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Literature Overview of Association Between Preeclampsia and Cardiovascular Risk

ABSTRACT

Around 5%-10% of fetal pregnancies impacting maternal and neonatal outcomes have been affected by hypertensive disorders of pregnancy. As a cardiovascular risk factor, pre-eclampsia is now really recognized for women throughout the world. Pre-eclampsia is one hypertensive disorder in pregnancy. It imposes far-reaching influences on women and poses a great threat to life as well, no matter mother or child. Around 2% to 8% of pregnancies worldwide are affected by it. It also gives rise to marked maternal and perinatal morbidity and mortality. The occurrence of cardiovascular diseases is the most severe complication observed in preeclamptic women. As clearly revealed by the newest evidence, remarkable association exists between cardiovascular disease and pre-eclampsia. The aim of our review is to highlight the correlation between pre-eclampsia and the possibility of cardiovascular disease. Moreover, it still cannot establish a clear dependency mechanism between pre-eclampsia and cardiovascular disease for their multifactorial nature.

Keywords: Cardiovascular risk, gestational hypertension, gestational physiology, heart rate, preeclampsia

INTRODUCTION

Pre-eclampsia (PE) is one of the most crucial problems in obstetrics; it affects 2%-8% of pregnancies worldwide in accordance with the World Health Organization (WHO).[1] It is a principal cause for maternal morbidity and mortality across the planet.

Pre-eclampsia affects multiple organ systems and is a complex disease process originating at the maternal–fetal interface.[2,3] Pre-eclampsia, characteristic signs of proteinuria and hypertension, usually presents after 20 weeks' gestation. Clinical symptoms include blurred vision, nausea, epigastric pain, headache, and vomiting. Laboratory investigations show elevated serum creatinine, thrombocytopenia, and abnormal liver function tests, especially heightened liver enzymes.[4] Pre-eclampsia is defined as an onset of hypertension after 20 weeks gestation (diastolic blood pressure higher than 90 mm Hg on 2 occasions that are 4-6 hours apart or systolic blood pressure higher than 140 mm Hg).[5] Notwithstanding the fact that the women will resolve the proteinuria and hypertension after pregnancy, women who develop PE are at increased risk of vascular diseases. Enough evidence proved that women who develop PE are at heightened risk of other vascular diseases. The American Heart Association has given rise to PE being recognized as a female-specific, cardiovascular risk factor.[6]

Pregnancy is called a maternal stress test. Meanwhile, in a woman's susceptibility to future cardiovascular diseases (CVDs), the development of obstetric complications conducts a potential role. Cardiovascular diseases and the etiologic pathways of pregnancy complications might also be linked.[7] The current guidelines elevated the significance of these associations; a pregnancy history has been recommended as a part of the routine evaluation of cardiovascular risk.[8,9]

Our review is intended to probe deep into the correlation between PE and the possibility of CVD in pregnant woman.

REVIEW

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PRE-ECLAMPSIA

Pre-eclampsia is a pregnancy-specific disease. Pre-eclampsia is defined as new-onset end-organ damage and new-onset hypertension after 20 weeks' gestation. The complex process pathophysiology exerts profound imposes far-reaching influences on multiple organ systems (Table 1).

Abnormal trophoblast invasion is the feature of PE's clinical syndrome, long before clinical manifestations become apparent.[2] It even appears before women know they are pregnant.[10] In normal implantation, the decidualized endometrium is invaded by trophoblasts, resulting in obliteration of the tunica media of myometrial spiral arteries and spiral artery remodeling.[11] Nevertheless, in PE, spiral artery remodeling and trophoblast invasion are impaired. An augment in angiogenic markers will be created by the resultant placental ischemia, such as soluble endoglin (sEng) and soluble fms-like tyrosine kinase-1 (sFlt-1).[12] Soluble fms-like tyrosine kinase-1 can bind to placental growth factor and vascular endothelial growth factor (VEGF) and then decreases their levels.[13] These factors mediate downstream which can impose a marked impact on a vasoconstrictive state, microemboli, oxidative stress and create endothelial dysfunction. As a consequence, the clinical features of PE will be affected.[14]

Not only endothelial dysfunction but also immunologic aberrations contribute to PE. T helper cells can be conducive to neutralizing placental reactive oxygen species, angiotensin II type 1 receptor (AT1R) auto-antibodies, proinflammatory cytokines, and endothelin-1 by shifting toward the anti-inflammatory Th2 phenotype in normal pregnancy. But, in PE, T helper cells shift toward the Th1 phenotype in contrast, giving rise to apoptosis and reduced trophoblast invasion by increasing the release of proinflammatory cytokines, such as IL-18 and IL-12, decreasing IL-10.[15] Additional augment in sFlt-1 and complement system dysregulation are designed by elevated complement levels in PE. Women with PE also suggestive of immune imbalance for lessening histocompatibility complex human leukocyte antigen-E and -G.[15]

