

Long-term cardiovascular morbidity is elevated among patients with a history of HDP. In the decades that follow an HDP-complicated pregnancy, the risk of heart failure, stroke, and ischemic heart disease are ≈4-, 2-, and 2-fold higher, respectively, than in women with normotensive pregnancies. A 2017 meta-analysis of 22 studies and >250000 women with preeclampsia suggested that prepregnancy hypertension played a role in the later development of CVD. In addition, the risks for developing stroke, heart failure, and ischemic heart disease were the highest 1 to 10 years postpartum, suggesting many women with a history of HDP may experience adverse cardiac events before middle age. A 2017 prospective cohort study similarly observed that by 1-year postpartum, 23% of patients affected by preeclampsia had stage B heart failure.

The effect of preeclampsia on subsequent cardiovascular disease is stronger with more severe and earlier onset. A 2018 meta-analysis of 22 studies found that a second pregnancy complicated by preeclampsia doubled the risks of subsequent hypertension, ischemic heart disease, and stroke, nearly tripled the risk of heart failure, and increased combined cardiovascular events by >50%. Fetal growth disorders (preterm and small-for-gestational age delivery) may exacerbate the already increased risk of developing CVD following an HDP.

HDP is also associated with CVD mortality. A retrospective observational study of >15000 postpartum patients over a 50-year period found an increase in CVD-related death among patients with preeclampsia. Studies evaluating the Medical Birth Registry of Norway observed that the association between preeclampsia and cardiovascular death was highest for preterm and singleton deliveries.

RACIAL DISPARITIES IN HDP AND CVD

Black women are 2.5 to 3 times more likely to die from pregnancy-related causes than their White counterparts regardless of socioeconomic status. Moreover, nearly every type of severe maternal morbidity is more likely among Black women with preeclampsia (eg, acute myocardial infarction, stroke, and inpatient mortality). A 2019 Centers for Disease Control and Prevention report argued that 60% of these deaths would have been preventable with better access to high-quality care and timely diagnosis. Several mechanisms including genetic predispositions and social stress have been proposed for the higher prevalence of preeclampsia among Black women. Conversely, African immigrants have lower risk for preeclampsia than their United States-born counterparts. Further work to identify the mechanisms by which socioeconomic and racial factors contribute to HDP and CVD risk are needed.

CARDIOVASCULAR RISK REDUCTION

In summary, women with HDP are at higher risk for cardiovascular morbidity and mortality. Although the mechanisms are unclear, the cardiovascular demands of pregnancy likely unmask latent cardiovascular risk factors and HDP fosters cardiovascular dysfunction that may occur early in the postpartum period. Thus, we recommend initiating screening and
prevention among these patients as soon as possible after delivery. In addition, we provide the following strategies and timeline for improving cardiovascular risk reduction as a starting place for a formal working group recommendation (Figures 1 and 2).

**Increase Awareness Among Care Providers and Patients**

Providers have historically been unaware of the increased CVD risk following HDP. An HDP patient focus group reported a barrier to earlier preventative efforts was lack of CVD risk awareness among providers. Obstetrics-gynecology clinics with minority patient populations are more attuned to the risk of CVD in women with HDP. This finding suggests that increased CVD and multicultural competency training may increase CVD risk following HDP.

Increased awareness among patients may also improve preventative efforts. We recommend that patients with HDP be educated during pregnancy, upon diagnosis, after delivery and before discharge, about their elevated risks and the importance of postpartum follow-up.

**Uninterrupted Postpartum Health Care**

Women frequently become disconnected from ongoing medical care after delivery and may not seek care again until mid-life after CVD risks have manifested. Postpartum follow-up programs may allow earlier initiation of CVD preventative measures. Guidelines remain inconsistent for postpartum follow-up recommendations. The American College of Obstetricians and Gynecologists recommends that all women affected by HDP have initial contact with an obstetric care provider within 3 weeks postpartum, followed by a comprehensive postpartum visit by 12 weeks postpartum, and annual cardiovascular follow ups thereafter. The American Stroke Association and European Society of Hypertension recommend formal cardiovascular risk assessment annually after HDP but do not give immediate postpartum recommendations. Finally, the National Institute for Health and Care Excellence recommends follow-up at 6 to 8 weeks and 3 months postpartum but does not specify long-term follow-up intervals. The American Heart Association recommends frequent cardiovascular follow-up after an HDP but does not give a specific timeline. Regardless of visit timings, guidelines should stress the importance of early follow-up. We propose a plan based on follow-up within first 2 weeks postpartum, 6 to 12 weeks postpartum with specialty follow-up for residual hypertension, proteinuria, or hyperglycemia at delivery discharge, and annually thereafter for all women with HDP (Figure S1 in the Data Supplement). Proposed strategies for encouraging follow-up include scheduling visits at the time of delivery discharge, standardizing antihypertensive regimens, and immediate referrals to cardiology and/or primary care. Telehealth including home BP telemonitoring may also help address the deficiency in postpartum hypertension management. Although few studies have examined home BP telemonitoring use among patients following HDP, this technology improved BP control in nonpregnant patients.

