Hypertension in pregnancy: an emerging risk factor for cardiovascular disease

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SUMMARY

Increasing evidence indicates that hypertension in pregnancy is an under-recognized risk factor for cardiovascular disease (CVD). Compared with women who have had normotensive pregnancies, those who are hypertensive during pregnancy are at greater risk of cardiovascular and cerebrovascular events and have a less favorable overall risk profile for CVD years after the affected pregnancies. One factor that might underlie this relationship is that hypertensive disorders of pregnancy (pre-eclampsia, in particular) and CVD share several common risk factors (e.g. obesity, diabetes mellitus and renal disease). Alternatively, hypertension in pregnancy could induce long-term metabolic and vascular abnormalities that might increase the overall risk of CVD later in life. In both cases, evidence regarding risk-reduction interventions specific to women who have had hypertensive pregnancies is lacking. While awaiting results of large-scale studies, hypertensive disorders of pregnancy should be screened for during assessment of a woman's overall risk profile for CVD. Women at high risk must be monitored closely for conventional risk factors that are common to both CVD and hypertensive disorders of pregnancy and treated according to current evidence-based national guidelines.

KEYWORDS cardiovascular disease, hypertension, pre-eclampsia, pregnancy

REVIEW CRITERIA

The following medical subject headings were used to search the Medline database for articles published since 1966: "risk factors", "female gender", "cardiovascular disease", "coronary heart disease", "stroke", "hypertension in pregnancy", "pre-eclampsia", "eclampsia", "endothelial dysfunction", "inflammation," and "oxidative stress". We identified 134 original and review articles. Data were analyzed for morbidity and mortality related to cardiovascular disease, the definition of which included hypertension, coronary heart disease, cerebrovascular disease and disorders of the peripheral vascular system.

CME

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INTRODUCTION

Cardiovascular epidemiologic research has historically focused on men, because male sex is one of the major risk factors for cardiovascular disease (CVD).[1] Consequently, numerous diagnostic and treatment strategies for CVD in women have been extrapolated from the results of studies conducted in men, and gender-specific factors have been ignored. It became apparent in the 1980s that the decline of cardiovascular mortality in men was not accompanied by the same rate of decline in women.[2,3] One of the reasons for this difference might be gender-based disparities in cardiovascular care; women have been both underevaluated for CVD and undertreated for modifiable risk factors for CVD.[4,5] In addition, female-specific conditions, such as hypertensive disorders of pregnancy, menopause and hormone use, might affect the onset of CVD, its clinical course, the efficacy of therapy and, ultimately, prognosis.

Box 1 Classification, definitions and clinical characteristics of hypertensive disorders of pregnancy.

Pre-eclampsia and eclampsia
A pregnancy-specific disorder that occurs in 3–5% of pregnancies, pre-eclampsia is a multisystem disease characterized by hypertension and proteinuria of 300 mg or greater in a 24 h urine sample. The convulsive form of pre-eclampsia, eclampsia, affects 0.1% of all pregnancies.

Chronic hypertension
Blood pressure greater than or equal to 140/90 mmHg before pregnancy or before the twentieth week of gestation. Most patients in this category will have a benign course, with normalization of blood pressure in midpregnancy.

Pre-eclampsia superimposed on chronic hypertension
Up to 30% of women with chronic hypertension develop pre-eclampsia, which is heralded by proteinuria that occurs for the first time in the third trimester and which is absent in uncomplicated chronic hypertension.

Gestational hypertension
Hypertension occurring for the first time during the second half of pregnancy in the absence of proteinuria. This category encompasses both women with pre-eclampsia who have not yet developed proteinuria and those with hypertension only; blood pressure remains elevated after delivery in a subset of patients with gestational hypertension, leading to the diagnosis of chronic hypertension.

