Consider Preeclampsia as a First Cardiovascular Event

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Abstract

Purpose of Review Cardiovascular disease (CVD) is the leading cause of death in women worldwide. Preeclampsia (PE) is an important and acknowledged female-specific risk factor. Women with a history of PE have an elevated risk to develop hypertension in the decade following their index pregnancy. In this paper, we aim to provide recent insights in the future risk of preeclampsia and describe how prevention strategies can be optimized.

Recent Findings The development of premature hypertension is caused by multiple factors such as genetics and a persistent enhanced inflammatory state after PE. Systemic inflammation accelerates endothelial dysfunction and promotes the process of atherosclerosis. In formerly preeclamptic women, signs of subclinical atherosclerosis are present at young age. Timely cardiovascular screening after PE is recommended; however, the how and when are yet to be determined. Given the large impact of a previous preeclamptic pregnancy on cardiovascular risk, the question arises whether we should not intensify secondary prevention in these high-risk women.

Summary Obstetric history can provide useful information about CVD risk in women after their reproductive life, especially if they had a pregnancy complicated by preeclampsia. Early detection of hypertension could optimize prevention and treatment strategies and mitigate CVD risk. For high-risk women, preeclampsia may be considered a first cardiovascular event that requires secondary prevention according to guidelines.

Keywords Preeclampsia · Cardiovascular disease · Risk factor · Hypertension · Inflammation · Atherosclerosis

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Introduction

Cardiovascular disease (CVD) is the leading cause of death in women worldwide. In the last two decades, overwhelming evidence has shown that CVD risk is elevated after a pregnancy complicated by preeclampsia (PE) [1–4]. Several global guidelines, such as the 2011 American College of Cardiology/American Heart Association's (ACC/AHA) guideline [5], the 2016 European Society of Cardiology (ESC) guideline CVD prevention [6], and the 2017 ACC/AHA guideline on high blood pressure [7], acknowledge preeclampsia as a female-specific cardiovascular risk factor and recommend timely risk monitoring after PE. As such, pregnancy acts as a window for future cardiovascular health [8]. It is yet to establish, however, whether preeclampsia is an independent risk factor for CVD or acts through traditional CVD risk factors [9]. The most common thought is that PE is driven by an enhanced susceptibility for CVD and interacts with environmental factors. This review aims to describe the current knowledge on preeclampsia as a risk factor for CVD later in life.

Preeclampsia and Subsequent Cardiovascular Risk

Preeclampsia is one of the hypertensive disorders of pregnancy (HDP) and accounts for the most severe form. The International Society for the Study of Hypertension (ISSHP) defines preeclampsia as new-onset hypertension after 20 weeks gestation in combination with either proteinuria (≥ 300 mg/day) or other maternal dysfunctions, such as renal insufficiency, liver involvement, neurological or hematological complications, or uteroplacental dysfunction [10]. Preeclampsia complicates 3–5% of all pregnancies, leading to maternal and fetal morbidity caused by growth restriction due to uteroplacental dysfunction. Moreover, it can potentially lead to intrauterine death [11]. In Western countries, such as the Netherlands, maternal mortality is low, but PE remains the most important cause [12].

Hypertension is diagnosed when the systolic blood pressure exceeds 140 mmHg or the diastolic blood pressure exceeds 90 mmHg on two occasions [10, 13]. After a preeclamptic pregnancy, women have at least a twofold increased risk of developing any manifestation of CVD. The risk of developing chronic hypertension is particularly elevated, with a four times higher risk compared with women having had a normotensive pregnancy [1, 2]. Furthermore, several meta-analyses showed a 2.0 to 2.5 elevated risk of developing ischemic heart disease [1, 3, 4]. In addition, the risk of future cerebrovascular disease is twice higher [1, 3], and a fourfold increased risk was observed for developing heart failure (HF) [4].

A retrospective cohort study in over 1.6 million pregnancies demonstrated corresponding risks and showed that cardiovascular complications of pregnancies, such as hypertensive disorders of pregnancy, can identify women at young age being at risk for premature CVD [14•]. In the 2.7 years following the pregnancy complicated by preeclampsia women had a 2.5-fold increased risk for myocardial infarction (MI), a 3.0-fold increased risk for HF, and a 2.3-fold increased risk for stroke, compared with women after normotensive pregnancies [14•]. Women with chronic hypertension with superimposed PE had the highest risk for MI, HF, and stroke.

Cardiovascular Risk Prediction

Common risk factors for both CVD and pregnancy complications such as preeclampsia include obesity, chronic hypertension, diabetes mellitus, renal disease, immune diseases, and black race. Hypertension is the most important risk factor for CVD, cerebrovascular disease, and chronic kidney disease.