Racial disparities persist after delivery, with up to 60% of Black women not receiving postpartum follow-up. Factors associated with lower follow-up include Black race and <5 prenatal visits. Reducing follow-up barriers may improve racial disparities in
postpartum morbidity and mortality. Specifically, a combination of patient and provider education, a standardized postpartum care protocols, and dedicated postpartum hypertension clinics improved follow-up and BP control among high-risk Black women, and may be useful for CVD risk reduction.\textsuperscript{83}

Another barrier to postpartum follow-up is access to health insurance coverage. A recent focus group identified loss of insurance postpartum as a barrier to CVD risk reduction following HDP.\textsuperscript{68,84} In a 2016 study of 6000 patients, Medicaid or no insurance coverage was associated with 40\% higher nonattendance at postpartum follow-up.\textsuperscript{85} Currently, health care coverage in the United States is not guaranteed beyond 6 weeks postpartum, which disproportionately affects Black, Hispanic, and American Indian and Alaska Native women. States with expanded Medicaid coverage under the Affordable Care Act reported a 50\% reduction in infant mortality, relative to nonexpansion states, suggesting access to care may improve outcomes in women at high risk for HDP-associated CVD.\textsuperscript{86,87} In support, the state of Illinois recently expanded Medicaid benefits from 60 days to 12 months postpartum.\textsuperscript{88}

**Earlier Risk Identification**

Recognition of the link between HDP and postpartum CVD has led to increased use of HDP-related metrics in cardiovascular risk assessment. Earlier identification of preeclampsia using biomarkers such as the sFlt1-to-PlGF ratio was discussed earlier. A 2016 study\textsuperscript{25} of 207 patients also found preeclampsia-specific antiangiogenic protein levels correlated with subclinical myocardial dysfunction during the third trimester. Other studies have observed similar findings.\textsuperscript{89–91} Adoption of these metrics may be particularly important for Black women, who have higher rates of early-onset preeclampsia, as discussed earlier.

Emerging evidence suggests that HDP-related biomarkers may also identify patients at high risk of postpartum cardiac morbidity.\textsuperscript{92} Activin A is an ongoing marker of cardiac dysfunction for at least 1-year postpartum and possibly up to 8 years after preeclampsia.\textsuperscript{37,39,93} Future work will clarify how best to use this biomarker in risk stratification and therapeutic intervention. Moreover, American College of Cardiology/American Heart Association guidelines now include gestational hypertension and preeclampsia in their CVD risk assessment.\textsuperscript{94}

**Evidence-Based Interventions**

Although existing evidence is incomplete, postpartum BP control is associated with lower stroke risk.\textsuperscript{95} One effective intervention for postpartum BP control is furosemide.\textsuperscript{96} Observational studies suggest breastfeeding may be associated with lower postpartum BP.\textsuperscript{97} However, current evidence is insufficient to identify optimal antihypertensive medication as well as BP targets for CVD reduction. In women with diabetes, strict BP control reduces stroke and diabetes-related mortality risks,\textsuperscript{98} but the effect of BP management on HDP-related morbidity and mortality remains unclear.

Evidence supporting the use of other long-term lifestyle interventions to reduce long-term CVD risk is also lacking. National Institute for Health and Care Excellence guidelines recommend keeping body mass index between 18.5 and 24.9 before the next pregnancy for those with a history of preeclampsia,\textsuperscript{99} due to excess risk for CHTN with higher body mass.
index following HDP. The Diabetes Prevention Program, consisting of weight reduction, reduced caloric intake, and exercise, achieved comparable long-term effects on CVD risk factors as the use of metformin. Currently, annual BP, lipid, body mass index, and fasting glucose monitoring are recommended following HDP until the age of 50 years, after which international cardiovascular prevention guidelines apply (Figure 2).

**CONCLUSIONS**

HDP are associated with an increased risk of early CVD. Although the mechanism is unclear, pregnancy may unmask latent subclinical cardiovascular risk factors in the form of pregnancy complications such as HDP. Emerging evidence suggests that HDP also independently induces cardiovascular dysfunction. Development of CVD-associated risk factors occur early after delivery and the most vulnerable period for developing CVD events occurs in the decade postpartum, before current cardiovascular screening guidelines. CVD prevention strategies must be initiated as soon as possible after delivery and before traditional CVD screening in general population.

