Pre-eclampsia and cardiovascular disease

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Received 18 November 2013; revised 20 January 2014; accepted 21 January 2014; online publish-ahead-of-print 13 February 2014

Heart disease is the leading cause of death in women in all countries. A history of pre-eclampsia, one of the most deadly hypertensive complications of pregnancy, increases cardiovascular risk by two to four times, which is comparable with the risk induced by smoking. Substantial epidemiological data reveal that pregnancy-related hypertensive complications are associated with a predisposition to chronic hypertension, premature heart attacks, strokes, and renal complications. In this review, we summarize clinical studies that demonstrate this relationship and also discuss the pathogenesis of these long-term complications of pre-eclampsia. Future studies should focus on strategies to prevent the progression of cardiovascular disease in women exposed to pre-eclampsia, thereby improving long-term cardiovascular health in women.

Keywords
Pre-eclampsia • Stroke • Cardiovascular disease • Angiogenesis • Chronic kidney disease • sFlt1 • Hypertension • Proteinuria

This article is part of the Review Focus on Pregnancy-mediated Heart and Vascular Disease.

1. Introduction

Heart disease is the leading cause of death in women in all developed countries. Efforts focusing on improving awareness, preventive strategies, and treatment have resulted in an overall decline in the number of cardiovascular deaths in the last decade. However, there has been a rise in cardiovascular disease death rates in women aged 35–54, which has been postulated to be secondary to the obesity epidemic. ¹ One gender-specific cardiovascular disease risk factor that is often overlooked is a history of a hypertensive complication during pregnancy. A history of pre-eclampsia, one of the most deadly hypertensive complications of pregnancy, increases cardiovascular risk by two to four times, which is comparable with the risk induced by smoking. Owing to this substantial increased cardiovascular risk, American Heart Association guidelines in 2011 recognized pre-eclampsia and gestation hypertension as independent gender-specific cardiovascular risk factors. ¹

2. Background of pre-eclampsia

2.1 Definition of hypertensive disease during pregnancy

In 2013, in recognition of the syndromic nature of pre-eclampsia, the American College of Obstetrics and Gynecology updated the definitions of the various hypertensive disorders of pregnancy, as discussed below. ²

Chronic hypertension

• Maternal blood pressure ≥ 140/90 before 20 weeks of gestation.

• Maternal blood pressure ≥ 140/90 after 20 weeks of gestation, the absence of proteinuria, and without resolution by 12 weeks post-partum.

Gestational hypertension

• Maternal blood pressure ≥ 140/90 on at least two separate occasions 4 h apart after 20 weeks of gestation, the absence of the features of pre-eclampsia (below), and resolution by 12 weeks post-partum.

Pre-eclampsia

• Maternal blood pressure ≥ 140/90 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; hypertension can be confirmed within a short interval (min) to facilitate timely antihypertensive therapy.

And one of the following:

• Proteinuria: based on one of the following:
  • Greater than or equal to 300 mg per 24-h urine collection (or this amount extrapolated from a timed collection).
  • Protein/creatinine ratio ≥ 0.3.
  • Dipstick reading of 1+ (used only if other quantitative methods are not available).
  • Thrombocytopenia: platelet count < 100 000/μL.
  • Renal insufficiency: serum creatinine concentrations > 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease.

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• Thrombocytopenia: platelet count < 100 000/μL.
• impaired liver function: elevated blood concentrations of liver trans-
aminases to twice the normal concentrations;
• pulmonary oedema;
• cerebral or visual symptoms.

Eclampsia
• Grand Mal seizures in the setting of pre-eclampsia in the absence of other neurological conditions.

2.2 Epidemiology
Pre-eclampsia occurs in 3–5% of pregnancies in developed countries and up to 7.5% pregnancies worldwide. As of 2013, pre-eclampsia remains one of the leading causes of maternal death. Risk factors for the development of pre-eclampsia are nulliparity, familial history of pre-eclampsia, multiple gestation, pre-existing diabetes, chronic hypertension, a rapidly growing hydatidiform mole, foetal hydrops, and extremes of maternal age. Women are less likely to develop pre-eclampsia if they smoke, but the reason is unclear.