The association between hypertension in pregnancy and adverse long-term cardiovascular outcomes has been increasingly recognized. We studied 4,782 women who participated in the Family Blood Pressure Program study.[6] Subjects were categorized as either women without a history of pregnancy lasting more than 6 months (n=718), women with normotensive pregnancies (n=3,421), or women with a history of at least one hypertensive pregnancy (n=643). All analyses were performed while controlling for race, education, smoking and BMI. Compared with women who had a history of normotensive pregnancies, women without a history of pregnancy lasting more than 6 months showed a trend towards a higher risk for stroke, but they were not significantly different with respect to their future risks for hypertension or coronary heart disease. A history of hypertension in pregnancy was associated with an increased risk, and earlier onset, of cardiovascular events later in life. Compared with those who had a history of normotensive pregnancies, women who had been hypertensive during pregnancy had hazard ratios for stroke, coronary heart disease and hypertension of 2.0, 1.5 and 1.5, respectively, in addition to higher urinary albumin:creatinine ratios after the age of 40 years.[6] Herein, we review the evidence that implicates hypertension in pregnancy as a risk factor for CVD later in life and the putative mechanisms underlying this association, including the possibility that hypertensive disorders of pregnancy increase the risk of future CVD by causing long-term metabolic, inflammatory and vascular changes. Note that we apply a broad definition of CVD, encompassing hypertension, coronary heart disease, cerebrovascular disease and disorders of the peripheral vascular system.

HYPERTENSION IN PREGNANCY: IMPLICATIONS FOR CVD

Normal pregnancy and cardiovascular physiology

Normal pregnancy is characterized by increases in cardiac output and blood volume, generalized vasodilatation, a decrease in blood pressure and resistance to pressor agents, such as norepinephrine and angiotensin II.[7] Metabolic changes in normal pregnancy, including hyperlipidemia and hypercoagulable and inflammatory states, are further accentuated in pre-eclampsia and are similar to those associated with an unfavorable risk profile for CVD. Some authors have postulated that even normal pregnancy might be atherogenic, and multiple pregnancies could increase the risk of CVD later in life.[8] An analysis of the relationship between parity and cause of death in 1.2 million women aged 45–74 years revealed that multiparous women had higher mortality from hypertension, ischemic heart disease and cerebrovascular disease than did nulliparous women.[9] It is probable, however, that other unmeasured confounding factors (e.g. socioeconomic status, changes in lifestyle after childbearing, and the relationship between gravidity or parity and weight), rather than reproductive factors *per se*, increased the overall risk for CVD.[10] Indeed, several lines of evidence have shown that women who have had normal pregnancies are at a lower risk of developing hypertension later in life.[11]

Hypertensive disorders of pregnancy

Hypertension affects 10% of pregnancies and is a leading cause of both maternal and fetal morbidity and mortality worldwide. Hypertension in pregnancy includes a spectrum of conditions,[12] including pre-eclampsia or eclampsia, pre-eclampsia superimposed on chronic hypertension, chronic hypertension and gestational hypertension (Box 1). Unlike other hypertensive disorders of pregnancy, pre-eclampsia is a multisystem disease. A distinctive feature is either sudden onset or worsening of pre-existing proteinuria.

The diagnosis of hypertension in pregnancy, and differential diagnosis of different hypertensive disorders of pregnancy, is not straightforward, despite the clearly defined criteria. Hypertension in pregnancy is defined as two recordings of a blood pressure of at least 140/90 mmHg at an interval of 6 hours. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure,[13] however, individuals who have a systolic blood pressure of 120–139 mmHg and/or a diastolic blood pressure of 80–89 mmHg should be considered prehypertensive. This recommendation suggests that the diagnostic threshold of 140/90 mmHg might be high for any population, and even more so for young females of childbearing age. This high threshold could lead to underestimation of the prevalence of hypertensive disorders of pregnancy. Furthermore, it is well recognized that blood pressure decreases in mid-pregnancy, and this fall is further exaggerated in patients who have pre-existing, chronic hypertension.[14] As blood pressure tends to increase to prepregnancy levels in the third trimester, women with pre-existing chronic hypertension could be diagnosed as hypertensive for the first time towards the end of pregnancy and diagnosed with chronic hypertension only in retrospect; that is, after their 'gestational hypertension' fails to normalize following delivery.

Major differences in the clinical presentation of pre-eclampsia and other hypertensive disorders (Box 1) probably result from differences in underlying mechanisms, which might have varying implications for CVD later in life. In the following discussion, distinctions between hypertensive disorders with respect to their reported effects on long-term CVD outcomes have been made if data are available.