Cardiovascular risk reduction following a HDP should involve increased education, empowerment, and awareness among patients and their providers; earlier CVD diagnosis or risk stratification; standardized postpartum care and better BP control; and evidence-based interventions to lower postpartum CVD risk and mortality (Figure 1 and Figure 2). These strategies must be implemented focused on racial and socioeconomic equity to decrease postpartum CVD burden. In addition, research is needed to clarify the pathophysiology of CVD after HDP; identify appropriate BP targets postpartum, create CVD risk stratification tools that include pregnancy history and biomarkers, and identify preventive interventions (Figure S2).

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Nonstandard Abbreviations and Acronyms**

- BP: blood pressure
- CHTN: chronic hypertension
- CVD: cardiovascular disease
- HDP: hypertensive disorders of pregnancy
- PI GF: placental growth factor
- sFlt1: soluble fms-like tyrosine kinase 1
- TNF-α: tumor necrosis factor-alpha
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Figure 1. Strategies for cardiovascular disease (CVD) risk reduction following hypertensive disorders of pregnancy.
Suggested strategies include a multidisciplinary team-based approach for early identification of CVD risk factors, consistent monitoring and education. HDP indicates hypertensive disorders of pregnancy; NP, nurse practitioner; and Ob-gyn, obstetrician-gynecologist.
Primary Prevention of CVD After HDP

1. **Immediately Postpartum**
   - Hypertension: follow-up according to national guidelines
   - Normotensive: follow the next steps

2. **6-12 Weeks Postpartum**
   - CVD risk assessment - simple (BMI, smoking, physical activity, BP)
   - Lifestyle modification support (dietary intake, activity, smoking cessation, healthy weight, etc.)

3. **1 Year Postpartum**
   - CVD risk assessment - extended (simple + family history, lipids, and glucose)
   - Lifestyle modification support and intervention as needed to minimize risk

4. **Every Year Until 50 Years of Age**
   - CVD risk assessment - simple
   - Lifestyle modification support and intervention as needed to minimize risk

5. **50 Years of Age**
   - CVD risk assessment - extended and risk scoring
   - Lifestyle modification support and intervention as needed to minimize risk
   - Evaluate need for therapy
   - Follow-up visits according to national guidelines

**Figure 2. Timeline for primary prevention of cardiovascular disease (CVD) following hypertensive disorders of pregnancy.**
Primary prevention of CVD should start early in the postpartum period and continue throughout the women’s life. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; and HDP, hypertensive disorders of pregnancy (Adapted from the Obstetrics Guidelines 2020 of the Norwegian Society of Gynecology and Obstetrics with permission).
### Table.

#### Hypertensive Disorders of Pregnancy Definitions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Chronic hypertension</td>
<td>Hypertension* diagnosed before 20 wks gestational age and persisting beyond 6 wks postpartum</td>
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<tr>
<td>Preeclampsia</td>
<td>Hypertension* diagnosed after 20 wks gestational age in the presence of:</td>
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<tr>
<td></td>
<td>Proteinuria†</td>
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<td></td>
<td>Or (in the absence of proteinuria) other signs of organ dysfunction (as described below)</td>
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<tr>
<td>Preeclampsia with severe features (above criteria plus any of the following)</td>
<td>Severe hypertension‡</td>
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<tr>
<td></td>
<td>Seizures (eclampsia)</td>
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<td></td>
<td>Thrombocytopenia (platelet count &lt;100,000×10⁹/L)</td>
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<td></td>
<td>Elevated transaminases (≥2-fold higher than the upper limit of normal)</td>
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<td>Renal insufficiency (serum creatinine &gt;1.1 mg/dL)</td>
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<td>Pulmonary edema</td>
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<td>Headache or visual disturbance</td>
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<tr>
<td>Gestational hypertension</td>
<td>Hypertension* diagnosed after 20 wks gestational age in the absence of proteinuria and other signs of organ dysfunction</td>
</tr>
<tr>
<td>Chronic hypertension with superimposed preeclampsia</td>
<td>Preexisting chronic hypertension that subsequently meets criteria for preeclampsia</td>
</tr>
</tbody>
</table>

* Hypertension is defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on 2 occasions at least 4 h apart.

† Proteinuria defined as ≥300 mg/24 h or a urine protein creatinine ratio ≥0.3.

‡ Severe hypertension defined as systolic BP ≥160 mm Hg and/or diastolic BP ≥10 mm Hg. Severe hypertension can be confirmed within a short interval to facilitate timely antihypertensive medication.