Review

Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

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Keywords

Cardiorenal syndrome · Cardiovascular disease · Chronic kidney disease · Preeclampsia

Abstract

Background: Preeclampsia is a multisystem vascular disorder of pregnancy that remains a leading cause of maternal and fetal morbidity and mortality. Preeclampsia remains an underrecognized risk factor for future cardiovascular and kidney disease in women and represents the confluence of preexisting vascular risk factors with superimposed endothelial injury from placental mediated anti-angiogenic factors. ***Summary:*** This review highlights the close relationship between preeclampsia and future cardiovascular and kidney disease. It describes the pathophysiology and current understanding of biomarkers that form the molecular signature for long-term endothelial dysfunction in preeclamptic women. Finally, it describes strategies for early identification and management of women with preeclampsia with elevated risk for cardiovascular and kidney disease. ***Key Messages:*** Future rigorous studies on cardiovascular risk modification in this phenotype of disease are essential to reduce the burden of cardiovascular and kidney disease, in women with preeclampsia.

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Introduction

Preeclampsia is a multisystem vascular disorder of pregnancy that usually occurs after 20 weeks of gestation, whose resolution is contingent on delivery of the placenta. Preeclampsia complicates in 3–5% of all pregnancies worldwide, and remains a leading cause of maternal and fetal morbidity and mortality [1]. In addition to the significant impact on maternal and

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161

Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

Table 1. American College of Obstetrics and Gynecology definitions for preeclampsia

- Maternal blood pressure ≥140/90 mm Hg on two occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously measured normal blood pressure
- Maternal blood pressure ≥160/110 mm Hg: hypertension can be confirmed within a short interval (min) to facilitate timely antihypertensive therapy. And one of the following:
  - Proteinuria: ≥300 mg in a 24-h urine collection
  - Protein/creatinine ratio ≥0.3
  - Dipstick reading of 1+ (used only if other quantitative methods are not available)
  - Thrombocytopenia: platelet count <100,000/mL
  - Renal insufficiency: serum creatinine concentrations ≥1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
  - Impaired liver function: elevated blood concentrations of liver transaminases to twice the normal concentrations
  - Pulmonary edema
  - Cerebral or visual symptoms

fetal outcomes during pregnancy, preeclampsia increases future cardiovascular disease risk in women by 2- to 4-fold [2]. The 2011 American Heart Association guidelines on the prevention of cardiovascular disease in women have recognized a history of preeclampsia and gestational hypertension as an independent cardiovascular risk factor [3]. Preeclampsia remains an underrecognized risk factor in the landscape of rising cardiovascular disease-related mortality in adult women, and specifically in women aged 35–54 years [3, 4].

Epidemiology, Definition, Clinical Phenotypes, and Risk Factors

Obstetric risk factors for the development of preeclampsia include nulliparity, a family history of preeclampsia, multiple gestation, hydatidiform mole, extremes of maternal age, change in paternity from prior pregnancy, prolonged interpregnancy intervals, and genetic factors [5]. Several cardiovascular risk factors are associated with a heightened risk of preeclampsia, such as insulin resistance, obesity, systemic inflammation, preexisting hypertension, diabetes mellitus, and chronic kidney disease [5, 6]. On the same continuum, women with a history of preeclampsia have an elevated risk of cardiovascular disease, including myocardial infarction, stroke, and heart failure, later in life [7]. Interestingly, smoking during pregnancy has a protective effect against preeclampsia [8], which, however, is outweighed by the significant fetomaternal risks associated with smoking.

In recognition of the multifaceted phenotype of preeclampsia, the American College of Obstetrics and Gynecology updated its definition of this condition in 2013, as outlined in Table 1.

Preeclampsia can also evolve into more severe clinical syndromes such as eclampsia, hemolysis, elevated liver enzymes, and low platelets, posterior reversible leukoencephalopathy syndrome, disseminated intravascular coagulation, and placental abruption with accompanying generalized endothelial dysfunction and fetomaternal morbidities [9].

Pathophysiology of Preeclampsia in the Era of Biomarkers

Defective Placentation: The Cardinal Role of Hypoxia and Altered Placental Perfusion
The placenta is the central organ in the pathogenesis of preeclampsia. Pathological examination of placentae from women with severe preeclampsia reveals several abnormalities

including infarcts, microthrombi, endothelial injury, and chronic inflammation [10]. During normal placentation, invading cytotrophoblasts adopt an endothelial phenotype, expressing adhesion molecules classically found on the surface of endothelial cells [11]. In preeclampsia, this process is incomplete with the uterine spiral arteries failing to be invaded and remodeled, resulting in constricted, high-resistance vessels [12]. This abnormal placentation is suggested to be the primary event that leads to placental hypoxia, which in turn may liberate soluble factors necessary for the maternal syndrome of generalized endothelial dysfunction [12]. This milieu of endothelial dysfunction from an imbalance of angiogenic proteins as outlined below, persists long term in women with a history of preeclampsia, and is implicated in the increased cardiovascular risk associated with women with preeclampsia [13].

