Reviews

PREVENTION

Preeclampsia and Hypertensive Disease in Pregnancy: Their Contributions to Cardiovascular Risk

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ABSTRACT

More women than men die each year of cardiovascular disease, which remains the leading cause of death in the United States. Sex-specific factors, including pregnancy-related disorders, should be considered when assessing cardiovascular (CV) risk in women. Hypertensive disorders of pregnancy have been associated with CV risk later in life and may identify women in whom earlier primary prevention may reduce their risk. This article reviews the physiologic changes in blood pressure during pregnancy, current definitions of hypertensive diseases of pregnancy and preeclampsia, and postulated pathophysiologic mechanisms leading to preeclampsia that might contribute to later CV risk. Also summarized are studies providing evidence on the association between hypertensive diseases of pregnancy and future CV risk.

Introduction

Cardiovascular disease (CVD) continues to be the leading cause of death in the United States. More women than men die each year of heart disease. Despite efforts to improve prevention, diagnosis, and treatment of CVD over recent years that have resulted in an overall reduction of cardiovascular (CV) death rates, CVD death rates are on the rise for women age <55 years.[1] This is in part due to gender-related differences in risk factors, symptoms, and treatment. Traditional risk factors and risk-stratification tools fail to take sex-specific risk factors for women into consideration. Gestational hypertension, diabetes mellitus (DM), and preeclampsia-eclampsia may be associated with increased risk of CVD later in life. Identification of these higher-risk women would provide the opportunity for closer surveillance and preventive programs to reduce CV risk. This article reviews the physiologic changes in blood pressure (BP) during pregnancy, current definitions of hypertensive disease of pregnancy and preeclampsia, postulated pathophysiologic mechanisms leading to preeclampsia that might contribute to later CV risk, and the evidence on the association between hypertensive diseases of pregnancy and future CV risk.

Two meta-analyses of the literature were published in 2007.[2,3] To provide current data on the association between hypertensive disease of pregnancy and later CV risk, we searched 3 databases—PubMed, Scopus, and Web of Science—for all articles in English, German, and Spanish language for studies published after the period covered in these meta-analyses with the following medical subject headings and keywords: cardiovascular disease risk or diagnosis, preeclampsia, hypertension pregnancy induced and diagnosis, hypertension pregnancy induced and epidemiology, pregnancy outcome, cohort study, systematic review. We included data from cohort and registry studies that had ≥100 subjects. Six studies met the criteria for inclusion in the article and are included in the section Hypertensive Pregnancy Disorders and Future Cardiovascular Disease: Review of Evidence.

Blood Pressure Course in Normal Pregnancy

Mean BP decreases in uncomplicated pregnancy in the fourth to sixth week after conception, mainly due to a fall in diastolic BP. During the third trimester, BP gradually increases to prepregnancy levels by term.[4,5] The fall in BP mainly results from maternal systemic vasodilation and to a lesser extent from the high-flow, low-resistance circuit in the uteroplacental circulation.[6] The underlying mechanisms are incompletely understood but include a relative refractoriness to pressor effects of angiotensin II and norepinephrine.[7] Preclinical data implicate several pregnancy hormones, such as estrogen, prolactin, human

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Table 1. Classification of Hypertensive Disorders of Pregnancy

Chronic hypertension	BP ≥140/±90 mm Hg before pregnancy or before the 20th week of gestation
Preeclampsia-eclampsia	A pregnancy-specific disorder that is a multisystem disease characterized by hypertension ≥140/±90 mm Hg on ≥2 occasions at least 6 hours apart, and proteinuria ≥300 mg in a 24-hour urine collection, after 20 weeks' gestation. The convulsive form of preeclampsia is eclampsia and affects 0.1% of all pregnancies.
Preeclampsia superimposed on chronic hypertension	Up to 30% of women with chronic hypertension develop preeclampsia, as heralded by the occurrence of de novo proteinuria in the third trimester. In women with chronic hypertension and preexisting proteinuria (ie, before 20 weeks of gestation), the diagnosis of superimposed preeclampsia is likely with any of the following findings: sudden increase in proteinuria, sudden worsening of previously well-controlled BP, new-onset thrombocytopenia, or elevated liver function tests.
Gestational hypertension	New onset of hypertension ≥140/±90 mm Hg on ≥2 occasions at least 6 hours apart, after 20 weeks' gestation, in the absence of proteinuria, <300 mg in a 24-hour urine collection. If BP returns to normal by 12 weeks postpartum, the diagnosis of transient hypertension of pregnancy can be assigned. If elevated BP persists, the diagnosis of chronic hypertension is made.