Hypertension in pregnancy and chronic hypertension later in life

A possible association between pre-eclampsia and the subsequent risk of developing hypertension was reported as early as the first part of the nineteenth century.[15] Early studies had several limitations, including retrospective designs, small sample sizes, inadequate durations of follow-up, difficulties establishing the diagnosis in a retrospective fashion owing to insufficient documentation, nonsystematic data gathering, and changes in the definition of, and diagnostic criteria for, hypertensive disorders of pregnancy over time. In addition, the specific effects of different hypertensive disorders of pregnancy were frequently ignored. A few studies that were performed between the 1950s and the early 1970s provided more evidence to indicate that hypertensive pregnancies and pre-eclampsia are associated with higher blood pressure later in life.[16,17] Children born to pre-eclamptic mothers commonly have a low birth weight, which is associated with an increased risk of cardiovascular mortality in adulthood.[18] An inverse relationship between maternal risk of CVD mortality and infant birth weight is well recognized.[19,20] Maternal outcomes, independent of the birth weights of offspring, have, however, attracted much less research interest, in part because of the data collected by Chesley and colleagues.[11,21] Chesley reported that the prevalence of hypertension and rates of overall mortality and mortality owing to CVD in primiparous eclamptic women were similar to those of age-matched controls after 33 years of follow-up. The limitations of these studies included small sample sizes and suboptimal control groups (i.e. women from previously published epidemiologic studies, rather than normotensive controls).

Several more-recent studies, both prospective[22,23] and retrospective,[24,25] have established an association between hypertension in pregnancy, pre-eclampsia or eclampsia and hypertension later in life. For example, in 1986, Sibai *et al.*[26] reported a significantly higher incidence of hypertension in patients with a history of pre-eclampsia or eclampsia during their first pregnancies compared with matched controls who had had normotensive first pregnancies. The risk was particularly high for patients with a history of recurrent pre-eclampsia or eclampsia and in those who presented with the condition before 30 weeks' gestation. Most of the differences were noted in individuals who were followed up for at least 10 years. The importance of the follow-up interval after delivery was further supported by an Italian study; half of the participating women with a history of pre-eclampsia were hypertensive 10 years after delivery compared with one-third who were hypertensive at a 5-year evaluation.[24]

Table 1 The association between cardiovascular events and a history of hypertensive disorders of pregnancy.

Study	Study design and location	Study group	Control group	Outcomes (study group vs control group)
Mann *et al.* (1976)[89]	Case–control study (1968–1972), UK	Women <45 years of age treated for myocardial infarction	Age-matched, treated for conditions other than myocardial infarction	Myocardial infarction: RR 3.0 for history of**[Au: changes OK for all?]** pre-eclampsia
Croft and Hannaford (1989)[28]	Nested case–control study (RCGP Oral Contraceptive Study), UK	Women with acute myocardial infarction	Women without acute myocardial infarction	Myocardial infarction: RR 2.8 (1.7–4.8) for history of 'toxemia'[a]
WHO (1995)[90]	Collaborative, case–control study, 21 centers in 17 countries	Women with venous thromboembolism[b]	Aged-matched, without venous thromboembolism	Venous thromboembolism: OR 1.66 (1.20–2.29) for history of hypertension in pregnancy in Europe and 1.16 (0.89–1.52) in developing countries
WHO (1996)[91]	Collaborative, case–control study, 21 centers in 17 countries	Women who suffered a cerebrovascular accident	Age-matched, without a cerebrovascular accident	Cerebrovascular accident: OR 1.94 (1.26–2.97) for history of hypertension in pregnancy in Europe and 2.54 (2.01–3.20) in developing countries
Brown *et al.* (2006)[92]	Population-based case–control study (Stroke Prevention in Young Women Study) (1992–1996), USA	Women who suffered a cerebrovascular accident	Women without a cerebrovascular accident	Cerebrovascular accident: OR 1.63 (1.02–2.62) for history of pre-eclampsia

[Au: are the ranges in the last column 95% CIs?]
[a]Toxemia is a synonym for pre-eclampsia that was used in the 1960s. [b]Venous thromboembolism includes deep venous thrombosis and pulmonary embolism.
Abbreviations: OR, odds ratio; RCGP, Royal College of General Practitioners; RR, relative risk

Several studies have also confirmed a higher incidence of subsequent hypertension in patients with recurrent pre-eclampsia, in addition to a lower incidence of hypertension in women with a history of normotensive pregnancies.