Anti-Angiogenic Proteins in Preeclampsia and Resultant Endothelial Dysfunction
The Role of the Vascular Endothelial Growth Factor and Placental Growth Factor Level in Vasculogenesis and in Maintaining Endothelial Integrity
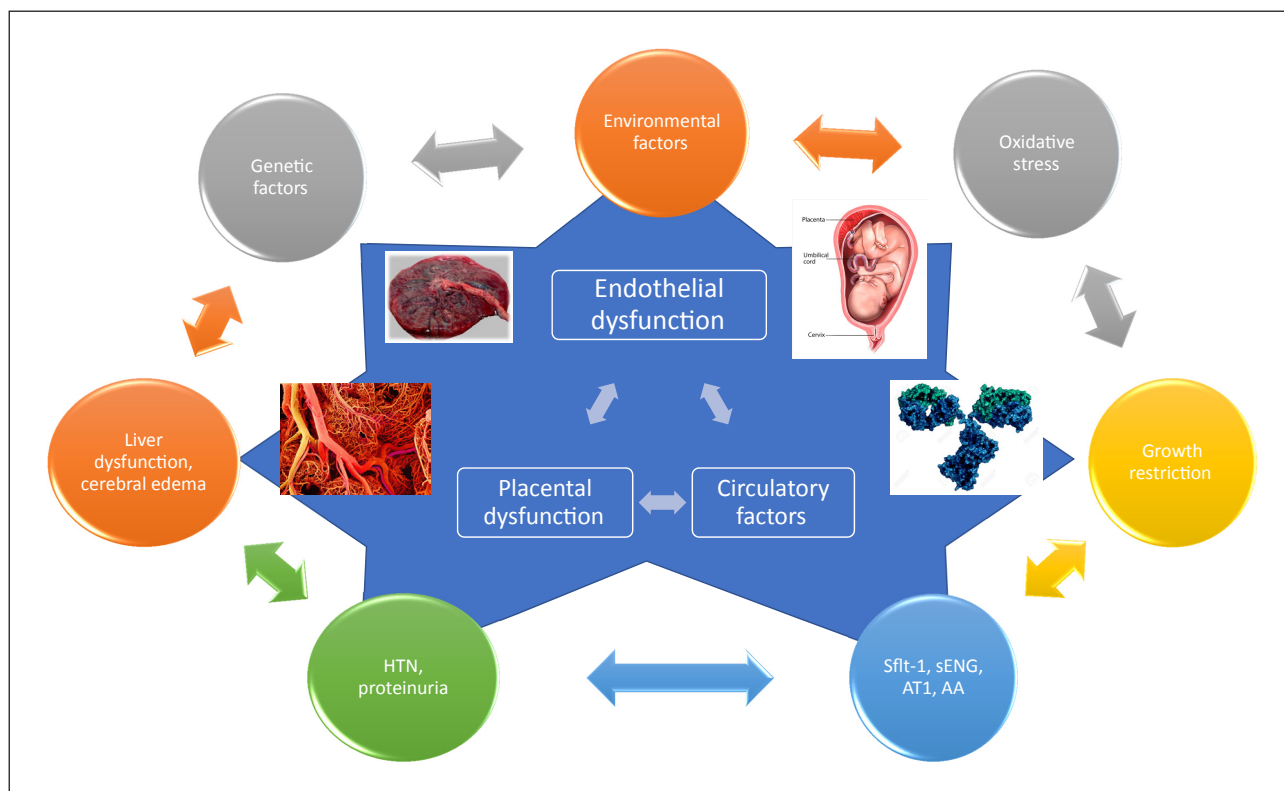
Vascular endothelial growth factors (VEGFs) are dimeric glycoproteins involved in vasculogenesis [14]. Placental growth factor is a VEGF homolog released by the placenta with pro-angiogenic activity and the ability to potentiate the effects of VEGF [15]. Besides its essential role in embryonic vasculogenesis, VEGF is involved in the survival of endothelial cells and vascular homeostasis in mature vessels and tissues. Side effects of targeted inhibition of VEGF in vivo, such as in patients undergoing anti-angiogenic chemotherapy, include hypertension, proteinuria, and glomerular endothelial damage, which strongly resemble the phenotype of endothelial injury seen in preeclampsia [16]. This suggests the role of a maternal anti-angiogenic milieu as a plausible cause of the endothelial dysfunction observed in preeclampsia, which is summarized in the next section.

Soluble fms-Like Tyrosine Kinase-1, Placental Growth Factor, and Soluble Endoglin and Their Role in the Pathogenesis of Preeclampsia

Maynard et al. [17] and others have elegantly defined the central role of soluble anti-angiogenic factors secreted by the placenta in the development of endothelial injury central to preeclampsia. Soluble fms-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic protein, is a soluble form of the VEGF/placental growth factor (PlGF) receptor Flt-1, which has been shown to be produced by the placenta and released into the maternal circulation. sFlt-1 is a potent inhibitor of VEGF and PlGF activity [18]. Blood levels of sFlt-1 are elevated in women with preeclampsia both during and before clinical signs and symptoms of the disease [19]. Consistent with the pathophysiology suggested by animal models, levels of free PlGF are also lower in women with preeclampsia before overt clinical manifestations [20]. In women with preterm preeclampsia, levels of another anti-angiogenic protein, soluble endoglin (sEng), begin to rise by 20 weeks of gestation, and more steeply after 33 weeks [21]. The combination of sFlt-1, PlGF, and sEng levels predict preeclampsia better than any single marker, converging the combined action of several angiogenic factors to produce the clinical phenotype of preeclampsia [21]. While sFlt-1 levels decline after delivery of the placenta, a persistent and subtle anti-angiogenic milieu may contribute to lasting endothelial dysfunction in women with a history of preeclampsia.

sFlt-1 and Future Cardiovascular Disease

Higher sFlt-1 levels have been shown to be associated with progression of atherosclerosis [22]. Elevated levels have also been documented in patients with chronic kidney disease (CKD), and in subjects with a history of stroke or myocardial infarction [23]. In a cohort of maintenance hemodialysis patients, levels of soluble VEGFR-1 independently predicted cardiovascular events and all-cause mortality [23].

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Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

163

Fig. 1. Summary of the pathogenesis of preeclampsia.