Abbreviations: BP, blood pressure.

chorionic gonadotropin, and human placental lactogen, in the reduction of vascular resistance and concomitant increase in blood volume and cardiac output.[8] Reduced aortic stiffness and increased endothelial prostacyclin and nitric oxide production may also be involved.[9,10]

Classification and Definitions of Hypertensive Pregnancy Disorders

Hypertension-preeclampsia are among the most common medical diagnoses made during pregnancy, with an incidence of 6%–8%.[11] The term "gestational hypertension-preeclampsia" includes a wide spectrum of hypertensive disease ranging from mild BP elevation to the potentially life-threatening hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. The definitions of the American College of Obstetrics and Gynecology are widely accepted and for practical reasons used in this review, as detailed in Table 1.[12,13]

Metabolic and Vascular Changes of Normal Pregnancy Are Further Potentiated in Preeclampsia

In normal pregnancy, insulin sensitivity is reduced to facilitate the transfer of glucose to the fetus, but this is exaggerated in preeclamptic pregnancies, usually lasting up to the third month postpartum.[14] The overall risk for developing DM is approximately 2-fold among women with prior preeclampsia or gestational hypertension.[15–18] Hyperlipidemia is another risk factor common to preeclampsia and CVD. The normal hyperlipidemia of pregnancy is characterized by an up to 3-fold increase in triglycerides and a 50% increase in total cholesterol, predominantly low-density lipoprotein (LDL) and phospholipids,[19,20] which return to normal by about 6 to 10 weeks postpartum. Normal gestational hyperlipidemia is exaggerated in preeclampsia. High-density lipoprotein levels decrease and total cholesterol and LDL levels are unchanged with an excessive increase in triglycerides, free fatty acids, apolipoprotein B/apolipoprotein A1 ratio, and small, oxidized LDL, changing the high-density lipoprotein/LDL ratio unfavorably.[18,21–23] Other markers of cardiometabolic risk, such as leptin and homocysteine, have been associated with preeclampsia/gestational hypertension.[18] Given these associations, preeclampsia has been proposed to be the metabolic syndrome of pregnancy.

Pathophysiologic Mechanisms of Preeclampsia and Vascular Effects

Several different mechanisms have been linked to endothelial dysfunction in preeclampsia. Those include hypoxia, excessive oxidative stress, the renin-aldosterone-angiotensin II axis, and more recently imbalance of placental angiogenic factors, favoring antiangiogenic-soluble form of the type 1 receptor of vascular endothelial growth factor (sVEGFR-1 or sFlt1), which binds and thus neutralizes proangiogenic VEGF and placental growth factor.[24–27] Ensuing endothelial dysfunction may further be worsened by several vasoactive markers that are elevated in preeclampsia, such as cellular fibronectin, endothelin, platelet-derived growth factor, soluble E-selectin, soluble tissue factor, and von Willebrand factor. In vitro experiments have shown endothelial dysfunction after incubation with serum from women with preeclampsia.[26] Several studies have evaluated short- and long-term endothelial function after preeclampsia, demonstrating ongoing vascular dysfunction measurable from 6 to 12 months[28] to 5 to 6 years[29] and even up to 15–25 years postpartum.[30]

Maternal endothelial injury in preeclampsia has probably best been studied in the kidney, characterized by glomerular endotheliosis, generalized swelling, vacuolization of the endothelial cells, loss of capillary space,[31] fibrin deposits under and within the endothelial cells, and loss of glomerular endothelial fenestrae.[32] Normal functioning of angiogenic factors, such as VEGF, are critical for maintenance of a healthy, intact endothelium, as demonstrated in animal studies where the lack of one VEGF allele in renal podocytes resulted in characteristic renal lesions seen in preeclampsia.[33]

Hypertensive Pregnancy Disorders and Future Cardiovascular Disease: Review of Evidence