Hypertension in pregnancy and CVD

A critical review of the relevant literature reveals two common study designs that support the role of hypertensive disorders of pregnancy as risk factors for future CVD. During the past 30 years, several studies have examined cohorts of women with CVD events and compared their pregnancy histories with those of age-matched women who were event-free (Table 1). Over the course of the past decade, population-based studies have associated hypertensive pregnancy histories with adverse long-term cardiovascular outcomes (Table 2). Despite differences in study design, conclusions have been similar: hypertensive disorders of pregnancy might identify women at increased risk of future CVD-related morbidity and mortality (i.e. that resulting from ischemic heart disease, stroke and thromboembolic events). Women with severe and recurrent pre-eclampsia seem to be at particularly high risk.[27] Several factors were identified that, if concomitant with hypertensive disorders of pregnancy, might further increase the risk of CVD. These include smoking,[28] parity,[29] preterm delivery,[20,30] low infant birthweight,[20] and older age at the time of the affected pregnancy.[31]

HYPERTENSION IN PREGNANCY: IMPACT ON THE RISK OF CVD

Although recent studies have consistently supported hypertension in pregnancy as a risk factor for CVD, the pathogenetic mechanisms underlying this association are not well understood. During hypertensive pregnancies, metabolic and vascular abnormalities are present that closely resemble those seen in CVD. It is plausible that these two conditions share common risk factors, which could result in hypertensive disorders of pregnancy and CVD at different times in a woman's life. The lack of data regarding the presence of CVD risk factors before affected pregnancies indicates that either these risk factors were present but not evaluated or—an intriguing possibility—hypertensive pregnancy itself induces changes that increase the risk of CVD. The supporting evidence for this mechanism comes from studies of women with histories of hypertensive pregnancies who continue to demonstrate adverse metabolic and vascular changes after delivery that might increase their risk of developing CVD. The discussion below summarizes the data from the literature that support the operation of each of these two mechanisms. Avenues for future research are also proposed.

Table 2 Patients with hypertensive disorders of pregnancy and their later-in-life cardiovascular events and outcomes: population-based and registry-based studies, and single-center and multicenter cohort studies.