In a cohort of 586 patients with angiographically documented coronary artery disease, sFlt-1 concentrations correlated negatively with estimated glomerular filtration rate and were associated with signs of heart failure, based on the New York Heart Association functional class, reduced left ventricular ejection fraction, and early mortality [24]. In a supporting animal protocol, rats treated with recombinant sFlt-1 showed a 15% reduction in left ventricular ejection fraction and a 29% reduction in cardiac output compared with control rats. High sFlt-1 concentrations were associated with a 15% reduction in heart capillary density (number of vessels/cardiomyocyte) and a 24% reduction in myocardial blood volume [24]. Overall, these findings suggest that a component of cardiovascular risk in CKD patients could be directly attributed to sFlt-1 (Fig. 1).

sFlt-1 as a Prognostic Biomarker in Critical Illness

In addition to its pivotal role in the downstream events that culminate in the clinical syndrome of preeclampsia, sFlt-1 has been studied as a biomarker of vascular permeability in conjunction with other endothelial markers such as VEGF and angiopoietin-2 (Ang-2). Skibsted et al. [25] investigated the association of endothelial-related markers with organ dysfunction and in-hospital mortality in patients with sepsis. In this study, all endothelial injury biomarkers were significantly associated with sepsis severity, with sFlt-1 demonstrating the strongest association with the Sequential Organ Failure Assessment score [25].

The Protocolized Care in Early Septic Shock (ProCESS) trial sought to analyze the effects of varying resuscitation strategies on circulating markers of endothelial cell permeability and hemostasis, and the association between vascular biomarkers, such as VEGF, sFLT-1, Ang-2, and tissue plasminogen activator with mortality [26]. Permeability (Ang-2 and sFLT-1) and

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164

Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

hemostasis (von Willebrand factor, thrombomodulin, tissue plasminogen activator) biomarkers were higher and VEGF levels were lower in nonsurvivors of sepsis. At baseline, sFLT-1 had the highest point estimate for mortality discrimination, similar to lactate and the Sequential Organ Failure Assessment score, and holds promise as a novel sepsis severity biomarker for future studies.

In its role as a circulating decoy molecule, sFlt-1 binds to VEGF and acts as a competitive inhibitor of VEGF signaling in endothelial cells, and neutralizes the pro-inflammatory effects of VEGF. In animal models of experimental endotoxic shock and sepsis, both VEGF and sFlt-1 were rapidly released from macrophages activated in vitro by lipopolysaccharide and in the plasma of endotoxemic mice. Administration of VEGF enhanced pro-inflammatory cytokine production and mediated a dramatic increase in mortality in endotoxemic mice. Treatment with sFlt-1 attenuated inflammatory responses, thus suggesting that increased levels of sFlt-1 may represent a critical component of the host anti-inflammatory response [27].

Insulin Resistance in Preeclampsia and Resultant Endothelial Dysfunction

Large retrospective cohort studies have documented a 3- to 7-fold increased risk of developing cardiovascular disease in women with preeclampsia later in life [28]. This increased risk is based on genetic determinants shared with metabolic syndrome and inflammation [29]. Preeclamptic women have lower insulin sensitivity and a higher prevalence of postpartum metabolic syndrome than women without preeclampsia [30]. VEGF-activated vasodilatory pathways converge with insulin metabolic signaling, linking these two pathways at a molecular level, as elegantly demonstrated by Scioscia et al. [31]. This convergence may contribute in a synergistic way to the pathogenesis of preeclampsia [32]. Subclinical insulin resistance and inflammation, well known to elevate the risk of cardiovascular disease, predisposes women to preeclampsia, and persist up to three decades postpartum [33].

Dysregulation of the Renin Angiotensin Aldosterone Axis in Preeclampsia

Levels of renin, angiotensin, and aldosterone are increased despite an overall decrease in systemic vascular resistance in a normal pregnancy [34]. In preeclampsia, this resistance is blunted resulting in increased sensitivity to angiotensin II compared with normotensive pregnant women. Circulating angiotensin receptor (AT1) activating antibody levels, which are elevated during and after preeclamptic pregnancies, may contribute to a higher risk of hypertension later in life [35].

Biomarkers as a Link between Preeclampsia and Future Cardiovascular and Kidney Disease

Persistent Endothelial Dysfunction and Metabolic Syndrome after Preeclampsia

Delivery of the placenta cures preeclampsia, yet affected women continue to have an elevated risk of cardiovascular disease many years postpartum. Large retrospective epidemiologic studies have consistently demonstrated an elevated risk for many types of cardiovascular disease in women with a history of preeclampsia. A recent meta-analysis demonstrated the prevalence of future hypertension in women with prior preeclampsia to be over 50%, with a 3- to 4-fold risk of hypertension compared to women without preeclampsia. Similarly, the risk of death from cardiovascular disease and cerebrovascular disease is about 2-fold greater in women with a history of preeclampsia [36].

Although levels of sFlt-1 decline after delivery of the placenta, a persistent and subtle anti-angiogenic milieu may contribute to lasting endothelial dysfunction and an elevated risk of cardiovascular disease in women with a history of preeclampsia. Some, but not all studies,

165

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Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An
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have shown that levels of sFlt-1 remained higher in women with a history of preeclampsia compared to those without preeclampsia for an average of 18 months postpartum, independent of body mass index (BMI), blood pressure, and smoking. The source of sFlt-1 in nonpregnant individuals may be related to the peripheral blood mononuclear cells, because monocytes in women with preeclampsia produce elevated levels of sFlt-1 compared to those from control subjects. A recent study in 130 patients with CKD suggested that elevated levels of sFlt-1 in this group of patients may contribute to endothelial dysfunction and risk of cardiovascular disease. Serum from these patients had anti-angiogenic activity compared to control serum, which could be attenuated with the administration of an anti-sFlt-1 antibody [36]. Also, sFlt-1 levels were elevated in subjects who had a history of myocardial infarction or stroke. Relatively high sFlt-1 levels are also associated with carotid intima-media thickness and progression of atherosclerosis in hypertensive subjects [37].