An increasing body of evidence suggests that preeclampsia is predictive of future CVD (Table 2). Two large systematic

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Table 2. Cohort Studies and Systematic Reviews of Preeclampsia and Gestational Hypertension and Risk of CVD

	Study Design	Size and Population Characteristics	Follow-Up Period	Outcome Measures	Risk for Future CVD
Meta-Analyses					
Bellamy et al, 2007[2]	Systematic review and meta-analysis; 25 papers published between 1960 and 2006	3,488,160 women	Mean: 14.5 y 11.7 y 10.4 y 14.1 y	 Overall mortality Ischemic heart disease Stroke Hypertension	*Relative Risk* all for PRE 1.49 (1.05–2.14) 2.16 (1.86–2.52) 1.81 (1.45–2.27) 3.7 (2.7–5.05),
McDonald SD, et al, 2008[3]	Systematic review and meta-analysis of 5 case control and 10 cohort studies	2,375,751 women	Not given due to mix of mean, median and not defined type of years of follow up	Cardiovascular mortality CVA Peripheral arterial disease	*Odds Ratio* 2.29 (1.73–3.04) 2.03 (1.54–2.67) 1.87 (0.94–3.73)
CV Risk Factor Outcomes					
Lykke, JA, et al, 2009[55]	Danish registry based cohort	782 287 women ages 15–50 with a first singleton delivery without previous CVD diagnosis	median 14.6 yrs	Hypertension Type 2 diabetes mellitus	*Hazard Ratio* 5.75 (5.28–6.2) GH 6.73 (6.04–7.49) PRE severe 3.12 (2.63–3.7) GH 3.68 (3.04–4.46) PRE
Magnussen, et al, 2009[56]	Medical birth registry of Norway ad Nord-Trondelag Heatlh study	15 065 women	mean 16.5 years	Diabetes mellitus Hypertension BMI Lipid panel	*Odds Ratio* *3.8 (2.1–6.6) PRE* *3.1 (2.2–4.3) PRE* $P < 0.05$ $P < 0.05$
Subclinical Atherosclerosis Outcome					
Cassidy-Bushrow AE, et al, 2009[58]	Rochester Family Heart Study cohort and cohort in vicinity of Rochester	498 women	mean 27 years	Coronary artery calcium score	*Odds Ratio* 2.4 (1.2–4.9) HDP
CVD outcomes					
Garovic VD, et al, 2010[57]	Family Blood Pressure Program Study Phase 2	4782 women	1996–2004	Hypertension Stroke	*Hazard Ratio* 1.88 (1.49–2.39) 2.10 (1.19–3.71)
Lykke, JA, et al, 2009[55]	Danish registry based cohort	782 287 women ages 15–50 with a first singleton delivery without previous CVD diagnosis	median 14.6 yrs	Ischemic heart disease Congestive heart failure Stroke	*Hazard Ratio* 1.64 (1.38–1.94) GH 1.75 (1.46–2.11) PRE 1.54 (1.1–2.16) GH 1.89 (1.35–2.65) PRE 1.58 (1.32–1.89) GH 1.66 (1.29 to 2.14) PRE
Mongraw-Chaffin, ML, et al, 2010[59]	Kaiser Permanente Health Plan in California	14,403 without previous diagnosed heart condition	median 37 yrs	CVD death	*Hazard Ratio* 2.14 (1.29–3.57) PRE 9.54 (4.5–20.6) PRE by 34 weeks of gestation
Lin YS, et al, 2011[60]	Taiwanese Population based cohort study based on birth registries linked to National Health Insurance hospital discharge data and death files.	1,132,064 parturients	At least 3 yrs postpartum	Major CV events: –any –any, without stroke –MI –HF –Stroke –related deaths	*Hazard Ratio* 12.6 (2.4–66.3) 7.3 (5.5–9.7) 13.0 (4.6–6.3) 8.3 (4.28–14.4) 14.5 (1.3–165.1) 2.3 (2.0–3.9)

(PRE)-Preeclampsia, (GH) gestational hypertension; *Maternal Placental Syndromes defined as: preeclampsia, gestational hypertension, placental abruption, placental infarction; (HDP) hypertension during pregnancy-defined as: gestational hypertension, transient hypertension of pregnancy, preeclampsia, and eclampsia. Model 1-controlled for preterm delivery, small for gestational age, placental abruption and stillbirth.