Several studies recently showed that the inclusion of HDP in any of the most frequently used CVD risk scores does not improve the prediction of future CVD events [15•, 16, 17]. A limitation of these studies however is that these risk prediction models were tested in women aged 50 years or older, when traditional CVD risk factors emerge as well. Stuart et al. analyzed data of women aged 40 years or older, showing that both HDP and parity were independently associated with CVD at ages 40 to 49 years [15•]. However, the addition of HDP to the atherosclerotic cardiovascular disease (ASCVD) risk score did not result in better risk stratification, as traditional cardiovascular risk factors and risk factors for preeclampsia, or HDP in general, widely overlap. Since systolic blood pressure and use of antihypertensive medication are important predictors in these risk models, these factors may explain the lack of effect of adding HDP to the models. Furthermore, women who have hypertension after PE have a twofold increased risk of developing CVD, compared with women who are normotensive after PE [18].

A discussion is currently evolving on whether we should consider PE and severe HDP not as risk factors for CVD, but as first manifestations of a cardiovascular event for which secondary prevention rules are more appropriate. A recent study showed that women after a pregnancy with PE have a twofold higher risk of identifiable coronary artery calcium (CAC) with CT scans at the age of 50 when compared with a reference population [19••]. This means that signs of subclinical atherosclerosis appear at a young age and many years earlier than usual [20]. As hypertension is the first important risk factor emerging after PE or severe HDP, a stricter blood pressure control than current guidelines indicate in HDP-affected patients may be the first important step forward for this high-risk group. As hypertension determines up to half of an individual's CVD risk [21], 38% of cardiovascular mortality in women could be prevented by eliminating this risk factor [22]. Moreover, patients with a CVD event in history without hypertension can benefit from antihypertensive treatment to reduce MI, HF, and cerebrovascular disease [23].

Onset of Hypertension After Preeclampsia

Over the last years, several studies have been done to obtain insight in the onset of hypertension and other CVD risk factors after PE [24, 25]. Other CVD risk factors, such as lipid levels, also show a less favorable profile after PE, but these are often determined when women are still premenopausal and flattered by their still high estrogen levels [26].

The timing to start screening for hypertension is still debated. Various studies showed that approximately 40% of women with early-onset PE had hypertension 10 years after pregnancy [24, 27]. This is in line with a more recent study by Heida et al. [28] that showed a mean age of 43.5 years at onset of chronic hypertension after HDP. A few studies [29–31] showed the strongest risks for development of chronic hypertension in the first 5 years after pregnancy. In one study, 41.5% of women already had hypertension 1 year after severe PE, of

which 17.5% had masked hypertension [32]. These findings highlight the shortcomings of incidental in-office blood pressure measurements and request other ways of measuring blood pressure, such as ambulatory blood pressure monitoring or home blood pressure monitoring.

As hypertension develops 10–15 years earlier in women after PE compared with women after normotensive pregnancies, screening from at least 35 years of age onwards is proposed [26]. Prepregnancy risk factors, such as family history of hypertension, obesity, and elevated blood pressure, are all important in the onset of hypertension and other CVD risk factors after pregnancy [33–35]. In a prospective cohort study, however, Egeland et al. [36] showed that the increased risk of hypertension persisted after adjustment for prepregnancy risk factors.

Enhanced Inflammation After Previous Preeclampsia

During PE, several markers of inflammation (cytokines) are substantially increased in the maternal circulation and the placenta, resulting in chronic systemic and local placental inflammation, which contributes to the complications that occur during PE. The most prominent markers are tumor necrosis factor α (TNF-α), interleukin (IL) 6, and IL-17 [37]. TNF-α signaling results in endothelial cell activation and a reduction in nitric oxide synthase (NOS), leading to endothelial dysfunction that explains all maternal clinical features. The levels of vasoconstrictor endothelin 1 (ET-1) are also increased. In contrast, the levels of IL-10, an anti-inflammatory marker that inhibits the activation of interferon γ (IFN-γ), IL-2, and TNF-α, are decreased in preeclamptic women [38]. This imbalance between proinflammatory and regulatory cytokines during a preeclamptic pregnancy suggests that PE is a state of dysregulated immune activation.

Women with a history of PE have alterations in several miscellaneous markers (TNF-α, IL-6, leptin, adiponectin, homocysteine, SE-selectin, and pregnancy-associated plasma protein-A (PAPP-A)) at 8–10 years after the index pregnancy compared with control subjects [39, 40]. Higher baseline levels of C-reactive protein (CRP), IL-6, and fibrinogen have been observed months to years after delivery in previously preeclamptic women [41]. An increase in the CRP response to vaccination and a consistent pattern of increased acute-phase responses (APRs) to vaccination for all inflammatory markers were also found among women after PE compared with controls, indicating that vascular responses have changed after PE [42]. This effect was independent of the traditional cardiovascular risk factors, which further enforces the concept that a preeclamptic pregnancy may be considered a first vascular event. However, not all women affected by PE seem to have an equally elevated CVD risk. It remains to be elucidated whether women with an elevated proinflammatory state after PE are at the highest risk of developing CVD in the years thereafter.