In women with the metabolic syndrome, the risk of gestational hypertension, preeclampsia, and diabetes in late pregnancy are significantly higher. Conversely, women with gestational diabetes were at a higher risk for persistent metabolic syndrome within the first year after delivery. Given the strong relationship between preeclampsia, insulin resistance, and the metabolic syndrome, lifestyle-based interventions and pharmacotherapy for these risk factors should be instituted before and after a preeclamptic pregnancy [37].

Persistence of Insulin Resistance and Increased Risk of Diabetes

While preeclampsia is recognized as a risk factor for cardiovascular disease and stroke, the relationship between preeclampsia and future diabetes has received less attention. McDonald et al. [36] reported an increased risk of late-onset diabetes among women with a history of preeclampsia. A registry study of 226,832 women in Norway showed that only 0.5% of women without gestational diabetes or preeclampsia had received a prescription to treat diabetes within 5 years of birth, while 2% of women with preeclampsia had received such a prescription, and 55% of women with both conditions had received a diabetes drug prescription [36]. Weissgerber et al. [38] similarly reported that the number of women that would need to be followed for 5 years to detect 1 case of diabetes was 123 for preeclampsia, 68 for gestational diabetes, and 31 for preeclampsia and gestational diabetes.

Increased Risk of Dyslipidemia in Preeclampsia

Several studies have identified pro-atherogenic patterns in lipid concentrations that precede clinical manifestations of preeclampsia. Preeclamptic women tend to have increased levels of Lp(a), of uncertain significance [37]. These gestations are also marked by higher levels of triglyceride, lower levels of high-density lipoprotein cholesterol, and greater fractionation of small, dense, atherogenic low-density lipoprotein particles. Elevated low-density lipoprotein fractions with lower high-density lipoprotein cholesterol levels appear to be more pronounced in women with gestational hypertension and diabetes, and preeclampsia [38, 39].

Preeclampsia as an Example of Type 5 Cardiorenal Syndrome

Preeclampsia and Future Maternal Risk of Hypertension

Hypertensive disorders in pregnancy induce long-term vascular, renal, and metabolic changes that increase future cardiovascular risk in women [41]. Despite normalization of blood pressure postpartum, these seemingly healthy women demonstrate unfavorable metabolic and vascular changes, such as an impaired brachial artery flow-mediated (endothelium-dependent) dilatation up to 3 years after the diagnosis of preeclampsia [42]. Microalbu-

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Cardiorenal Med 2018;8:160–172

166

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Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An
Underrecognized Entity in Women's Cardiovascular Health

minuria, which is a marker of endothelial dysfunction and/or renal injury, has also been reported to be more prevalent following a preeclamptic pregnancy. Glomerular endotheliosis, the classic renal histological lesion associated with preeclampsia, is associated with subtle alterations in kidney function after pregnancy that may contribute to hypertension later in life.

Several studies have indicated that structural cardiac changes, which occur during hypertensive pregnancies, do not revert to normal upon delivery. Eccentric and concentric ventricular remodeling, impaired contractility, and diastolic dysfunction have been reported with the hypertensive syndromes of pregnancy [40]. Echocardiographic studies of women with preeclampsia performed 1 year postpartum show an increased risk of altered left ventricular geometry (concentric remodeling, eccentric hypertrophy), impaired left ventricular relaxation with global diastolic dysfunction, and mildly impaired systolic function (ejection fraction 45–55%), compared to those with normotensive pregnancies. Conceivably, these persistent abnormalities may contribute to the risk of heart disease, including heart failure and arrhythmias, which have recently been associated with maternal placental syndromes [40].

Preeclampsia and Increased Vascular Stiffness

Arterial stiffness has been shown to be higher in preeclamptic pregnancies when compared to normotensive pregnancies. A recent meta-analysis showed a significant increase in all arterial stiffness indices in women with preeclampsia versus women with normotensive pregnancies (standardized mean difference 1.62, 95% confidence interval [CI] 0.73–2.50) [43]. Arterial stiffness measurements may also be useful in predicting preeclampsia and may play a role in the increased risk of future cardiovascular complications seen in women with a history of preeclampsia [43, 44].
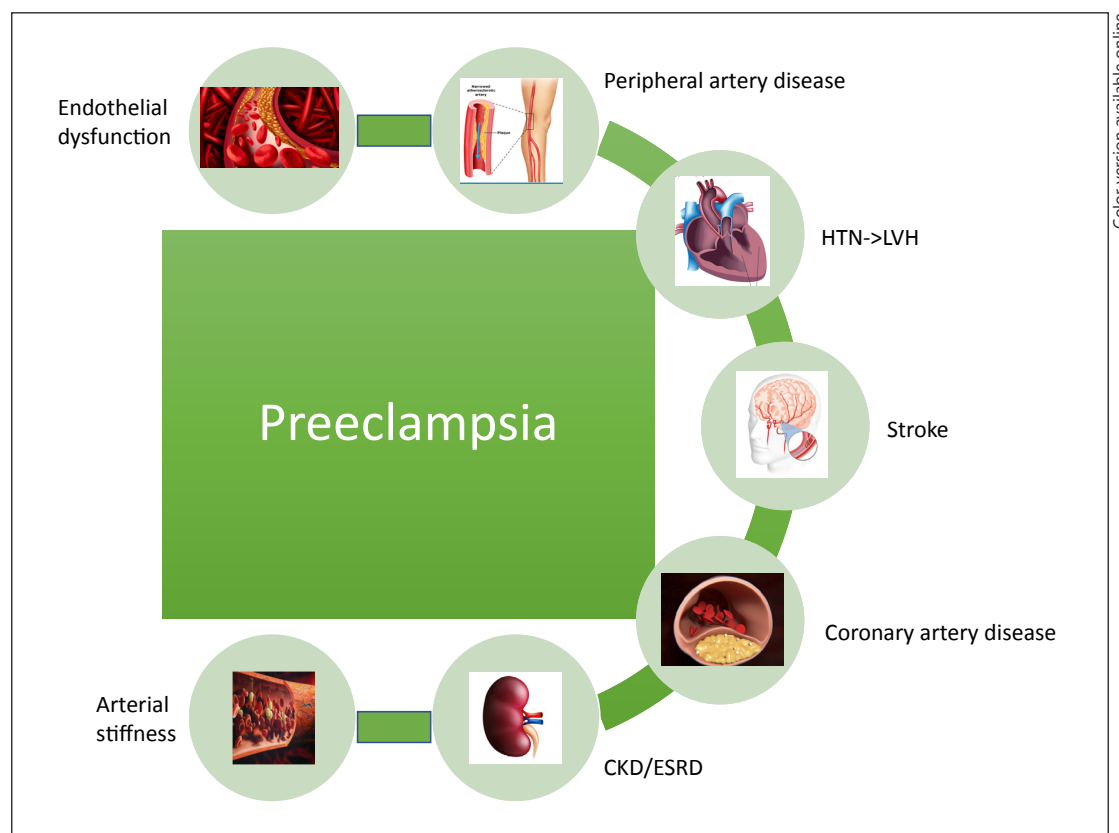
Cardiovascular Disease in Women with Preeclampsia