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meta-analyses of CV outcomes in women with preeclampsia-eclampsia have been published. Bellamy et al[2] included prospective and retrospective cohort studies from 1960 to December 2006; McDonald et al[3] included case-control and cohort studies of preeclampsia-eclampsia from 1966 to January 2006 and included many of the same studies.[2,3,34–54] Women with preeclampsia had a 3- to 4-fold increased risk of developing hypertension, a 2-fold risk for ischemic heart disease, and increased stroke risk compared with women without a history of preeclampsia. The absolute risk for a CV event at age 50–59 for a woman with a history of preeclampsia was 17.8%, vs 8.3% for a woman without a history of preeclampsia. Furthermore, the greater the severity of preeclampsia, the greater the risk of future cardiac disease (mild preeclampsia, relative risk [RR]: 2.00, 95% confidence interval [CI]: 1.83–2.19; moderate preeclampsia, RR: 2.99, 95% CI: 2.51–3.58; severe preeclampsia, RR: 5.36, 95% CI: 3.96–7.27). A correlation between preeclampsia and future peripheral artery disease was also found (RR: 1.87, 95% CI: 0.94–3.73).[3]

Studies that followed provide additional evidence that women with gestational hypertensive disorders have higher risk for later CVD risk factors,[55–57] subclinical atherosclerosis,[58] and clinical CVD outcomes.[45,55,57,59,60] In addition, early-onset preeclampsia (before 34 gestational weeks) has been associated with a hazard ratio of 9.5 for CVD death[59] and recurrent disease (ie, in >1 pregnancy) was associated with a 6-fold increase in risk for subsequent hypertension[55] (Table 2).

Most cohort studies on preeclampsia/gestational hypertension and future CVD risk enrolled predominantly white populations, and little data are available in other ethnic groups. Recently a large population-based cohort study of Asian women from Taiwan examined the association between preeclampsia-eclampsia and major adverse cardiovascular events including myocardial infarction, heart failure, percutaneous cardiac intervention, coronary artery bypass grafting, malignant dysrhythmia, cardiac shock, thrombolysis, and implantable cardiac defibrillator.[60] Consistent with previous reports, the investigators found that women with preeclampsia-eclampsia had a significantly greater risk of major adverse cardiovascular events, especially myocardial infarction and stroke during pregnancy. This elevated risk remained significantly high throughout the early years postpartum (≥36 months) (Table 2). This study is limited by the short follow-up, limited data on concomitant CV risk factors, and lack of adjudication of reported outcomes.

There is additional evidence supporting the association between hypertensive pregnancy disorders with subclinical atherosclerosis identified by coronary artery calcium score (CAC), which has been shown to be a marker of clinical CVD events.[61] A history of hypertensive disease of pregnancy was positively associated with presence of CAC (odds ratio [OR]: 2.6, 95% CI: 1.3–5.3), and similarly for extent of CAC even after adjusting for age, body size, blood pressure, serum creatinine, and urinary albumin/creatinine ratio, suggesting that hypertensive diseases of pregnancy may increase CVD later in life independent of traditional risk factors.[58]

Hypertensive Pregnancy Disorders and Future Cardiovascular Disease: Possible Mechanisms

The same conditions that have been implicated in the pathogenesis of preeclampsia are also strong risk factors for future development of CVD, including insulin resistance, DM, obesity, chronic hypertension, systemic inflammation, and renal disease.[62–64] Thus, shared risk factors rather than a causative relationship could explain the apparent associations between preeclampsia and later CVD.[65,66] Data from a Norwegian population-based study found that the association of gestational hypertensive disease and postpregnancy CV risk factors could largely be attributed to shared risk factors that are present prior to pregnancy.[67]

Results from a prospective cohort study provided evidence suggesting that women with a history of preeclampsia or gestational hypertension, especially those with recurrent disease, were at higher risk for developing modifiable CVD risk factors such as a higher body mass index, elevated BP, unfavorable lipid profile, and DM. These findings suggest that this patient population could benefit from earlier intervention to prevent CVD.[56] Most of the evidence indicating that preeclamptic pregnancies can result in vascular changes that could modify the woman's risk for future CVD results from studies showing endothelial dysfunction measured at 6–12 months,[28] 1 year,[68] 5–6 years,[29] and even up to 15–25 years[30] after a pregnancy complicated by preeclampsia. It is hypothesized that these changes in vascular endothelial function that "outlive" the initial inciting preeclamptic event may be responsible for predisposing women to the development of atherosclerosis and CVD later in life.