Study	Study design and location	Study group	Outcomes (study group vs control group)[a]
Jonsdottir *et al.* (1995)[29]	Retrospective review of maternity records (1931–1947) and IHD death, Iceland	1. Eclampsia 2. Pre-eclampsia 3. Hypertension in pregnancy **[Au: 'Gestational hypertension'?]**	1. IHD death: RR 2.61 (1.11–6.12) 2. IHD death: RR 1.90 (1.02–3.52) 3. IHD death: RR 1.47 (1.05–2.02)
Hannaford *et al.* (1997)[93]	Retrospective analysis of a subgroup of women from the RCGP Oral Contraceptive Study who never used contraceptives, UK	Women with a history of 'toxemia'[b]	Hypertension: RR 2.35 (2.08–2.65) Acute myocardial infarction: RR 2.24 (1.42–3.53) Venous thromboembolism**[Au: does this require a footnote similar to that of Table 1?]**: RR 1.62 (1.09–2.41)
Irgens *et al.* (2001)[30]	Population-based study of medical birth registry (1967–1992), Norway	Pre-eclampsia, either term or preterm deliveries[c]	All-cause death: HR 1.20 (1.02–1.37) Cardiovascular death for term pre-eclampsia: HR 1.65 (1.01–2.70) Cardiovascular death for preterm pre-eclampsia: HR 8.12 (4.31–15.33)
Smith *et al.* (2001)[94]	Population-based study of morbidity record system (1981–1985), Scotland	Pre-eclampsia	IHD: HR 2.0 (1.5–2.5)
Kestenbaum *et al.* (2003)[95]	Population-based study of Washington State Birth Event Record database (1987–1998), USA	1. Gestational hypertension 2. Mild pre-eclampsia 3. Severe pre-eclampsia	1. Acute CVD event: HR 2.8 (1.6–4.8) 2. Acute CVD event: HR 2.2 (1.3–3.6) 3. Acute CVD event: HR 3.3 (1.7–6.5)
Wilson *et al.* (2003)[96]	Population-based study of Aberdeen maternity and neonatal databank (1951–1970), Scotland	Pre-eclampsia and eclampsia	Hypertension: OR 3.98 (2.82–5.61) Fatal stroke: IRR 3.59 (1.04–12.4)
Arnadottir *et al.* (2005)[31]	Case–control study, University Hospital Reykjavik (1931–1947), Iceland	Gestational hypertension, pre-eclampsia and eclampsia	IHD death: RR 1.66 (1.27–2.17) CVA death: RR 1.46 (0.94–2.28)
Funai *et al.* (2005)[97]	Population-based Jerusalem Perinatal Study (1964–1976), Israel	Pre-eclampsia	All-cause death: RR 2.13 (1.79–2.53) CVD death: RR 3.07 (2.18–4.34)
Wikström *et al.* (2005)[27]	Cross-sectional population study of medical birth registry (1973–1982), Sweden	1. Gestational hypertension 2. Mild pre-eclampsia 3. Severe pre-eclampsia	1. IHD: IRR 1.6 (1.3–2.0) 2. IHD: IRR 1.9 (1.6–2.2) 3. IHD: IRR 2.8 (2.2–3.7)
Ray *et al.* (2005)[98]	Population-based study of Ontario Health Insurance Plan (1990–2004), Canada	1. MPS 2. pre-eclampsia	1. CVD: HR 2.0 (1.7–2.2) 2. CVD: HR 2.1 (1.8–2.4)

[Au: are ranges in the last column 95% CIs?]
[a]Where numbered, the outcomes correspond to a difference between the respective study group (labeled with the same number) and its control; for all studies, the control group consisted of women with normotensive pregnancies, with the exception of the study by Jonsdottir *et al.*, in which the outcomes were compared with those from the general population. [b]'Toxemia' is a synonym for pre-eclampsia that was used in the 1960s. [c]Term delivery is delivery at ≥37 weeks' gestation; preterm delivery is delivery at 16–36 weeks' gestation. Abbreviations: CVA, cerebrovascular accident; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; IRR, incidence rate ratio; MPS, maternal placental syndromes (gestational hypertension, pre-eclampsia, placental abruption and placental infarction); OR, odds ratio; RCGP, Royal College of General Practitioners; RR, relative risk.

MECHANISMS COMMON TO HYPERTENSIVE DISORDERS OF PREGNANCY AND CVD

Endothelial dysfunction

There is a growing body of evidence to indicate that, as in CVD, endothelial dysfunction has a crucial role in the pathogenesis of pre-eclampsia (Figure 1). Clinical studies have indicated that a relative deficiency of nitric oxide might worsen the state of generalized vasoconstriction reported in pre-eclampsia.[32] In addition, several other potent mediators of endothelial cell dysfunction are upregulated in pre-eclampsia, including cellular fibronectin,[33] von Willebrand factor,[34] cell adhesion molecules (P selectin,[35] vascular cell adhesion molecule 1 and intercellular adhesion molecule 1[36]), and cytokines (interleukin 6[37] and tumor necrosis factor[38]). For the most part, it is unclear whether these substances contribute to endothelial dysfunction or whether their dysregulation is a marker of endothelial injury. Nevertheless, the net result of these abnormalities is a state of systemic vasoconstriction, leading to systemic ischemia, which provides the pathologic substrate for hypertension and multisystem dysfunction. Studies have provided evidence that pre-eclampsia is associated with elevated levels of the soluble receptor for vascular endothelial growth factor, commonly referred to as soluble fms-like tyrosine kinase receptor 1 (sFlt1) **[Au: ok?]**. By antagonizing the proangiogenic effects of vascular endothelial

