Seminars in Perinatology 39 (2015) 276–283

Available online at www.sciencedirect.com

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Preeclampsia and future cardiovascular disease in women: How good are the data and how can we manage our patients?

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ARTICLE INFO

Keywords:
preeclampsia
hypertension
pregnancy
cardiovascular disease
women's health

ABSTRACT

Women with a history of preeclampsia have double the risk of future heart disease and stroke, and elevated risks of hypertension and diabetes. The American Heart Association (AHA) and the American College of Obstetrics and Gynecology now include preeclampsia as a risk factor for future cardiovascular disease (CVD) with the recommendation of obtaining a history of preeclampsia and improving lifestyle behaviors for women with such a history. Research has progressed from asking *whether* preeclampsia is associated with CVD to *how* preeclampsia is associated with CVD, and the implications for prevention of CVD among women with a history of preeclampsia. A history of preeclampsia "unmasks" future CVD risk; research is inconclusive whether it also causes vascular damage that leads to CVD. For women with prior preeclampsia, the AHA recommends CVD risk reduction actions similar to those for other "at risk" groups: cessation of cigarette smoking, physical activity, weight reduction if overweight or obese and counseling to follow a "DASH" like diet. The efficacy of these lifestyle modifications to lower risk of CVD in women with prior preeclampsia remains to be determined. Barriers exist to implementing lifestyle improvement measures in this population, including lack of awareness of both patients and clinicians of this link between preeclampsia and CVD. We review patient, provider, and systems level barriers and solutions to leverage this information to prevent CVD among women with a history of preeclampsia.

Introduction

For decades, it had been postulated that women with a history of prior preeclampsia were at elevated risk of future hypertension, coronary heart disease (CHD), and stroke.[1] However, it is only in the past several years that the association of preeclampsia with cardiovascular disease (CVD) has received concerted attention from researchers and clinicians. Now, meta-analyses including more than 40 studies have consistently demonstrated that women with

This work was funded in part by a grant, CER-1306-02603, from the Patient Centered Outcomes Research Institute (PCORI), Washington, DC, USA to the authors.

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http://dx.doi.org/10.1053/j.semperi.2015.05.006
0146-0005/

prior preeclampsia are at increased risk for CVD.[2–4] The strength and magnitude of these data have led to the American Heart Association (AHA) recommendation that a history of preeclampsia be considered a major risk for CHD and cerebrovascular disease.[1] These guidelines recommend that clinicians obtain a pregnancy history for preeclampsia in all women to assess risk for CVD.[5,6] However, many questions remain unanswered. These include an understanding of the pathophysiologic mechanism(s) mediating the link between preeclampsia and future CVD and evidence-based recommendations to optimize the clinical management of women with a history of preeclampsia.

Prior preeclampsia and cardiovascular events

The association of preeclampsia with future CVD events has been reported in dozens of case–control and cohort studies. There have been three meta-analyses of this body of work.[2–4] The most recent, published in 2013, reports relative risks pooled from 43 studies of 2.28 (95% confidence interval: 1.87–2.78) for CHD and 1.76 (1.43–2.21) for cerebrovascular disease, comparing women with a history of preeclampsia or eclampsia to women with normotensive pregnancies.[4] The literature is notable for its consistency, with near unanimity across studies in detecting elevated risks of CVD among women with a history of preeclampsia. In the larger studies (including more than 200 cases), relative risks associated with prior preeclampsia for CHD disease range from 1.4 to 5.5 and for stroke from 1.2 to 2.4.[4] When population differences are considered, similar estimates are derived from case–control studies and cohort studies and from higher-quality compared with lower-quality studies.[2–4]