Limitations of Available Data

The long timeline between pregnancy and clinical CVD has been a major barrier to designing the ideal cohort study where prepregnancy data, pregnancy-associated measurements, interpregnancy data, and longer-term CVD risk profiles would be carefully measured with standardized definitions of the variables of interest. Much of the published data derive from birth registries linked to medical or death registries from Scandinavia, involving countries with widely available antenatal care. These findings need to be validated in other ethnic and socioeconomic groups. Importantly, in the past a lack of unified definitions of hypertensive disorders of pregnancy may have led to diagnosis misclassification, disease underreporting, and reduced registry sensitivity for the detection of preeclampsia. Out-of-hospital events that would be managed as an outpatient, such as hypertension, thromboembolic disease, or metabolic syndrome, may not be captured by registries or in cohort studies that rely on hospital records for outcomes. These latter studies would be biased to report more severe outcomes that resulted in hospitalization or in death. Outcome variables available for analysis within registries may be limited, and information on confounding variables, including CVD risk factors, may not be collected.

Many ongoing longitudinal cohort studies seek retrospective information on pregnancy-related exposures from participants >10 or even 20 years after childbirth. The issue of accurate recall is of particular concern. The positive

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predictive value for diagnosis of preeclampsia in the registry was 74.4%, whereas the positive predictive value of the women's own reports of preeclampsia was 59.2% in one larger study of approximately 3000 women.[69] Another study to validate a self-administered questionnaire concerning the diagnosis of preeclampsia yielded a sensitivity of 80% and specificity of 96%.[70] These results are certainly registry specific but do reflect the significant limitations of classifying pregnancy hypertensive disease based on patient recall. Other important limitations include publication bias and loss of follow-up, as risk profiles may change over time.

Importance of the Issue

Current guidelines identify gestational hypertension or preeclampsia as a risk factor for CVD later in life. It is less clear how this should influence healthcare providers' long-term clinical management of CVD risk in women, as it is not known whether early identification of women at risk for preeclampsia and prevention of its development would decrease CVD risk later in life. Further research evaluating the impact of early screening and interventions on clinical outcomes is needed. However, it has been proposed that pregnancy is a stress test for CVD.[71] It is also not known in women who develop gestational hypertension/preeclampsia, what would be a reasonable time interval before they are reassessed for CV risk factors. Women receive fragmented care, frequently seeing the obstetrician for a brief period during their reproductively fertile life and then transitioning to family-medicine practitioners or internists later in life. A detailed pregnancy history is often not included in the internal medicine history. However, the published data support hypertensive pregnancy disorders as identifying women with a potentially higher risk profile for CVD later in life. The significance of an increased risk for CVD of 2- to 3-fold can be compared with the fact that smokers have 2–4× the risk of CVD as nonsmokers.[1] Research would be helped by standardized definitions for the gestational disorders of hypertension, preeclampsia, and eclampsia. Consistent education of the patient about her pregnancy-related disorders would also facilitate linking pregnancy data with later-life evaluation of subclinical and clinical atherosclerosis if accuracy of patient recall were improved. Longitudinal follow-up of the metabolic abnormalities is needed in women with and without gestational hypertension disorders to evaluate rate of change of vascular dysfunction and the development of early atherosclerosis. Evaluation of women prior to pregnancy and follow-up during pregnancy is needed to determine the role of shared risk factors. Regular medical follow-up and earlier screening for CVD should be considered in this population. At least, current screening guidelines should be followed and these women should receive advice on established preventive lifestyle measures and on treatment strategies that should be implemented by all women regardless of a previous history of gestational hypertension/preeclampsia.[72] Whether targeting women with a history of hypertensive pregnancy disorders or preeclampsia for earlier therapeutic interventions with more aggressive targets would reduce risk in a cost-effective manner remains to be answered.

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