2.3 Pathogenesis of pre-eclampsia
Pre-eclampsia is proposed to progress in two stages. The first stage involves inadequate development of maternal spiral arteries resulting in deficiency in placental perfusion. The second stage involves widespread endothelial dysfunction resulting in hypertension, proteinuria, and oedema. Foetal perfusion is supplied by the maternal blood supply through spiral arteries, which are terminal branches of radial arteries. In normal pregnancies, the spiral arteries are invaded by trophoblastic cells that replace the endothelium of these arteries and promote remodelling of the vascular wall with dilation of the blood vessels. In pre-eclampsia, the placental invasion of these arteries is insufficient, resulting in narrower blood vessels and hypoperfusion of the placenta. This placental damage results in increased shedding of syncytial micro-particles and other vascular toxins from the foetal unit into the maternal circulation and is thought to contribute to stage 2 where there is generalized endothelial dysfunction. Two anti-angiogenic proteins have been identified that are overproduced by the pre-eclamptic placenta and gain access to the maternal circulation and are the leading candidate molecules responsible for the pre-eclampsia phenotype. Both soluble Fms-like tyrosine kinase 1 (sFlt-1), an endogenous inhibitor of vascular endothelial growth factor and placental growth factor signalling, and soluble endoglin (sEng), a circulating co-receptor of transforming growth factor-β, have been shown to be increased in the serum of pre-eclamptic women, when compared with normal pregnancy. Serum levels of sFlt-1 and sEng rise weeks before the appearance of overt clinical manifestations of pre-eclampsia and correlate with the severity of disease. In addition, when these proteins are injected into rodents, the animals develop systemic endothelial dysfunction resulting in a syndrome that phenocopies maternal pre-eclampsia, including severe hypertension, proteinuria, glomerular endotheliosis, cerebral oedema, and features resembling HELLP syndrome (haemolysis, elevated liver enzymes, low platelets). It is believed that these anti-angiogenic proteins act synergistically with syncytial micro-particles to provoke endothelial cells to release pro-inflammatory factors. This is thought to induce maternal leucocytosis and activation of neutrophils that contribute to vascular damage resulting in a pro-thrombotic state.

Various pathways have been proposed to be linked to the production of soluble pathogenic factors by the placenta. These include deficient haeme oxygenase expression, placental hypoxia, genetic factors, autoantibodies against the angiotensin receptor, oxidative stress, inflammation, altered natural killer cell signalling, and, more recently, deficient catechol-O-methyl transferase. While there is compelling evidence in animal studies demonstrating an important role for these upstream pathways, the underlying events that induce placental disease activating the cascade of placental damage and anti-angiogenic factor production remain unknown in humans.

The cause of gestational hypertension is unclear, but it is believed that this entity occurs in women destined to have essential hypertension later in life (analogous to women with gestational hyperglycaemia who eventually develop type 2 diabetes). A significant proportion of patients with gestational hypertension may represent an early phase of pre-eclampsia in which proteinuria has not yet appeared. Renal biopsy studies support the latter hypothesis.

Normal pregnancy is also associated with changes in traditional cardiovascular risk factors with relative insulin resistance and increase in triglycerides, total cholesterol (predominately LDL), phospholipids, and free fatty acids, all of which are thought to benefit foetal growth. In normal pregnancy, blood pressure begins to decrease as early as 7 weeks of gestation until ~32 weeks when it gradually increases back to normal. The decrease in blood pressure is thought to be secondary to low resistance flow in the placenta as well as hormonal factors causing dilation such as oestrogen, progesterone, prostaglandin, prolactin, prostacyclin, and relaxin, and increased production of nitric oxide.

Normal pregnancy is thought to be a state of ‘mild-controlled inflammation’ and pre-eclampsia a state of exaggerated inflammatory response. In contrast to normal pregnancy, the inflammatory response during pre-eclampsia becomes uncontrolled and in addition to the well-known hypertensive and proteinuric complications, it is also associated with exaggerated insulin resistance and worsened lipid profile and is sometimes referred to as the metabolic syndrome of pregnancy.

3. Long-term complications
The syndrome of pre-eclampsia resolves with delivery of the placenta with normalization of blood pressure and renal function and any associated liver, neurological, and thrombotic complications. However, substantial epidemiological data have been accumulated that reveals long-term risks associated with a history of gestational hypertensive disorders. As pre-eclampsia is associated with endothelial dysfunction, proteinuria, and a metabolic syndrome picture, it is not surprising that the long-term complications include a predisposition to chronic hypertension, cardiovascular complications, and renal complications. The data in support of these correlations are reviewed below.

