

Preeclampsia and the Future Risk of Hypertension: The Pregnant Evidence

Vesna D. Garovic · Phyllis August

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Abstract Cardiovascular death rates continue to rise for women under age 55, underlying the importance of focusing on female-specific conditions that may increase cardiovascular risk, including pregnancy-related disorders. Hypertension complicates about 5–10 % of pregnancies. Preeclampsia, a pregnancy-specific condition, is characterized by hypertension and proteinuria after 20 weeks of gestation and remains one of the major causes of maternal deaths in the United States. In addition, preeclampsia may have an impact on women's health beyond their pregnancies, and has been associated with increased risks for future hypertension and cardiovascular disease, such as coronary heart disease and stroke. In this review, we discuss the evidence supporting the association between preeclampsia and future hypertension; possible mechanisms that underlie this association; current approach to women with a history of preeclampsia; and future research that is needed in this field in order to deliver optimal and timely medical care to the affected women.

Keywords Hypertension · Pregnancy · Preeclampsia · Cardiovascular disease · Risk factors · Metabolic abnormalities · Inflammatory response · Hypercoagulability

Introduction

Hypertensive pregnancy disorders cover a spectrum of conditions, including preeclampsia (de novo or superimposed on preexisting chronic hypertension), chronic and gestational hypertension (Table 1) [1]. Preeclampsia and related conditions, its convulsive form, eclampsia, and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome, remain leading causes of fetal and maternal mortality and morbidity. Over the last 50 years, much progress has been made in improving treatment of preeclampsia with respect to blood pressure control and prevention of eclamptic seizures. However, the etiology and pathogenesis of this condition remain elusive, resulting in a failure to develop specific preventive and treatment strategies. Delivery remains the mainstay of therapy for severe forms and anticipated life-threatening complications, frequently resulting in preterm delivery, and fetal/neonatal complications related to immaturity. A study of the number of delivery hospitalizations in the United States in women with hypertensive disorders in pregnancy in 1986–2006 showed that this number is increasing, and that these hospitalizations are associated with a substantial burden of severe obstetric morbidity, particularly in the presence of severe preeclampsia/eclampsia. [2•]

There is accumulating evidence suggesting that endothelial dysfunction, caused by placental factors that enter the maternal circulation, may play a central role in the pathogenesis of preeclampsia. The fact that hypertension rapidly resolves upon the removal of products of conception has led to several theories implicating structural and/or functional changes in the developing placenta as factors causing preeclampsia. In preeclampsia, the placental spiral arteries fail to lose their musculoelastic layers, ultimately leading to

V. D. Garovic
Division of Nephrology and Hypertension, Mayo Clinic
College of Medicine, 200 First St SW,
Rochester, MN 55905, USA
e-mail: garovic.vesna@mayo.edu

P. August (✉)
Division of Nephrology and Hypertension Center,
Weil Cornell Medical College, 450 East 69th St,
New York, NY 10021, USA
e-mail: paugust@med.cornell.edu

Table 1 Hypertensive pregnancy disorders: classification and diagnostic criteria

Preeclampsia	Preeclampsia is a pregnancy-specific disorder characterized by hypertension $\geq 140/90$ mmHg on at least two occasions, 6 h apart, and proteinuria of 300 mg or greater in a 24-h urine, after 20 weeks of gestation. Severe forms include: <ul style="list-style-type: none"> • Eclampsia, a convulsive form of preeclampsia that affects 0.1 % of all pregnancies. • HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome
Preeclampsia superimposed on chronic hypertension	Up to 30 % of women with chronic hypertension develop preeclampsia, heralded by either new-onset or worsening of preexisting proteinuria in the third trimester.
Chronic hypertension	BP greater than or equal to 140/90 mm Hg prior to pregnancy, or before the 20th week of gestation.
Gestational hypertension	Hypertension ($\geq 140/90$ mmHg on at least two occasions, 6 h apart), occurring for the first time after 20 week gestation, in the absence of proteinuria. The diagnosis of transient hypertension is entertained if BP returns to normal by 12 weeks post-partum. If hypertension persists, the diagnosis of chronic hypertension is made.