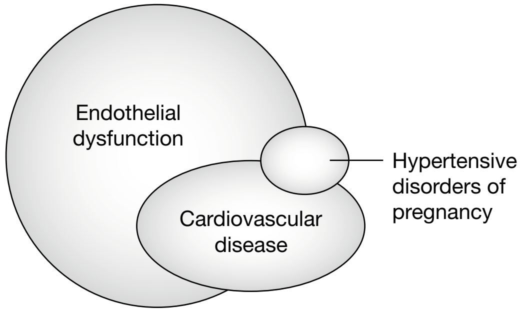

Figure 1 Endothelial dysfunction is common to both cardiovascular disease and several hypertensive disorders of pregnancy, particularly pre-eclampsia. Hemodynamic changes in pregnancy might unmask underlying endothelial dysfunction, leading to the clinical syndromes of pre-eclampsia or eclampsia that resolve with termination of pregnancy. Pre-eclamptic patients might be at a higher risk of developing cardiovascular disease later in life, as indicated by several observational and case–control studies.[29,30]

growth factor, increased levels of sFlt1 can induce endothelial dysfunction, and thus hypertension and proteinuria.[39] Regardless of the primary mechanism, once established, endothelial dysfunction can be potentiated further by ongoing oxidative stress, inflammation and a hypercoagulable state, leading to a vicious cycle of progressive vascular damage.

Metabolic abnormalities

Striking similarities exist between the abnormalities of metabolism that are associated with increased risks for CVD and pre-eclampsia; these include obesity, insulin resistance and lipid abnormalities.[40,41] Patients with prepregnancy obesity are at greater risk of pre-eclampsia.[42] In diabetic pregnancies, the risk of hypertension in pregnancy or pre-eclampsia is doubled compared with normal, nondiabetic controls.[43] The pattern of increased levels of both small dense LDL and triglycerides ('pattern B') is particularly atherogenic and has been described in patients with coronary artery disease[44] and women with pre-eclampsia.[45,46] Small dense LDL is readily oxidized, and levels of lipid peroxides responsible for this oxidation are increased in pre-eclampsia.[47] The oxidized LDL particles are taken up preferentially by macrophages to form lipid-laden macrophages, or foam cells, producing 'acute atherosis' in the placental bed, which is characteristic of pre-eclampsia and resembles atherosclerotic plaques.

Recent studies have identified leptin, an adipocyte-derived hormone that promotes satiety and suppresses appetite,[48] as a marker of increased risk for CVD.[49] Elevated levels of leptin are suggestive of resistance to its metabolic effects and might promote platelet aggregation.[50] Levels of biologically active leptin are increased significantly in pre-eclamptic mothers.[51]

Oxidative stress

In pre-eclampsia, as in atherosclerosis,[52] oxidative stress resulting from free-radical generation contributes to endothelial dysfunction. Evidence for oxidative stress in pre-eclampsia includes increased lipid peroxidation, coupled with the diminished activities of antioxidant enzymes (superoxide dismutase and glucose 6 phosphate dehydrogenase),[53] decreased plasma ascorbate levels,[54] and an increased capacity of pre-eclamptic placental cells to generate reactive oxygen species.[55] A pilot study of the efficacy of antioxidant treatment with vitamins C and E showed markedly reduced levels of biomarkers of pre-eclampsia (e.g. the plasminogen activator inhibitor type 1 [PAI1] to PAI2 ratio) and a decreased rate of pre-eclampsia in treated patients.[56] By contrast, an adequately powered randomized, placebo-controlled follow-up trial in women at increased risk of developing pre-eclampsia showed that vitamins C and E did not prevent pre-eclampsia and actually increased the risk of low infant birth weight.[57] Similarly, data on the use of antioxidants in the primary prevention of coronary heart disease are conflicting.[58,59]