3.1 Pre-eclampsia and chronic hypertension
Initially, primigravid pre-eclampsia was thought to carry no long-term cardiovascular sequelae; however, substantial evidence now shows an association with future chronic hypertension. Studies done using more accurate definitions of pre-eclampsia and larger sample sizes clearly demonstrate that the risk of future hypertension is about three to four times higher when compared with women with uncomplicated pregnancies. A prospective cohort study performed in the UK followed 17,202 women for 12.5 years and found an increased risk of hypertension in women who had a prior hypertensive disease of pregnancy, which included gestational hypertension, pre-eclampsia, and eclampsia. Additionally, in 2003 a retrospective cohort study of 3,593 women from Scotland also noted an increased incidence of hypertension in women with prior hypertension during pregnancy. A large meta-analysis by Bellamy et al. in 2007 examined multiple prospective and retrospective cohort studies dating as far back as the 1960s, and
found an increased risk of developing hypertension after a hypertensive pregnancy (RR: 3.39, 95% CI: 2.7–5.0).

Substantial data support the concept of a ‘dose effect’ with more severe pregnancy-associated hypertensive disorders carrying a greater risk of future hypertension. The study by Lykke et al. demonstrated that future risk of hypertension correlated with the severity of hypertensive disease of pregnancy and Magnussen et al. showed that multiple episodes of pre-eclampsia further predisposed women to a higher chance of future hypertension. Additional studies demonstrated that the onset of pre-eclampsia earlier in the pregnancy correlated with a higher risk of future hypertension. A small study done by Lazdam et al. in 2012 looked at 45 women with early onset pre-eclampsia (<34 weeks of gestation), 45 women with late onset pre-eclampsia (≥34 weeks of gestation), and 50 patients with normotensive pregnancies. They discovered that although both pre-eclamptic groups had higher blood pressures on follow-up, patients with early onset pre-eclampsia had a more significant increase. Specifically, ambulatory blood pressures measured in a subset of women in each of the three groups found that daytime systolic blood pressures were higher in both pre-eclamptic groups compared with the control; however, only those with early onset pre-eclampsia had elevated night-time blood pressures when compared with controls.23

### 3.2 Pre-eclampsia and future cardiovascular disease and stroke

Studies have shown that women diagnosed with hypertensive complications during pregnancy have a two-fold increased risk of future ischaemic heart disease and stroke. Additionally, more severe hypertensive pregnancy complications, as well as hypertensive pregnancies with pre-term birth or fetal growth restriction are associated with further increased future cardiovascular risk. A few of the studies demonstrating these relationships are highlighted below. A comprehensive summary can also be found in Table 1.

In 2001, a retrospective cohort study done by Smith et al. evaluated ischaemic heart disease- and cardiovascular-related death rates after pregnancies based on three characteristics: the lowest birthweight quintile for gestation age, pre-term delivery, and pre-eclampsia. They selected a cohort of 129,920 women with singleton births in Scotland with 15–19 years of follow-up. This study concluded that each one of the above characteristics were risk factors for future cardiac disease. The risk of each of these characteristics was independent and additive with the strongest risk associated with low birthweight. Women with all three of these factors were seven times more likely to develop ischaemic heart disease than the reference population.24

Irgens et al. in 2001 focused on a Norwegian cohort with 13 years of follow-up and also demonstrated that pre-eclampsia was associated with a higher risk of cardiovascular-related death. In their study, pre-eclampsia associated with pre-term birth had the highest association with cardiovascular-related death. Interestingly, women with term pre-eclampsia had only a slight increase in cardiovascular-related death but no significant increase in stroke in this study. These observations were also confirmed by Funai et al. in an Israeli cohort of 37,061 women where the relative risk of all-cause death after pre-eclampsia was 2.1 with cardiovascular disease as the strongest contributor.25

A large retrospective cohort study called CHAMPS published in 2005 looked at cardiovascular outcomes in women with maternal placental syndromes, including pre-eclampsia, gestational hypertension, placental abruption, and placental infarction. The study was based in Ontario, Canada and consisted of a cohort of 1.03 million women followed for an average of 8.7 years. Their results revealed that pre-eclampsia was associated with a doubling of these cardiovascular risks. In addition, women with pregnancies complicated by poor foetal growth or intrauterine foetal death had a more substantial increased risk of cardiovascular disease.

A meta-analysis done by Bellamy et al. showed that women with pre-eclampsia were at a higher risk of hypertension, stroke, venous thrombo-embolism, and fatal as well as non-fatal ischaemic heart disease, and that pre-eclampsia occurring before 37 weeks of gestation was associated with a further increased risk of heart disease to eight times of that of the reference population. Another meta-analysis done by McDonald et al. in 2008 looking at case control as well as cohort studies found that having pre-eclampsia or eclampsia confers a two to three times greater risk of cardiac disease. Furthermore, the severity of pre-eclampsia was associated with an increased risk of cardiovascular disease, with mild disease having a relative risk of 2, whereas severe disease had a relative risk >5.25

### 3.3 Pre-eclampsia and renal disease

Recent studies suggest that hypertensive diseases of pregnancy are also associated with worsened renal outcomes. The two main outcome measures studied are renal function and albuminuria. Overall, data support increased albuminuria and a three- to five-fold risk of future end-stage renal disease (ESRD) in women with previous hypertensive diseases of pregnancy.