Multiple studies have shown the relationship between preeclampsia and cardiovascular disease [45]. In the Cardiovascular Health after Maternal Placental Syndromes study (CHAMPS study), 75,380 women who were diagnosed with a maternal placental syndrome (preeclampsia, gestational hypertension, placental abruption, and placental infarction) were followed longitudinally. The incidence of cardiovascular disease was 500 per million person-years in women with a history of a maternal placental syndrome, compared with 200 per million in women without such a history (adjusted hazard ratio [HR] 2.0, 95% CI 1.7–2.2). This risk was higher in the combined presence of a maternal placental syndrome and poor fetal growth (3.1, 2.2–4.5) or a maternal placental syndrome and intrauterine fetal death (4.4, 2.4–7.9).

The Rochester Family Heart Study highlighted that the risk factors for preeclampsia coincide with risk factors for future cardiovascular disease including insulin resistance, diabetes mellitus, obesity, chronic hypertension, systemic inflammation, and renal disease [45]. Data from a Norwegian population-based study found that the association of gestational hypertensive disease and postpregnancy cardiovascular risk factors could largely be attributed to shared risk factors that are present prior to pregnancy [46]. These findings suggest that this patient population could benefit from earlier and aggressive intervention to reduce future cardiovascular disease risk (Fig. 2).

Risk of CKD and End-Stage Kidney Disease after Preeclampsia

Risk factors for cardiovascular and renal disease are often mutual, and the risk of CKD and end-stage kidney disease is significant in women with preeclampsia. Magnussen et al. [47] reported that women with preeclampsia in their first pregnancy had a considerably increased risk of developing kidney disease that needed future workup with a kidney biopsy.

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Cardiorenal Med 2018;8:160–172

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167

Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

Fig. 2. Vascular complications of preeclampsia.

In another study by Stillman et al. [48], women who previously had preeclampsia had a 4–5 times increased risk of future end-stage kidney disease, independent of baseline renal function. The increased risk remained significant throughout the follow-up period of nearly 40 years.

Several mechanisms might explain the observed association between preeclampsia and subsequent renal disease. As hypertension, endothelial dysfunction, and obesity are important risk factors for both preeclampsia and CKD, these shared risk factors can partly explain the association between preeclampsia and kidney disease [48]. However, preeclampsia is associated with a 4- to 5-fold risk of future CKD and microalbuminuria, suggesting possible direct renal endothelial damage from preeclampsia.

While the extensive glomerular changes during preeclampsia are believed to completely resolve after pregnancy, no studies have routinely performed kidney biopsy months after the preeclamptic pregnancy. The fact that as many as 20–40% of subjects have microalbuminuria after a preeclamptic pregnancy may argue for permanent glomerular damage in these women [47]. Furthermore, several investigators argue that proteinuria itself causes progressive renal dysfunction via increased interstitial inflammation, and the same might be true for microalbuminuria. Interestingly, in a longitudinal study using data from the Medical Birth Registry in Norway of 89 preeclamptic women and 69 controls, preeclampsia was not associated with an increased risk of persisting long-term microalbuminuria, highlighting the heterogeneity in different study populations, clinical phenotype, and sample size [49].

When interpreting the data on preeclampsia and future kidney disease, it should be remembered that preeclampsia might unmask asymptomatic or undiagnosed CKD, which

168

Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

may precede the pregnancy. A prepregnancy estimated glomerular filtration rate <60 mL/min/1.73 m^2 is associated with future preeclampsia risk in hypertensive women [49]. Furthermore, previous studies have shown that as many as 5–20% of women with severe preeclampsia meet criteria for CKD shortly after pregnancy, thus leaving the question whether these women had true preeclampsia or merely an exacerbation of their kidney disease.

Increased Risk of Stroke in Preeclampsia

Although women with cerebrovascular manifestations of preeclampsia are thought to be out of danger when the placenta is delivered, observational data show that women with preeclampsia are at risk for stroke and cerebrovascular disease well after the postpartum period and child-bearing years. A meta-analysis investigated the link between preeclampsia and cardiovascular disease and stroke and demonstrated close to a 4-fold increase in the odds of developing hypertension (OR 3.7, 95% CI 2.70–5.05), a 2-fold risk of ischemic heart disease (OR 2.16, 95% CI 1.86–2.52), and a 2-fold increase in fatal and nonfatal stroke risk with prior preeclampsia (RR 2.16, 95% CI 1.86–2.52) [50].