UNDERLYING GENETICS

Nowadays, a major impact had been made on clinical practices by advances in genetic technology.[16] Exome sequencing and clinical genome, as crucial tools conduct a paramount role in the individualized medicine and implementation of prognostic.[17] There is an increasing body of research searching for relation between genetics and PE.[18] During a study in 2004, Swedish families with PE and gestational hypertension were examined. Compared with half-sisters, full sisters and mothers–daughters shared more similarities regarding gestational hypertension and PE. As persuasively revealed by the conclusion drawn from this research, there was gestational hypertension in 20%, heritability PE in 31%, and pregnancy-induced hypertension in 28% of cases.[19]

Compared with fathers who themselves were born from a pregnancy complicated by PE, and fathers who previously conceived a pregnancy complicated by PE with another partner, the incidence of PE is higher in mothers who were born from pregnancies complicated by PE.[20] Johnson et al[21] examined the genetic dissection locus on chromosome 2q22, single nucleotide polymorphisms (SNPs). Their lab identified PE to be remarkably associated with 4 independent SNPs. Apart from that, these SNPs were similar with several quantitative CVD-related traits, which indicates that the underlying genetic mechanisms are shared in these 2 diseases.[21]

Table 1. Diagnostic Criteria for Preeclampsia

Always necessary
Hypertension
• SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg on 2 occasions at least 4 h apart after 20 weeks' gestation in a woman with previously normal BP
• SBP ≥ 160 mm Hg or DBP ≥ 110 mm Hg on 1 occasion
And one of the following
Proteinuria
• ≥300 mg per 24 h urine collection (or extrapolated from timed collection), or
• Protein/creatinine ratio of ≥ 0.3 mg/dL, or
• Dipstick reading of 2 + (used only when other methods are not available)
OR any one of the following (in the absence of proteinuria)
Thrombocytopenia
• Platelet count < 100 000/mm^3
Renal insufficiency
• Serum creatinine concentration > 1.1 mg/dL or a doubling of serum creatinine concentration in the absence of other renal disease
Impaired liver function
• Elevated concentration of liver transaminases to 2×normal
• Severe persistent right upper quadrant or epigastric pain unresponsive to medication
Pulmonary edema
• Diagnosed by physical examination or chest x-ray
Neurological signs
• New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms
• Visual disturbances
Fetal growth restriction
• Estimated fetal weight < 10th percentile

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

HIGHLIGHTS

- We need to concentrate on disease prevention by a yet population-specific and holistic approach to eventually yield measurable data.
- As forcefully demonstrated by the newest evidence, striking correlation exists between cardiovascular disease (CVD) and pre-eclampsia (PE).
- The evidence distinctly reveals that PE is a significant risk factor for future CVD, and the challenge will influence future maternal, as well as offspring.

A study performed in Australia also found a correlation between CVD risk factors and SNPs, such as glucose levels, blood triglycerides, and body weight.[22] In the future, we may eliminate such SNPs using genetic engineering techniques by turning off their expression. Yu et al[23] found that the lessened postnatal vasculogenesis was associated with the upregulation of miR-146a expression in human umbilical vein endothelial cells (HUVECs). During the first 3 months of life, the miR-146a levels may also be a desirable predictor of microvascular development.[23]

The majority of the tested polymorphisms and genes are directly associated with the alterations underlying both CVDs and PE, which were observed in the pathological processes. How to identify the common transcriptomic signatures involved in CVDs and PE was one of the most significant studies of this kind.[24] A novel, bioinformatic meta-analysis by Sitras et al[24] included investigating placental tissue samples from preeclamptic women and gene expression profiles from cardiovascular patient blood samples. It found that 925 and 181 genes differentially expressed in PE and CVD and 22 genes severally were common for both disorders. Numerous factors were found to participate in the complex pathogenesis of both the diseases, such as chemokines, inflammation-mediated cytokines, interleukin signaling, oxidative stress, and B-cell activation.[25-29]

As a peroxisomal enzyme physiologically, ACOX2 is bound up with one of the stages in the degradation of bile acid and branched-chain fatty acids. Bile acid and fatty acid will be accumulated by subsequent ACOX2 deficiency and downregulation of its gene.[30] During the study conducted by Johansson et al[31] they found that ACOX2 level was inversely correlated with triglyceride levels. The theory of heightened circulating triglyceride levels associated with the downregulated ACOX2 was suggested.[31] Endothelial dysfunction and elevated oxidative stress are associated with an abnormal lipid profile.[32] Aside from that, high triglyceride levels, as well-known CVD risk factors, were proven to be elevated together with total serum free fatty acid level in preeclamptic patients. Hence, ACOX2 may be a possible genetic risk factor between PE and related CVDs.[33-36]