decreased placental perfusion [3, 4]. Placental hypoxia is viewed frequently as an early event that may cause placental production of soluble factors leading to endothelial dysfunction [5]. The clinical syndrome of preeclampsia ensues, which has been attributed to complex interactions among maternal constitutional factors (e.g., pre-existing metabolic abnormalities), placenta-derived products (exemplified by the imbalance between pro-angiogenic and anti-angiogenic factors, favoring the latter), and the exaggerated adaptive mechanisms that normally occur during pregnancy (features of the metabolic syndrome, an inflammatory response, and a hypercoagulable state). Decreased placental perfusion coupled with maternal hypertension result in serious maternal and fetal complications, most notably placental abruption and infarction, fetal growth restriction, and intrauterine fetal demise. In addition, hypertensive pregnancy disorders may have an impact on women's health well beyond the affected pregnancies. Women with a history of hypertensive pregnancy disorders, particularly preeclampsia that develops remote from term, are at an increased risk for cardiovascular disease (CVD) later in life, including coronary heart disease, stroke, thromboembolic disease, heart failure, and arrhythmias [6, 7••]. The increased risk for hypertension in these women may contribute to their overall increased rates of CVD years after their affected pregnancies.

Preeclampsia and Future Hypertension: Review of the Evidence

The earliest report of an association between 'hypertensive toxemia of pregnancy', as preeclampsia was once called, and chronic cardiovascular disease was by Corwin in 1927 [8]. In this study, 165 women, average age 29 years, with "hypertensive toxemia of pregnancy" were followed up for a period of 6 months to six years post-partum. Of these, 37 % showed persistent hypertension, defined as a systolic blood pressure >140 mm Hg. This view was challenged by the classic work of Leon Chesley [9, 10], who reported

that the prevalence of hypertension in 206 primiparous eclamptic women an average of 33 years later was similar to that in age-matched women from 11 epidemiological studies of blood pressure. Chesley's work has been given considerable weight since the women he followed had eclampsia, and were nulliparas, thus minimizing the heterogeneity in diagnosis. Chesley further suggested that, among women with eclampsia, those who are multiparous are different and should be analyzed separately, as the prevalence of chronic hypertension was increased among 64 multiparous women who survived eclampsia. In fact, Chesley recognized that pregnancy hypertension in multiparous women or in those without proteinuria (i.e., gestational hypertension) was most likely an early manifestation of an increased risk for later essential or renal hypertension. Although remarkable for the serious effort on the part of Dr. Chesley to track down women decades after delivery, Chesley's study design raised methodological questions—most specifically, what is the appropriate control group with which to compare women with hypertension in pregnancy? The control group in Chesley's study was a historical control group of women from previously published epidemiologic studies, and thus may have included women with hypertensive pregnancy disorders which may have led to bias towards the null hypothesis.

Chesley's study had a profound impact and, for many years, authors of chapters and review articles concluded that hypertensive diseases of pregnancy are limited to the affected pregnancy, and have few, if any, long-term maternal effects. There have been multiple epidemiological studies since that time that have supported an association between hypertensive pregnancy disorders and future chronic hypertension (Table 2) [11], ischemic heart disease, stroke, venous thromboembolism, and cardiovascular death [6, 12]. In 1986, Sibai et al. [13] reported a significantly higher incidence of hypertension in patients with histories of preeclampsia or eclampsia during their first pregnancies compared to matched normotensive controls. The risk was increased further by a history of recurrent preeclampsia or