Although most studies were small and demonstrated a trend towards increased albuminuria in patients with hypertensive pregnancies, a meta-analysis done by Mcdonald et al. in 2010 pooled data from seven cohorts and confirmed the association between pre-eclampsia and albuminuria in the long term. At an average of 7.1 years post-partum, 31% of women who had pre-eclampsia developed microalbuminuria in contrast to only 7% of women who had uncomplicated pregnancies. Most recently, these findings were also confirmed in the second Family Blood Pressure Program Study.

Initial studies that evaluated the presence of chronic kidney disease were also small and had mixed results, but two larger and more recent studies showed an increased risk of renal disease. A large retrospective cohort study done in Norway consisted of 570,433 women and an average follow-up of 17 years after initial pregnancy. The relative risk of ESRD in women who had pre-eclampsia in the first pregnancy was close to 5. Women with two or three episodes of pre-eclampsia had a 15-fold increase in the risk of developing ESRD. As with hypertension and cardiovascular disease, a low birthweight and pre-term birth in the setting of pre-eclampsia were also associated with an enhanced risk of ESRD. Wang et al. in 2013 confirmed this association in a Taiwanese cohort of 240,048 women. They found that women with hypertensive disorders during pregnancy had a three-fold risk of progression to ESRD. They also found that the severity of hypertensive disease during pregnancy correlated with progression to ESRD.

### 3.4 Pre-eclampsia and endocrine and metabolic disorders

There are also studies suggesting an association between hypertensive complications of pregnancies with subsequent development of hypothyroidism, hyperlipidaemia, and diabetes mellitus (DM). More recently, Finnish investigators demonstrated that there was a significantly increased
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Follow-up (years)</th>
<th>Population</th>
<th>Findings</th>
<th>HTN (RR)</th>
<th>IHD (RR)</th>
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<td>UK</td>
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<td>Pre-eclampsia (term)</td>
<td>1.65 (1.01–2.70)</td>
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<td>Pre-eclampsia (pre-term)</td>
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<td>Severe pre-eclampsia</td>
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<td>Previous spontaneous abortion</td>
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<td>Lowest birthweight quintile plus pre-term delivery plus previous spontaneous abortion</td>
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<td>MPS and poor foetal growth</td>
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<td>Jerusalem</td>
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**Pre-eclampsia and cardiovascular disease**

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<td>Lin et al.</td>
<td>Taiwan</td>
<td>1,132,064</td>
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<td>Skjærvén et al.</td>
<td>Norway</td>
<td>836,147</td>
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<tr>
<td>Wang et al.</td>
<td>Taiwan</td>
<td>240,048</td>
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IHD, ischaemic heart disease; CVA, cardiovascular accident/stroke; HTN, hypertension; MPS, maternal-placental syndrome; ESRD, end-stage renal disease; VTE, venous thrombo-embolism; OR, odds ratio; RR, relative risk; HR, hazard ratio. All hypertension includes essential hypertension as well as gestational hypertension, pre-eclampsia, and eclampsia.

*Not statistically significant.*
risk of hypothyroidism among women with a history of late onset pre-eclampsia in a cohort of 15,935 women with 20–40 years of follow-up (HR: 1.82, 95% CI: 1.04–3.19). Lykke et al. found an increased incidence of future DM in their study, with the relative risk of future DM in women with hypertensive complications during pregnancy being three times that of controls. There have also been other studies showing that there is a trend towards a less favourable lipid profile and increased inflammatory markers in women who had a history of pre-eclampsia. Small studies have also suggested an association between pre-eclampsia and major depressive disorders in the long term. Depression is associated with high sympathetic tone, elevated catecholamines, and increased inflammatory markers, and may directly contribute to adverse cardiovascular outcomes.