Inflammatory response

Similar to atherosclerosis,[60] leukocyte adhesion to the endothelium has an important role in promoting inflammation that might contribute to the development of pre-eclampsia. The inflammatory response is one of the physiologic adaptations that occur during normal pregnancy and that probably reflect a maternal immune reaction to fetal antigens.[61,62] This inflammatory response is exaggerated in pre-eclampsia, as evidenced by elevated levels of markers of neutrophil activation compared with normal pregnancy,[63] such as neutrophil elastase[64] (which can impair vascular integrity by damaging the vascular basement membrane), vascular cell adhesion molecule 1, intercellular adhesion molecule 1,[65] tumor necrosis factor[38] (which might mediate neutrophil adherence to the endothelium), interleukin 6 (which upregulates superoxide production and contributes to oxidative stress)[37,66] and small dense LDL (which is easily oxidized and, in its oxidized form, stimulates leukocyte adhesion to endothelium).[67] **[Au:**

OK?] Finally, and similar to the situation in CVD, elevated C-reactive protein levels have been associated with an increased risk of pre-eclampsia.[68]

Hypercoagulability

The hypercoagulable state of normal pregnancy is further potentiated in pre-eclampsia, as evidenced by an imbalance between fibrinolysis and coagulation in favor of the latter process. Studies have shown increased expression of procoagulant proteins, such as tissue plasminogen activator, PAI1, von Willebrand factor,[34] fibronectin,[69] homocysteine[70] and thrombomodulin,[71] and reduced levels of anticoagulant proteins, including antithrombin III, protein C and protein S in women with pre-eclampsia.[72] The interaction between a hypercoagulable state and endothelial dysfunction seems to be complex, because these mechanisms can potentiate each other, resulting in cumulative vascular damage. Conceivably, endothelial dysfunction and the resultant endothelial cell activation lead to the release of procoagulants and a hypercoagulable state. In turn, the presence of a maternal hypercoagulable state, in the setting of low-pressure placental blood flow, might trigger the deposition of fibrin and formation of thrombi, leading to placental ischemia and the release of vasoactive mediators.[73] The latter hypothesis is supported by studies showing that, compared with women who have a history of normal pregnancies, the incidences of activated protein C resistance, protein S deficiency, anticardiolipin antibodies, factor V Leiden and hyperhomocysteinemia are higher among those with a history of pre-eclampsia.[74] Similarly, elevated levels of procoagulants, most notably homocysteine[75] and PAI1,[76] have been associated with an increased risk of CVD.

HYPERTENSIVE DISORDERS OF PREGNANCY MIGHT INCREASE THE RISK OF CVD

Most hypertensive disorders of pregnancy abate if pregnancy is terminated. Recent studies have shown that, despite normalization of blood pressure, these seemingly healthy women continue to be affected by adverse physiological changes that might modify or increase their overall risk of developing CVD later in life.

Patients with a history of pre-eclampsia tend to maintain an unfavorable lipid profile later in life, including decreased levels of HDL and increased levels of apolipoprotein B, small dense LDL and total cholesterol later in life.[77] This profile predisposes such patients to recurrent hypertensive disorders of pregnancy, in addition to future CVD. A study of women 17 years after their pre-eclamptic pregnancies detected mild hyperinsulinemia compared with matched, normotensive-pregnancy controls.[78] The degree of hyperinsulinemia correlated positively with triglyceride levels and blood pressure and negatively with levels of HDL; this pattern is typical, and therefore highly suggestive, of the insulin resistance syndrome. Chambers *et al.*[79] demonstrated that brachial artery flow-mediated (endothelium-dependent) dilatation was impaired in women 3 years after diagnosis of pre-eclampsia; this impairment diminished following administration of ascorbic acid. These data indicate that endothelial dysfunction that persists after termination of the affected pregnancy is, at least in part, secondary to oxidative stress. Women with pre-eclampsia have microalbuminuria, a marker of preclinical atherosclerosis, for up to 5 years after delivery,[80] which might be associated with an increased risk of CVD years after the affected pregnancy. Our recent study[6] showed an increased frequency of microalbuminuria in women with histories of hypertensive pregnancies compared with those who had had normotensive pregnancies (16.8% vs 11.7%; $P=0.003$).