Cardiovascular Disease in the Offspring of Preeclamptic Women

There is an emerging body of data on the impact of maternal preeclampsia on the cardiovascular health of the offspring. In a meta-analysis of 18 studies with cumulative data on 45,249 individuals, in utero exposure to preeclampsia was associated with a 2.39 mm Hg higher systolic blood pressure (95% CI 1.74–3.05; $p < 0.0001$) and a 1.35 mm Hg higher diastolic blood pressure (95% CI 0.90 1.80; $p < 0.00001$) during childhood and young adulthood. Associations were similar in children and adolescents, for different genders, and varying birth weights [51].

A large cohort of 2,608 mother-offspring pairs from the Mater University of Queensland Study of Pregnancy (MUSP) study demonstrated higher blood pressures in the offspring of preeclamptic mothers at 21 years of age, when adjusted for other cardiovascular risk factors [50]. In 2,868 young adult offspring of women enrolled during pregnancy into the Western Australia Pregnancy Cohort Study, offspring of hypertensive pregnancies were 2.5 times (95% CI 1.32–4.56, $p = 0.004$) more likely to have global lifetime risk scores above the 75th centile. Preeclampsia or hypertension resulting in preterm birth was associated with a 3-fold (95% CI 1.3–7.0, $p = 0.01$) greater risk of being hypertensive by age 20 years, with no differences in BMI [52, 53].

Another large UK study of maternal-offspring pairs ($n = 3,537–4,654$), assessed at age 9–12 years, looked at the associations of maternal gestational hypertension and preeclampsia with offspring blood pressure [54]. Offspring of women with preeclampsia had a higher systolic blood pressure by 2.04 mm Hg (95% CI 1.33–2.76) and a higher diastolic blood pressure by 1.10 mm Hg (95% CI 0.47–1.73) in analyses adjusted for maternal and offspring BMI, offspring dietary sodium intake, and other potential confounders [54]. The Helsinki Birth Cohort Study observed that the offspring of preeclamptic pregnancies had almost double the lifetime risk of stroke (HR 1.9, 95% CI 1.2–3.0; $p = 0.01$) [52, 55].

Jayet et al. [56] described elevated pulmonary artery pressures (by approximately 30%) on Doppler echocardiograms, and lower flow-mediated vasodilation (also by 30%) in children (mean age 13 ± 7 years) born to preeclamptic mothers. In a cross-sectional study of myocardial function in 45 children (5–8 years) of preeclamptic women, abnormal findings included increased baseline heart rate and increased late diastolic velocity (A' wave) at mitral valve attachments compared to the control group. All of these findings support a chain of logic that preeclampsia may lead to the development of heart failure later in life. An increased risk of

Table 2. Spectrum of complications seen in the offspring of women with preeclampsia

- Hypertension
- Stroke
- Pulmonary arterial hypertension
- Coronary artery disease
- Increased baseline heart rate
- Congenital heart defect
- Chronic kidney disease
- Insulin resistance

congenital heart defects, predominantly atrioventricular septal defects, has also been reported in the offspring of preeclamptic mothers [57] (Table 2).

In addition to maternal risk, children born to mothers with preeclampsia pregnancies may also be at increased risk for neurological problems and stroke. The Helsinki Birth Cohort traced offspring of the original cohort born between 1934 and 1944 in Helsinki, Finland. The HR for all forms of stroke in offspring of mothers with preeclampsia was 1.9 (95% CI 1.2–3.0), and the HR was 1.4 for those born to women with pregnancies complicated by gestational hypertension (95% CI 1.0–1.8). Severe preeclampsia was also associated with a reduced head circumference at birth [51].

Management of Cardiovascular Disease Risk in Women with Prior Preeclampsia

The 2011 AHA guidelines for the prevention of cardiovascular disease in women identify a history of gestational hypertension and preeclampsia as a major cardiovascular risk factor, on par with smoking, hypertension, a family history of premature cardiovascular disease, and evidence of advanced subclinical atherosclerosis [58]. The development of preeclampsia in response to the metabolic milieu of pregnancy is viewed as a failed endothelial "stress test," unmasking early or underlying endothelial dysfunction and vascular disease. Thus, appropriate risk reduction strategies should commence from the postpartum period in conjunction with appropriate specialty input for cardiorenometabolic risk reduction. A detailed history of obstetric complications including gestational diabetes, preeclampsia, gestational hypertension, and preterm birth should be part of routine cardiovascular screening and risk stratification in all women.

Despite the elevated risk of ischemic heart disease and stroke observed in a large meta-analysis in preeclamptic women (1.89 [IQR 1.76–1.98] and 1.55 [IQR 1.40–1.71]), dietary modification, exercise, and smoking cessation successfully reduced cardiovascular risk with an OR of 0.91 (IQR 0.87–0.96) [59]. Physical inactivity is listed as a major cardiovascular risk factor in the 2011 AHA guidelines for the prevention of cardiovascular disease in women, and has a major impact when present in conjunction with a history of preeclampsia [58]. In a prospective cohort study of preeclamptic women who completed self-reported physical activity in MET-min/week using the International Physical Activity Questionnaire, 38% of women failed to meet the physical activity recommendation [60]. Lack of physical activity was associated with a history of severe preeclampsia, Cesarean section, admission to the neonatal intensive care unit, low gestational age at delivery, and low birth weight (all $p <$ 0.05). Thus, a careful assessment of physical activity and tailored lifestyle interventions are crucial in sedentary women with a history of preeclampsia. The risk of postpartum depression, posttraumatic stress disorder and health-related poor quality of life are higher in women

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170

Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An
Underrecognized Entity in Women's Cardiovascular Health

with severe preeclampsia, and are opportunities to recognize and optimize their impact on future cardiovascular risk profile [61].