4. Mechanistic insights

4.1 Shared risk factors/lifestyle

The pervading theory to explain enhanced cardiovascular risk in women with a history of pre-eclampsia is that pregnancy is a ‘stress test’ and the development of hypertensive disorders during pregnancy identifies a woman destined to develop cardiovascular disease. This is based on ample data revealing overlapping risk factors for pre-eclampsia and cardiovascular disease. Both cardiovascular disease and pre-eclampsia have shared risk factors including genetic factors, diabetes, hypertension, increased insulin resistance, and increased homocysteine concentration. Whether these common associations are causative or correlative is difficult to discern. One study done by Skjærven et al. showed that mothers with only one pregnancy had a higher risk of overall death and cardiovascular death compared with women with more than one child. They also found that pre-eclampsia with term births did not have a higher cardiovascular mortality compared with those without (only a higher incidence of cardiovascular disease). In general, these studies cannot control for lifestyle modifications that might be associated with single births that might also be associated with cardiovascular risk. Using longitudinal data from two consecutive studies, Romundstad et al. noted that women with a history of pre-eclampsia or gestational hypertension also had substantially higher body mass index and systolic and diastolic blood pressures and unfavourable lipids compared with those with normotensive pregnancies. Importantly, after adjustment for pre-pregnancy risk factors, the correlation with body mass index was attenuated by >65%, and the increase in blood pressure following pre-eclampsia was reduced by ~50%. Interestingly, foetal growth restriction alone without pre-eclampsia is also associated with impaired vascular function in the long term. These data provide support for the theory that the positive association of placental disorders with cardiovascular disease may be due to shared risk factors.

4.2 Vascular damage secondary to pre-eclampsia

One novel emerging theory regarding the mechanism for pre-eclampsia-enhanced cardiovascular risk is the potential for permanent vascular damage sustained during the pre-eclamptic episode from inflammatory stress, coagulation dysregulation, and endothelial damage to contribute directly to cardiovascular disease pathogenesis. Recently, animal studies revealed that experimental pre-eclampsia induces long-term changes in the global plasma protein profile (proteome) that correlate with changes associated with cardiovascular disease. The absence of hypertension in the siblings of women with pre-eclampsia who might be expected to have more similar risk of cardiovascular disease based on genetic and other environmental factors supports this theory. The dose effect with an increased risk of cardiovascular disease in women with more severe or recurrent pre-eclampsia supports the idea that pre-eclampsia per se may contribute directly to the progression of cardiovascular disease.

Although levels of anti-angiogenic proteins such as 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 pre-eclampsia. We have shown that levels of sFlt-1 remained modestly higher in women with a history of pre-eclampsia compared with those without pre-eclampsia, however, the role of anti-angiogenic proteins in the pathophysiology of cardiovascular disease has not been well worked out. Recently, pilot studies by our group suggested that women with a history of pre-eclampsia or gestational hypertension also had substantially higher body mass index and systolic and diastolic blood pressures and unfavourable lipids compared with those without pre-eclampsia.

5. Conclusion

Ample data support the association between pre-eclampsia and a heightened risk of remote vascular disease in the form of hypertension, cardiovascular disease, and renal disease. This important association can be used to screen for women with an increased risk to better target counselling on lifestyle modifications such as weight loss, exercise, and a healthier diet. While the association between pre-eclampsia and chronic vascular disease is clear, the mechanism for the association is not known. Current evidence suggests that pre-pregnancy risk factors and pre-eclampsia itself may both contribute to the development of this long-term cardiovascular disease risk. Now that we have animal models of pre-eclampsia that faithfully reproduce the disorder, further studies can be performed to better elucidate the complicated physiology that occurs during pre-eclampsia in a way that is difficult if not impossible to do in humans. Currently, the only definitive treatment for pre-eclampsia is delivery of the foetus and placenta. Using animal models that recapitulate the human condition, we may have a better chance of discovering a method to prevent pre-eclampsia. Moreover, these models enable the investigation of the long-term sequelae of vascular disease to better differentiate the effects of underlying shared risk factors from those of permanent vascular damage as a consequence of pre-eclampsia. Such studies have the potential to identify strategies to prevent the progression of cardiovascular and renal disease in women who experienced pre-eclampsia, thereby improving long-term cardiovascular health in women.

Conflict of interest: S.A.K. is a co-inventor on multiple patents related to angiogenic markers in pre-eclampsia that are held by Beth Israel...
Deaconess Medical Center, which have been out-licensed to multiple companies. S.A.K. has served as a consultant to Roche and Siemens, and has a financial relationship with Aggamin LLC. All other authors report no conflict.

Funding
C.W.C. is supported by an NIH training grant. S.A.K. is an investigator of the Howard Hughes Medical Institute. I.Z.J. is supported by grants from the NIH (HL095590-05) and the AHA (GIA0855920D).

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