Signs of Subclinical Atherosclerosis After Preeclampsia

Systemic inflammation accelerates endothelial dysfunction, atherosclerosis, and premature arterial stiffness [43]. Therefore, the enhanced inflammatory state after a preeclamptic pregnancy may induce hypertension and subclinical atherosclerosis. A widely used non-invasive measure to evaluate subclinical atherosclerosis is carotid intima-media thickness (cIMT) [44]. An increased cIMT value is a predictor of coronary artery disease in both pre- and postmenopausal women [45]. Two recent meta-analyses showed that cIMT values are higher in women after preeclampsia compared with those in women experiencing a normotensive pregnancy, both at time of pregnancy and in the first 10 years postpartum [46, 47].

In a review on shared pathophysiological mechanisms, De Jager and colleagues [48] showed that many common determinants are involved in both PE and atherosclerotic plaque erosions. Especially, IL-6 and TNF-α are major contributors to the inflammatory response in these conditions.

The shared inflammatory response in PE and atherosclerotic disease and the elevated cIMT values all suggest that formerly preeclamptic women have an increased risk of having subclinical coronary atherosclerosis at a younger age.

In 2018, the first study was published that compared the prevalence of coronary atherosclerosis using coronary artery calcification (CAC) score in women aged 45 to 55 years [19••]. Thirty percent of formerly preeclamptic women showed signs of CAC around the age of 50 years compared with 18% in the reference group [19••]. However, women with a history of PE also had hypertension more often, which may have contributed to the higher CAC scores. When having an acute coronary syndrome (ACS), nearly all women with a previous preeclampsia had chronic hypertension [49].

Preeclampsia Should Be Considered a First Cardiovascular Event

Since CVD risk prediction models are not suitable to distinguish high-risk women after PE adequately, we have to identify better which women after PE are at highest risk. For those with an enhanced inflammatory state and/or signs of subclinical atherosclerosis, we should seriously consider to apply our secondary prevention guidelines to prevent cardiovascular disease. This implicates that we need a more stratified follow-up program for women after a pregnancy with PE, which may facilitate treatment decisions for elevated blood pressure in a more timely manner than is currently done.

The first step in the follow-up of these women is adequate lifestyle advice and support provided by primary care physicians and dieticians. In addition, exercise training may improve physical condition [50]. Patient awareness of normal levels of CVD risk factors, especially blood pressure levels, is correlated with an increase in physical activity and improvements in diet. However, most women do not know their numbers and are not aware of normal thresholds [51]. Patient empowerment in lifestyle management and knowledge on normal values of the traditional risk factors will improve their awareness and motivation [52]. Self-measurement of blood pressure using eHealth facilities may be helpful to detect elevated blood pressure on time for adequate treatment.

Conclusion

Obstetric history can provide useful information about cardiovascular disease risk in women after their reproductive life, especially if they had a pregnancy complicated by preeclampsia. Evidence suggests that screening for cardiovascular risk factors, such as hypertension, to prevent cardiovascular disease should start soon after pregnancy. Early detection of hypertension could optimize prevention and treatment strategies and mitigate CVD risk. For high-risk women, preeclampsia may be considered a first cardiovascular event that requires secondary prevention guidelines.

Future investigations should focus on optimal screening methods for individual cardiovascular risk among women with preeclamptic pregnancies.

Compliance with Ethical Standards

Conflict of Interest Hella E.C. Muijsers, Nel Roeleveld, Olivier W.H. van der Heijden, and Angela H.E.M. Maas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations *ACC*, American College of Cardiology; *ACS*, acute coronary syndrome; *AHA*, American Heart Association; *APRs*, acute-phase responses; *ASCVD*, atherosclerotic cardiovascular disease; *CAC*, coronary artery calcium; *CIMT*, carotid intima-media thickness; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *ESC*, European Society of Cardiology; *HDP*, hypertensive disorders of pregnancy; *HF*, heart failure; *IFN-γ*, interferon γ; *IL*, interleukin; *ISSHP*, International Society for the Study of Hypertension; *MI*, myocardial infarction; *NOS*, nitric oxide synthase; *PE*, preeclampsia; *TNF-α*, tumor necrosis factor α

Search Strategy We searched PubMed with the following terms: "preeclampsia," "pre-eclampsia," "cardiovascular disease," and "cardiovascular disease risk factors." We focused on research published in the last 5 years, but made an exception for older key publications.

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14.• Arnaout R, Nah G, Marcus G, Tseng Z, Foster E, Harris IS, et al. Pregnancy complications and premature cardiovascular events among 1.6 million California pregnancies. Open Heart. 2019;6(1): e000927. https://doi.org/10.1136/openhrt-2018-000927 **Arnaout et al. demonstrated in a retrospective cohort study in over 1.6 million women that HDP can predict future myocardial infarction, heart failure, and stroke. The authors showed that hypertensive disorders of pregnancy were associated with a 1.4-fold to 7.6-fold higher risk of MI, HF, and stroke. These findings support the close monitoring of women with HDP for the prevention of CVD events.**

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