Table 2 The association between history of preeclampsia and future hypertension

Author, year, country	Study design	Study group	Mean follow up	Relative risk (95 % CI)
Sibai 1986, USA [13]	Prospective cohort	406 women with severe preeclampsia /eclampsia and 409 women with normotensive pregnancies	7.3 years	2.64 (1.66–4.17)
Nissel 1995, Sweden [64]	Retrospective cohort	45 women with preeclampsia, and 44 normotensive controls	7 years	8.8 (1.16–66.59)
North 1996, New Zealand [60]	Retrospective cohort	50 women with and 50 women without a history of preeclampsia	5 years	20.00 (2.79–143.38)
Hannaford 1997, UK [65]	Prospective cohort	17,202 women from the Royal College of General Practitioners Study	12.5 years	2.35 (2.08–2.65)
Marin 2000, Spain [66]	Prospective and retrospective cohort	273 women and 86 normotensive controls	14.2 years	3.70 (1.72–7.97)
Hubel 2000, Iceland [67]	Retrospective cohort	30 women with a history of eclampsia and 30 normotensive controls	32.7 years	5.00 (1.19–20.92)
Wilson 2003, Scotland [68]	Retrospective cohort	Population-based study of Aberdeen Maternity and Neonatal Databank (1951–1970),	32 years	2.62 (1.77–3.86)
Sattar 2003, Scotland [69]	Retrospective cohort	40 women with preeclampsia and 40 normotensive controls	19 years	3.50 (0.77–15.83)
Diehl 2008, USA [70]	Retrospective cohort	103 women with a history of preeclampsia and 100 women with a history of normotensive pregnancies	27.4 years	2.2 (1.45–3.36)

eclampsia, and early preeclampsia (<30 weeks gestation). Most of the differences were noticed in individuals who had been followed up for at least 10 years. In the work of Selvaggi et al. [14], half of the participating women with histories of preeclampsia were hypertensive 10 years after delivery, compared with only one-third who were hypertensive 5 years after delivery, further supporting the importance of an adequate follow-up after the affected pregnancies when assessing this association.

As most of the published studies clearly have been underpowered [11], a systematic review and meta-analysis assessing the risks of CVD in women with histories of preeclampsia and eclampsia was performed by Bellamy et al. [6]. They conducted a search of Medline and Embase between 1960 and December 2006; both positive and negative studies were included in the analysis. A total of 13 studies involving 21,030 women examined the risk of hypertension subsequent to a preeclamptic or eclamptic pregnancy. Over a mean follow-up of 14.1 years, the authors found that 1885 of 3658 women with preeclampsia developed hypertension later in life, providing a relative risk of 3.7.

It is important to acknowledge the limitations of published studies related to their retrospective designs, including inadequate durations of follow-up, difficulties in establishing the diagnosis of preeclampsia in a retrospective fashion, and changes in the definition of and diagnostic criteria for hypertensive pregnancy disorders over time. Making distinctions among different categories of hypertension in pregnancy, and particularly contrasting preeclampsia to other hypertensive pregnancy disorders, is challenging and has been hampered by the lack of a suitable biomarker

that clearly distinguishes preeclampsia from chronic or gestational hypertension [15]. It is likely that differences in the clinical presentations of preeclampsia and other hypertensive pregnancy disorders (Table 1) probably result from differences in their underlying mechanisms, which might have varying implications for future hypertension and CVD later in life. For example, although recent clinical guidelines from Australia and New Zealand have minimized the importance of proteinuria for the purposes of clinical care [16], it is possible, and perhaps likely that this clinical feature identifies an important subset of the disease with respect to mechanisms and prognosis. Further complicating the interpretation of some studies is the use of index codes or self-reported events rather than accepted diagnostic criteria to make a diagnosis of preeclampsia and other hypertensive pregnancies. Finally, several studies failed to exclude women with chronic hypertension that occurs before pregnancy, and then persists during pregnancy and after delivery. In these women, chronic hypertension predates pregnancy and does not occur subsequent to, or as a result of, a hypertensive pregnancy disorder. A single cohort study included only women who developed hypertension after the age of 40, with the rationale that most pregnancies are likely to occur by that age. In other words, by looking at the onset of hypertension at age 40, chances are that these women were not hypertensive before their pregnancies, but rather became hypertensive after their pregnancies. Compared with women with histories of normotensive pregnancies, those with histories of hypertensive pregnancies had an increased hazard ratio of 1.53 (95 % CI 1.25–1.87, $P < 0.001$) for the diagnosis of hypertension after the age of 40, after controlling for race, family