An enzyme involved inter which called microsomal EPHX1 plays a paramount role in regulation of the oxidation status of xenobiotic-derived intermediates.[37] Just illustrated by a study in vitro assessing the influence of EPHX1 on embryo development in coculture, EPHX1 conducts a protective role against oxidative stress.[38] What is more, EPHX1 is probable altered variants of the enzyme to disrupt its proper function, then influencing the development of CVDs and PE by epoxide-related cytotoxic damage and oxidative stress-mediated. An enzyme, another remarkable polymorphism concerns, eNOS can take part in nitric oxide (NO) synthesis in the vascular endothelium. Nitric oxide is implicated inter alia in regulating myocardial contractility, vascular tone and inhibiting platelet aggregation as a crucial relaxing factor.[39] The altered expression of eNOS results in NO synthesis defects which possibly spawned from gene polymorphism. Apart from that, hyperlipidemia, hypertension, and metabolic insulin resistance were found in eNOS-deficient mice.[40] Among what was previously described, it seems plausible that eNOS genetic variants may be relevant to the disease outcome.

PRE-ECLAMPSIA AND CARDIOVASCULAR RISK

The association between future maternal CVDs, even offspring, PE has been shown by several studies.[41-44]

PRE-ECLAMPSIA AND MATERNAL CARDIOVASCULAR RISK

A myriad of studies has proved the relation between PE and maternal cardiovascular risk. During recent metaanalysis, after adjusting for potential confounders, such as body mass index, age, and diabetes mellitus, PE was still correlated with an elevated risk of stroke (RR: 1.18; 95% CI: 0.95-1.46), death on account of coronary artery disease (RR: 2.10; 95% CI: 1.25-3.51), death of CVD (RR: 2.21; 95% CI: 1.83-2.66), heart failure (RR: 1.6, 95% CI: 0.73-3.5), more than 10 years after affecting by PE. During the first decade after PE, the risk for CVD-related death, stroke, and heart failure increase even higher.[44]

Risk factors are shared by PE and CVDs except for age and pregnancy-specific factors. But a direct causative correlation was not determined between them. In the study by Kestenbaum et al[44], among women with previous severe PE, a higher number of thromboembolic events (hazard ratio (HR): 2.3; 95% CI: 1.3-4.2) and more than a 3-fold increment in cardiovascular events (stroke, percutaneous coronary artery interventions, or hospitalizations as a result of myocardial infarction (MI) were shown during a mean follow-up of approximately 8 years.[45] The British CALIBER (Cardiovascular Research using Linked Bespoke Studies and Electronic Health Records) reported in the first 9 years after a delivery complicated by PE overall first-time cardiovascular event incidence of 2.77%, while in women after an uncomplicated pregnancy, the rate is 1.4% in contrast.[46] Furthermore, a median 13-year follow-up from a Norwegian population-based cohort study, CVD-related death in women with a history of PE during pregnancy was augmented, such as, disease of the pulmonary circulation, coronary artery disease, or other diseases affecting the heart (RR: 1.65; 95% CI: 1.01-2.70), but compared to women with a history of uncomplicated pregnancy, the risk of CVD-related death was markedly higher (RR: 8.12; 95% CI: 4.31-15.33).[47]

Aside from that, an increasing amount of evidence reported among women with recurrent PE a higher frequency of cerebrovascular disease (HR: 3.0; 95% CI: 1.70-4.61) and heart failure (HR: 4.2; 95% CI: 2.9-6.1) compared to women with unaffected pregnancy.[48]

PRE-ECLAMPSIA AND CARDIOVASCULAR RISK OF THE OFFSPRING

A heightening amount of evidence revealed that children may have long-term cardiovascular sequelae after in utero exposure to PE.[49] Pre-eclampsia has 2 manifestations, fetal and maternal, which had been proposed before (Figure 1).

As mentioned above, mothers following preeclamptic pregnancies may have long-term cardiovascular sequelae.

In 1993, the Barker hypothesis that children may also appear to suffer this risk after in utero exposure was proposed.[50] During a systematic review by Davis et al[51] in children and youngsters born to preeclamptic mothers, there is a 1.35 mm Hg rise in diastolic blood pressure (DBP) and a 2.39 mm Hg increment in systolic blood pressure (SBP). Andraweera and Lassi[52] performed a meta-analysis, where the offspring of preeclamptic mothers compared to offspring of non-preeclamptic mothers showed higher mean values of both DBP and SBP, with a 4.06 mm Hg and 5.17 mm Hg increase separately.[52] These findings confirm children born to preeclamptic mothers have a noticeable increment in mean blood pressure. A 2.4 mm Hg rise in SBP is correlated with augmented mortality from stroke by 12% and from ischemic heart disease by 8%.