Luft[81] hypothesized that microvascular injury leading to hypertension later in life develops as a result of increased vascular reactivity to angiotensin II, which is characteristic of pre-eclampsia.[82] Indeed, women with pre-eclampsia were found to develop agonistic autoantibodies against the angiotensin AT_1 receptor, which could mediate the development of vascular lesions in these patients.[83] Angiotensin AT_1 receptor-activating antibodies might exert vascular effects beyond pregnancy; these antibodies were detected in 17% of women with a history of pre-eclampsia but in only 3% of those with previous uncomplicated pregnancies, at an average of 18 ± 9.7 months postpartum.[84] Finally, women with pre-eclampsia have elevated levels of sFlt1 not only during their pregnancies, but also more than 1 year postpartum. Elevated sFlt1 levels, in addition to the impaired insulin resistance that was detected in the same group of patients, could contribute to the risk of developing CVD later in life.

FUTURE PERSPECTIVES

A growing body of evidence links hypertension in pregnancy to future CVD. On the basis of the available data, it is not possible to establish hypertension in pregnancy as an independent risk factor for CVD later in life; such confirmation will depend on future studies proving that the association remains significant after controlling for established risk factors,[85] such as diabetes, obesity and lipid abnormalities. It is probable that pregnancy functions as a 'physiological stress test'; that is, hemodynamic changes in pregnancy unmask underlying defects, such as endothelial dysfunction, that will ultimately lead to CVD later in life. In that case, hypertension in pregnancy might be recognized as a dependent risk factor; that is, one that is not associated with CVD if the above risk factors common to both conditions are controlled for. To date, no studies have addressed this particular issue.

It is particularly intriguing to hypothesize that hypertension in pregnancy can itself increase the risk of CVD. Future studies, longitudinally comparing risk factors, intermediary end points and cardiovascular events before, during and after pregnancy between women who remain normotensive and those who develop hypertension during pregnancy could determine whether hypertensive disorders of pregnancy cause CVD. If this is the case, then it could have a major impact on screening and primary prevention strategies in women and on the treatment of hypertensive disorders of pregnancy.

Some authors argue that women with hypertensive pregnancies do not differ from the general population with respect to the risk of developing CVD later in life. These authors attribute the observed increase in CVD in women who have had hypertensive pregnancies compared with normotensive, uncomplicated pregnancies to a decreased overall risk of CVD in the latter group.[86] Future studies should, therefore, include not only a head-to-head comparison of women with a history of hypertensive versus normotensive pregnancies, but also a comparison with an age-matched cohort from the general population, including nulliparous women.

CONCLUSIONS

Hypertensive disorders of pregnancy are probably under-recognized risk factors for atherosclerotic disease that should be screened for during assessment of a patient's risk profile for CVD. This might be particularly relevant for women with histories of severe forms of pre-eclampsia.[87] Future directives are crucially dependent on long-term, prospective, multicenter trials, adequately powered with respect to sample size and duration of follow-up, that address and confirm these associations. Until the results of such trials become available, women with a history of hypertensive pregnancy should be counseled about their increased risks for both recurrent problems during pregnancy and future CVD and they should be monitored closely for the risk factors common to the two conditions. Primary prevention in these patients should focus on lifestyle modifications (smoking cessation, healthy diet, exercise and weight loss) and early detection of risk factors for CVD. Blood pressure, urine albumin level, fasting lipid panel and fasting glucose level should be monitored regularly (annual screening can be considered) and treatment given according to the evidence-based national guidelines for prevention of CVD in women.[88]

KEY POINTS

- Compared with women who have a history of normotensive pregnancy, those who have a history of hypertensive disorders of pregnancy are at higher risk of cardiovascular and cerebrovascular events, and have a less favorable cardiovascular disease (CVD) risk profile, years after the affected pregnancy
- Hypertensive disorders of pregnancy and CVD share several common risk factors; for example, obesity, diabetes and renal disease
- Hypertension in pregnancy might modify the future risk of CVD by inducing long-term metabolic and vascular changes
- Increasing evidence indicates that a history of hypertensive pregnancy is an under-recognized risk factor that could aid early identification of women who are at an increased risk of developing CVD
- Women with a history of hypertensive pregnancy must be monitored closely for comorbidities and conventional risk factors for CVD and treated according to current evidence-based guidelines

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