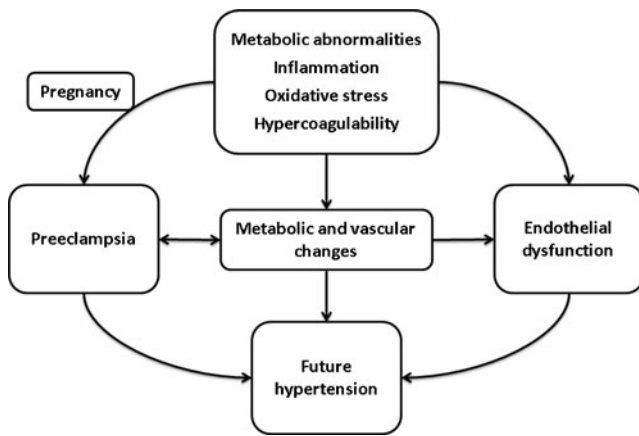


Fig. 1 Possible mechanisms underlying the association between preeclampsia and future hypertension. These two conditions share common risk factors, such as oxidative stress and hypercoagulability, which could result in preeclampsia and hypertension/CVD at different times in a woman's life. Alternatively, preeclampsia may result in irreversible metabolic and vascular changes that may contribute to the risk of developing hypertension/CVD later in life

history of cardiovascular disease, education, diabetes (time-dependent), smoking status, and body mass index (BMI) [17]. The major limitation of this study was that hypertension in pregnancy was self-reported and, therefore, subject to recall bias.

Studies published to date, despite their limitations, provide compelling evidence that supports the association between preeclampsia and future hypertension and CVD. However, these women are frequently lost to follow-up after their deliveries. If their hypertension either persists or occurs soon after their affected pregnancies, it frequently remains under-recognized and under-treated. The limitations of the fragmented medical care that these women receive have been recognized recently by the guidelines for the prevention of cardiovascular disease in women, which recommend referral of women with a history of hypertensive pregnancy to primary care or cardiology [18••]. Monitoring and control of CVD risk factors, and hypertension, in particular, in the affected women, may prevent future CVD.

The Mechanism(s) Underlying the Association Between Preeclampsia and Future Hypertension

Endothelial dysfunction plays a crucial role in the pathogenesis of both preeclampsia and future hypertension and CVD. Hypertensive pregnancy disorders, including preeclampsia, have been suggested to be a 'failed stress test', with pregnancy unmasking underlying endothelial dysfunction and a predisposition to cardiovascular disease. These two conditions share several common risk factors, such as diabetes

and obesity, which may lead to preeclampsia and future hypertension and CVD at different times of a woman's life. An alternative explanation is that preeclampsia itself may induce irreversible vascular and metabolic changes that may increase the overall risk for hypertension and CVD (Fig. 1).

Preeclampsia and Future Hypertension: Common Mechanisms

Preeclampsia and cardiovascular disease share common risk factors (Fig. 1), such as metabolic abnormalities (insulin resistance, dyslipidemia, obesity), inflammation, oxidative stress, and hypercoagulability; these shared risk factors may result in endothelial dysfunction and increased risks for both preeclampsia and future hypertension and CVD [11, 19]. Several potent mediators of endothelial cell dysfunction have been shown to be up-regulated in preeclampsia, including cellular fibronectin [20], von Willebrand factor [21], cell adhesion molecules such as P-selectin [22], vascular endothelial adhesion molecule-1 (VCAM-1), and inter-cellular adhesion molecule-1 (ICAM-1) [23], and cytokines, such as interleukin-6 (IL-6) [24] and tumor necrosis factor- α (TNF- α) [25]. Relative nitric oxide deficiency may contribute to the generalized vasoconstriction seen in preeclampsia [26]. Oxidative stress due to free radical generation contributes to endothelial dysfunction both in preeclampsia and atherosclerosis [27]. Elevated levels of the soluble receptor for vascular endothelial growth factor (VEGF), commonly referred to as sFlt-1 (from fms-like tyrosine-kinase receptor-1), may be the missing link between placental ischemia on one side and endothelial dysfunction, mediated by sFlt-1 neutralization of VEGF and placental growth factor (PlGF), on the other. By antagonizing the pro-angiogenic effects of VEGF, increased levels of sFlt-1 can induce endothelial dysfunction, and thus hypertension and proteinuria [28]. Most published studies suggest that measurements of these markers, although not predictive of late-onset preeclampsia in term pregnancies, may be useful in predicting early onset and severe disease. These findings raise the possibility of using these tests in special patient subgroups. A recent study suggested that angiogenic factors may be useful to facilitate diagnosis of superimposed preeclampsia in women with chronic hypertension [29].