Defects in the pulmonary and systemic circulation of the offspring were stemmed from PE with vasculotoxic factors that cross the placenta. It can lead to exaggerated hypoxic pulmonary hypertension, and then premature CVD may occur in the systemic circulation later in life.[53] In previous British studies, a comprehensive study of maternal–offspring pairs included 4654 children and their 3537 mothers. This research demonstrated the association between PE and gestational hypertension and higher blood pressure in offspring. Nevertheless, the study did not confirm any established associations.[54]

Researchers from Israel studied long-term cardiovascular effects in offspring in a cohort of 231 298 deliveries, including 0.9% pregnancies complicated by severe PE and 3.2% by mild PE. In this exploration, CVDs included pulmonary heart disease (n=32), cardiomyopathy (n=38), arrhythmias (n=303), hypertension (n=153), and others (n=559). A linear correlation between CVD and PE was observed, and the risk increases with the severity of PE. This research demonstrated an association between PE and heart failure or arrhythmias. Furthermore, severe PE as an independent risk factor was found for long-term cardiovascular morbidity in term-born children.[55]

Congenital heart disease (CHD) is not only the major reason of infant mortality and morbidity but also the most ubiquitous birth defect. A study that was performed in Nigeria examined the possible connection between PE and CHD. It exhibited CHD in 3.3% of newborns from healthy mothers and in 21.2% of newborns from women with PE in contrast by the end of the 4th week of life.[56]

CONCLUSION

Nowadays, most current studies about the association between PE and cardiovascular risk are concentrated on common risk factors and clinical similarities. Nonetheless, the basis of pre-pregnancy factors may be influenced the possibility that augmented risk for both disorders, genetic aspects should be the main aspect in the future.[57]

In the future, it is essential for us to continuously conduct in-depth exploration on the basis of larger study populations and understand the pathogenesis of complex PE and PE-related CVDs by follow-ups. Apart from that, it is essential to dedicate to clearly defined ethnic populations-specific gene. It is imperative for us to concentrate on disease prevention by a yet population-specific and holistic approach to eventually yield measurable data.

From the literature overview, the evidence distinctly illustrates that PE is a significant risk factor for future CVD, and the challenge will influence future maternal, as well as offspring. Over time, more evidence may become available, and guidelines need to be introduced and developed into clinical practice, which can manage and recognize PE and the possible subsequent CVD events. It has been a pivotal public health issue in the identification of CVD risk factors early. Our review supports shared risk factors for CVD and PE, especially long-term maternal CVDs risk is strongly associated with PE.

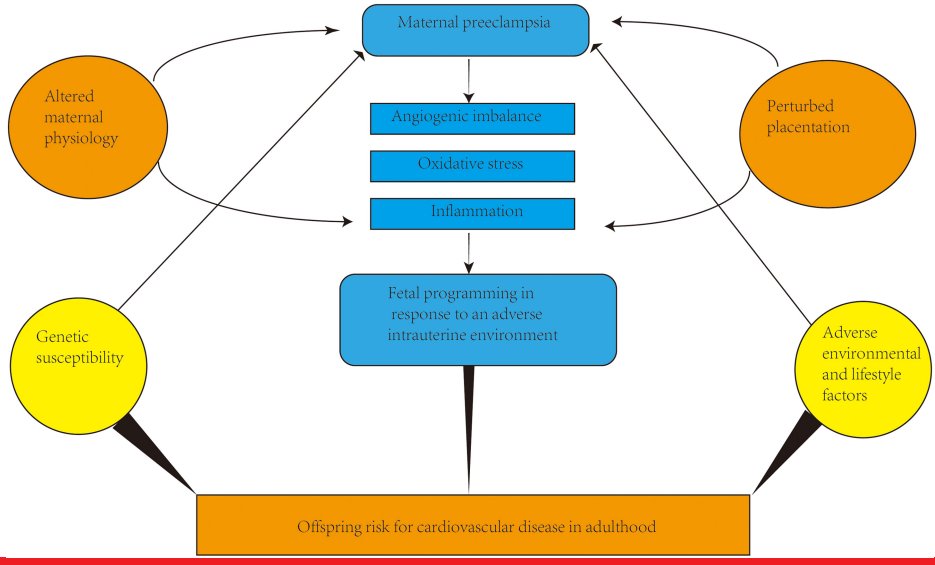

Figure 1. Potential mechanistic link between exposure to PE in utero and offspring risk for CVD. CVD cardiovascular disease; PE, pre-eclampsia.

On account of its multifactorial nature, it is still difficult to establish a clear causal mechanism between CVD and PE. Though the role of epigenetics and genetics has been proved, it is still impossible to determine the type and severity of inherited susceptibility to the disease. As a consequence, both the standards of treatment and the screening tests model must be determined to develop effective preventive strategies for the risk of CVDs.

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