The World Health Organization (WHO), American College of Obstetrics and Gynecology (ACOG), and the United States Prevention and Screening Task Force (USPSTF) all recommend the use of low-dose aspirin in women at high risk for preeclampsia at various time points of gestation [62]. Recently, Rolnik et al. [63] published results of a large multicenter randomized placebo-controlled double-blinded trial of low-dose aspirin (150 mg) versus placebo in the prevention of preterm preeclampsia in 1,776 high-risk women.

The use of aspirin resulted in a 62% relative risk reduction in the incidence of preterm preeclampsia when compared to placebo, with 38 women needing to be treated to prevent one primary outcome. The findings of Rolnik et al. [63] support recommendations for the use of prophylactic low-dose aspirin in high-risk women in concordance with the ACOG and USPSTF guidelines. However, the effects of aspirin on several clinically important, preeclampsia-associated complications – in particular, perinatal mortality – remain unproven.

No specific recommendations on the use of low-dose aspirin in primary prevention of cardiovascular adverse events in women with a history of preeclampsia are available at this time. The use of cholesterol-lowering statins and blood pressure modification, based on annual cardiovascular disease risk as outlined in the 2011 AHA guidelines for the prevention of cardiovascular disease in women, are applicable in women with a history of preeclampsia [63].

Conclusions and Future Directions

Preeclampsia offers a unique window of opportunity to identify maternal endothelial dysfunction and preexisting cardiovascular disease. It remains an underrecognized cause of cardiovascular and kidney disease in women and represents the confluence of preexisting vascular risk factors with superimposed endothelial injury from placental mediated anti-angiogenic factors. Future studies in cardiovascular risk modification in this phenotype of disease are essential to reduce the burden of cardiovascular disease in women. A deeper understanding of the feto-placental-maternal interface will help delineate the biological aspects of future cardiovascular disease in these women and their offspring.

References

1 Roberts JM, August PA, Bakris G, et al: Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–1131.
2 Powe CE, Levine RJ, Karumanchi SA: Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation 2011;123:2856–2869.
3 Mosca L, Benjamin EJ, Berra K, et al: Effectiveness-based guidelines for the prevention of cardiovascular disease in women – 2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011; 57:1404–1423.
4 Roger VL, Go AS, Lloyd-Jones DM, et al: Executive summary: heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation 2012;125:188–197.
5 Duckitt K, Harrington D: Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005;330:565.
6 Wolf M, Kettyle E, Sandler L, et al: Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol 2001;98:757–762.
7 Ahmed R, Dunford J, Mehran R, et al: Pre-eclampsia and future cardiovascular risk among women: a review. J Am Coll Cardiol 2014;63:1815–1822.
8 Weinberg CR, Shi M, et al: Season of conception, smoking, and preeclampsia in Norway. Environ Health Perspect 2017;125:067022.

Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

9   Sibai BM, Ramadan MK, Usta I, et al: Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993;169:1000–1006.

10 Salafia CM, Pezzullo JC, Minior VK, et al: Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. Obstet Gynecol 1997;90:830–836.

11 Zhou Y, Damsky CH, Chiu K, et al: Preeclampsia is associated with abnormal expression of adhesion molecules by invasive cytotrophoblasts. J Clin Invest 1993;91:950–960.

12 Zhou Y, Damsky CH, Fisher SJ: Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? J Clin Invest 1997;99:2152–2164.

13 Sattar N, Ramsay J, Crawford L, et al: Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension 2003;42:39–42.

14 Leung DW, Cachianes G, Kuang WJ, et al: Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246:1306–1309.

15 Park JE, Chen HH, Winer J, et al: Placenta growth factor. Potentiation of vascular endothelial growth factor bioactivity, in vitro and in vivo, and high affinity binding to Flt-1 but not to Flk-1/KDR. J Biol Chem 1994;269:25646–25654.

16 Patel TV, Morgan JA, Demetri GD, et al: A preeclampsia-like syndrome characterized by reversible hypertension and proteinuria induced by the multitargeted kinase inhibitors sunitinib and sorafenib. J Natl Cancer Inst 2008;100:282–284.

17 Maynard SE, Min JY, Merchan J, et al: Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649–658.

18 Kendall RL, Thomas KA: Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. Proc Natl Acad Sci USA 1993;90:10705–10709.

19 Levine RJ, Maynard SE, Qian C, et al: Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350:672–683.

20 Thadhani R, Mutter WP, Wolf M, et al: First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. J Clin Endocrinol Metab 2004;89:770–775.

21 Levine RJ, Lam C, Qian C, et al: Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med 2006;355:992–1005.

22 Shin S, Lee SH, Park S, et al: Soluble fms-like tyrosine kinase-1 and the progression of carotid intima-media thickness – 24-month follow-up study. Circ J 2010;74:2211–2215.

23 Di Marco GS, Reuter S, Hillebrand U, et al: The soluble VEGF receptor sFlt1 contributes to endothelial dysfunction in CKD. J Am Soc Nephrol 2009;20:2235–2245.

24 Di Marco GS, Kentrup D, Reuter S, et al: Soluble Flt-1 links microvascular disease with heart failure in CKD. Basic Res Cardiol 2015;110:30.

25 Skibsted S, Jones AE, Puskarich MA, et al: Biomarkers of endothelial cell activation in early sepsis. Shock 2013;39:427–432.

26 Wilson BJ, Watson MS, Prescott GJ: Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003;326:845.

27 Hou PC, Filbin MR, Wang H, et al: Endothelial permeability and hemostasis in septic shock: results from the ProCESS Trial. Chest 2017;152:22–31.

28 Tsao PN, Chan FT, Wei SC, et al: Soluble vascular endothelial growth factor receptor-1 protects mice in sepsis. Crit Care Med 2007;35:1955–1960.