The interactions among endothelial dysfunction and metabolic abnormalities, oxidative stress, inflammation and a hypercoagulable state, appear quite complex in preeclampsia; these mechanisms may potentiate each other, resulting in cumulative, multisystem vascular damage. The sum effect of these abnormalities is a state of systemic vasoconstriction, resultant ischemia, and multisystem dysfunction.

Metabolic Abnormalities

Several common metabolic abnormalities are shared risk factors for CVD and preeclampsia, including obesity, insulin resistance, and lipid abnormalities [11, 19, 30, 31]. “Acute atherosclerosis” of the placental bed vessels, commonly encountered in preeclampsia, closely resembles atherosclerotic plaques [32••]. Patients who are obese before pregnancy are at a greater risk for preeclampsia [33]. The risk for hypertension in pregnancy and/or preeclampsia is doubled in diabetic compared to non-diabetic controls [34]. The pattern of increased small, dense low-density lipoprotein (LDL) and triglycerides (pattern B) is known as particularly atherogenic and has been described in patients with coronary artery disease [35] and in women with preeclampsia [36, 37]. In addition, elevated levels of leptin (an adipocyte-derived hormone), which are suggestive of resistance to its metabolic effects, are associated with both CVD [38] and preeclamptic pregnancies [39]. Elevated levels of leptin may promote platelet aggregation [40], thus further potentiating the hypercoagulable state which is present in preeclampsia.

Inflammatory Response

Pregnancy is characterized by hormonal modulation of both innate and adaptive immunity (T-cell-mediated cellular immune system and B-cell-mediated humoral immune system), in order to establish maternal immune tolerance to a semi-allogeneic fetus expressing both maternal and paternal antigens. However, while the innate immune response is enhanced, the cellular immune response (which, through activation of cytotoxic T-cells and natural killer cells, may damage trophoblast and result in pregnancy loss), is down-regulated [41, 42]. During normal pregnancy, the maternal immune reaction to fetal antigens manifests as an exaggerated inflammatory response [43, 44]. This inflammatory response is further potentiated in preeclampsia, as evidenced by elevated levels of markers of neutrophil activation compared to normal pregnancy [24, 25, 37, 45–48]. As to the mechanism of leukocyte activation, it is possible that it may occur when leukocytes circulate through the intervillous space and are exposed to oxidized lipid secreted by the placenta [47]. Similar to CVD, elevated C-reactive protein levels have been associated with an increased risk for preeclampsia [48]. Likewise, and similar to atherosclerosis [49], leukocyte adhesion to the endothelium plays an important role in promoting inflammation that may contribute to the development of preeclampsia.

Hypercoagulability

In preeclampsia, the hypercoagulable state of normal pregnancy is further potentiated, as evidenced by an imbalance

between fibrinolysis and coagulation, in favor of the latter [11, 19]. Most notably, procoagulant proteins such as tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI-1), von Willebrand factor [21], fibronectin [50], homocysteine [51], and thrombomodulin [52], are elevated, while levels of anticoagulant proteins, including antithrombin III, protein C and protein S [53], are reduced. Women with histories of preeclampsia, compared to women with histories of normotensive pregnancies, have a higher incidence of activated protein C resistance, protein S deficiency, anticardiolipin antibodies, factor V Leiden mutations and hyperhomocysteinemia [54, 55]. Similarly, an increased risk for cardiovascular disease has been associated with elevated levels of homocysteine [56] and PAI-1 [57]. Mechanistically, in the setting of low-pressure placental blood flow, the presence of a maternal hypercoagulable state may trigger deposition of fibrin and formation of thrombi, further worsening endothelial dysfunction and placental ischemia [58].

Preeclampsia and Future Hypertension: A Causative Relationship?