An area of disagreement relates to the strength of the association of future CVD with preterm preeclampsia compared to term preeclampsia. We are aware of five cohort studies that have presented relative risks for the association of preterm preeclampsia with CVD.[7–11] The recent meta-analysis by Brown et al.[4] obtained data from three of these studies to directly compare the risks of CHD for preterm preeclampsia compared to term preeclampsia. They concluded that prematurity itself does not confer excess CHD risk in the context of preeclampsia (pooled relative risk 1.32) (95% CI: 0.79–2.22). However, this analysis omitted two large studies that reported particularly high CVD risks among women with a history of preterm preeclampsia. In the California Health and Development Study, women with prior preterm (<34 weeks) preeclampsia had a 9.5-fold increased risk of CVD death compared to women with normotensive pregnancies (in contrast to a 2.1-fold risk when all preeclampsia was compared to normotensive pregnancy). In a Norwegian study, the rate ratio for CVD death associated with preterm preeclampsia (<37 weeks) compared to normotensive pregnancy was 3.7 (compared to a 1.6 times higher risk among women with prior preeclampsia at term compared to women with normotensive pregnancy history).[11] The American College of Obstetricians and Gynecologists (ACOG) recommendations for enhanced CVD risk screening, discussed below, are applied only to women with preterm or recurrent preeclampsia.[12] Thus, more data are needed to determine the extent to which preterm and term preeclampsia vary in their prediction of future CVD risk.

Another emerging question is the extent to which *recurrent* preeclampsia is associated with high CVD risk. Preeclampsia often occurs only in first pregnancies. The recurrence risk of preeclampsia is relatively low, with preeclampsia arising in only 15% of second pregnancies following a first pregnancy complicated by preeclampsia.[13] Fewer than 1% of parous women experience preeclampsia twice; however, those who do, appear to be at especially high risk of CVD. In a registry-based cohort study from Denmark, multiparous women had a 1.3 (95% confidence interval: 1.1–1.5) increased risk of future CHD if their first pregnancy was preeclamptic, and a 2.8 (2.3–3.4) increased risk after two pregnancies complicated by preeclampsia when compared to multiparas without hypertensive disease. The equivalent relative risks for stroke were 1.2 (1.1–1.4) and 1.5 (1.2–1.9).[7] In a study using the Norwegian National Birth and Death Registries, the differences in CVD risk among women with non-recurrent and recurrent preeclampsia were more subtle. Multiparous women with preeclampsia in only their first pregnancy had a relative risk of CVD mortality of 1.5 (1.2–1.9), while women with two preeclamptic pregnancies had a relative risk of 2.0 (1.2–3.3) when compared to multiparas with normotensive pregnancies.[11] This study also pointed out that women whose last pregnancy was preeclamptic had especially high CVD mortality; perhaps the high risk borne by women who "stop" their reproductive careers after a preeclamptic pregnancy is a marker of a preeclampsia episode severe enough to discourage or contraindicate future pregnancies.

Prior preeclampsia and cardiovascular risk factors

Hypertension is a major risk factor for both CHD and stroke. The most recent meta-analysis estimates that women with a history of preeclampsia are three times more likely to develop chronic hypertension than women with normotensive pregnancies [pooled relative risk 3.1 (2.5–3.9)].[4] With recurrent preeclampsia, there appears to be a sixfold higher risk of hypertension.[7] This increased relative risk of hypertension is strongest within the 5 years after pregnancy, although the magnitude of the absolute excess risk persists and grows over decades. In the U.S. Nurses' Health Study II, in the four decades after first birth, there were 146 excess cases of hypertension per 1000 women whose first birth had been complicated by preeclampsia.[14] Notably, women who develop preeclampsia tend to have slightly higher blood pressures before the pregnancy,[15] indicating that preeclampsia may reveal a subclinical trajectory toward hypertension that started before the pregnancy.

Women with a history of preeclampsia may also bear higher risks of diabetes mellitus. In a Danish registry-based cohort study, women with prior preeclampsia were more than three times likely to develop subsequent diabetes mellitus, compared to women with normotensive pregnancies.[7] A study based on the Ontario Diabetes Database reported a doubling of later diabetes risk for women with a history of preeclampsia followed for a median 8.5 years after delivery.[16] Given the registry-based study designs, no