29 Giguère Y, Charland M, Thériault S, et al: Linking preeclampsia and cardiovascular disease later in life. Clin Chem Lab Med 2012;50:985–993.

30 Stekkinger E, Zandstra M, Peeters LL, et al: Early-onset preeclampsia and the prevalence of postpartum metabolic syndrome. Obstet Gynecol 2009;114:1076–1084.

31 Scioscia M, Nigro M, Montagnani M: The putative metabolic role of d-chiro inositol phosphoglycan in human pregnancy and preeclampsia. J Reprod Immunol 2014;101–102:140–147.

32 Thadhani R, Mutter WP, Wolf M: First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. J Clin Endocrinol Metab 2004;89:770–775.

33 Hubel CA, Powers RW, Snaedal S, et al: C-reactive protein is elevated 30 years after eclamptic pregnancy. Hypertension 2008;51:1499–1505.

34 Weir RJ, Paintin DB, Robertson JI, et al: Renin, angiotensin and aldosterone relationships in normal pregnancy. Proc R Soc Med 1970;63:1101–1102.

35 Paauw ND, Joles JA, Spradley FT, et al: Exposure to placental ischemia impairs postpartum maternal renal and cardiac function in rats. Am J Physiol Regul Integr Comp Physiol 2017;312:R664–R670.

36 McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ: Kidney disease after pre-eclampsia, a systematic review and meta-analysis. Am J Kid Dis 2010;55:1026–1039.

37 Powe CE, Levine RJ, Karumanchi SA: Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation 2011;123:2856–2869.

38 Weissgerber TL, Mudd LM: Preeclampsia and diabetes. Curr Diab Rep 2015;15:579.

39 Mukherjee M: Dyslipidemia in pregnancy. http://www.acc.org/latest-in-cardiology/articles/2014/07/18/16/08/dyslipidemia-in-pregnancy.

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172

Rangaswami et al.: Preeclampsia as a Form of Type 5 Cardiorenal Syndrome: An Underrecognized Entity in Women's Cardiovascular Health

40 Garovic VD, August P: Preeclampsia and the future risk of hypertension: the pregnant evidence. Curr Hypertens Rep 2013;15:114–121.
41 Meekins JW, Pijnenborg R, Hanssens M, McFadyen IR, van Asshe A: A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. Br J Obstet Gynaecol 1994;101:669–674.
42 Freeman DJ, McManus F, Brown EA, Cherry L, Norrie J, Ramsay JE, Clark P, Walker ID, Sattar N, Greer IA: Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension 2004;44:708–714.
43 Hausvater A, Giannone T, Sandoval YH, et al: The association between preeclampsia and arterial stiffness. J Hypertens 2012;30:17–33.
44 Kianpour M, Norozi S, Bahadoran P, et al: The relationship between metabolic syndrome criteria and preeclampsia in primigravid women. Iran J Nurs Midwifery Res 2015;20:263–268.
45 Valdiviezo C, Garovic VD, Ouyang P: Preeclampsia and hypertensive disease in pregnancy: their contributions to cardiovascular risk. Clin Cardiol 2012;35:160–165.
46 Ahmed R, Dunford J, Mehran R, et al: Pre-eclampsia and future cardiovascular risk among women: a review. J Am Coll Cardiol 2014;63:1815–1822.
47 Magnussen EB, Vatten LJ, Lund-Nilsen TI, et al: Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ 2007;335:978.
48 Stillman IE, Karumanchi SA: The glomerular injury of preeclampsia. J Am Soc Nephrol 2007;18:2281–2284.
49 Sandvik MK, Hallan S, Svarstad E: Preeclampsia and prevalence of microalbuminuria 10 years later. Clin J Am Soc Nephrol 2013;8:1126–1134.
50 Wabnitz A, Bushnell C: Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. Cephalalgia 2015;35:132–139.
51 Davis EF, Lazdam M, Lewandowski AJ, et al: Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. Pediatrics 2012;129:e1552–e1561.
52 Mamun AA, Kinarivala MK, O'Callaghan M, et al: Does hypertensive disorder of pregnancy predict offspring blood pressure at 21 years? Evidence from a birth cohort study. J Hum Hypertens 2012;26:288–294.
53 Davis EF, Lewandowski AJ, Aye C, et al: Clinical cardiovascular risk during young adulthood in offspring of hypertensive pregnancies: insights from a 20-year prospective follow-up birth cohort. BMJ Open 2015;5:e008136.
54 Lawlor DA, Macdonald-Wallis C, Fraser A, et al: Cardiovascular biomarkers and vascular function during childhood in the offspring of mothers with hypertensive disorders of pregnancy: findings from the Avon Longitudinal Study of Parents and Children. Eur Heart J 2012;33:335–345.
55 Kajantie E, Eriksson JG, Osmond C, et al: Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. Stroke 2009;40:1176–1180.
56 Jayet PY, Rimoldi SF, Stuber T, et al: Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. Circulation 2010;122:488–494.
57 Liu S, Joseph KS, Luo W, et al: Effect of folic acid food fortification in Canada on congenital heart disease subtypes. Circulation 2016;134:647–655.
58 Mosca L, Benjamin EJ, Berra K, et al: Effectiveness-based guidelines for the prevention of cardiovascular disease in women – 2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011;57:1404–1423.
59 Berks D, Hoedjes M, Raat H, et al: Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG 2013;120:924–931.
60 Hoedjes M, Berks D, Vogel I, et al: Postpartum physical activity after preeclampsia. Pregnancy Hypertens 2012;2:143–151.
61 Hoedjes M, Berks D, Vogel I, et al: Poor health-related quality of life after severe preeclampsia. Birth 2011;38:246–255.
62 Sarma A, Scott NS: Aspirin use in women: current perspectives and future directions. Curr Atheroscler Rep 2016;18:74.
63 Rolnik DL, Wright D, Poon LC, et al: Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613–622.

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