It is possible that hypertensive disorders in pregnancy may induce long-term vascular, renal and metabolic changes that may increase future cardiovascular risk (Fig. 1). The supporting evidence comes from studies showing that, despite normalization of blood pressure post-partum, these seemingly healthy women may demonstrate unfavorable metabolic and vascular changes [19], such as an impaired brachial artery flow-mediated (endothelium-dependent) dilatation, a measure of endothelial dysfunction, three years after the diagnosis of preeclampsia [59]. Microalbuminuria, which may be a marker of endothelial dysfunction and/or renal injury, has also been reported to be more prevalent following a preeclamptic pregnancy [60]. The renal lesion associated with preeclampsia, glomeruloendotheliosis, believed to be reversible, may in fact be associated with subtle alterations in kidney function after pregnancy that may contribute to hypertension later in life. In addition, several studies have indicated that cardiac changes, which occur during hypertensive pregnancies and may contribute to future heart disease, do not revert to normal upon delivery. During a hypertensive pregnancy, there may be eccentric and concentric ventricular remodeling [61•], impaired contractility, and diastolic dysfunction [62]. Increased left atrial size has been reported, as well as global right ventricular systolic-diastolic dysfunction. Echocardiographic studies of women with preeclampsia performed one year post-partum showed an increased risk of altered left ventricular geometry (concentric remodelling, eccentric hypertrophy), impaired left ventricular relaxation with global diastolic dysfunction, and mildly impaired radial systolic function (ejection

fraction 45 %–55 %), compared to those with normotensive pregnancies [61]. At six months post-partum, a four-fold increase in the risk of diastolic dysfunction was observed in women who had placental syndromes, which, in addition to preeclampsia, included gestational hypertension, HELLP syndrome, placental abruption and fetal growth restriction [63]. Conceivably, these persistent abnormalities may contribute to the risk of future hypertension and heart disease, including heart failure and arrhythmias, which recently have been associated with maternal placental syndromes [7].

Future Perspectives

The precise relationship between hypertensive disorders of pregnancy and later onset of hypertension remains incompletely resolved. Additional research is needed to address the mechanisms underlying the associations between preeclampsia and future hypertension and CVD, leading to specific diagnostic, preventive, and therapeutic measures. If, indeed, hypertension in pregnancy and preeclampsia, in particular, leave permanent vascular and inflammatory changes that increase the risk for hypertension and CVD later in life, improved screening and treatment of hypertension in pregnancy may not only optimize pregnancy outcomes, but may have a long-term positive impact on women's cardiovascular health. A growing body of evidence demonstrating persistent cardiovascular abnormalities and inflammatory responses may result in a change in clinical practice, and the current guidelines for the management of hypertensive pregnancy, which recommend lenient blood pressure control in the absence of end organ damage [1]. Carefully designed and adequately powered studies are needed to confirm and address the nature of these associations. Until then, treatment of hypertension in pregnancy should remain a matter of carefully weighing the risk/benefit ratio for each individual patient, with the goal to improve maternal and fetal pregnancy outcomes. After pregnancy, regular (annual) surveillance of blood pressure, urine albumin level, fasting glucose and lipid panel, and treatment according to the national guidelines for CVD prevention in women should be implemented, coupled with primary prevention focusing on lifestyle modifications (smoking cessation, healthy diet, exercise and weight loss), in order to optimize maternal cardiovascular health.

Conclusion

Increasing evidence suggests that preeclampsia is associated with increased risks for hypertension and CVD later in life. Preeclampsia may simply serve as a marker for women at

risk or, alternatively, it may induce irreversible vascular and metabolic changes that may increase the risk for future hypertension and CVD in the affected women. Future studies are needed to elucidate the mechanisms underlying these associations. Irrespective of the underlying mechanism, a history of preeclampsia may help identify women at CVD risk early in life, thus offering an opportunity for timely screening, and preventive and treatment strategies. A detailed history of pregnancy outcomes should become a standard portion of the risk assessment visit with a doctor; primary prevention in these women should include lifestyle modification. Their modifiable risk factors should be monitored regularly and treated in a timely fashion.

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- Of major importance

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