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Preeclampsia as a risk factor of the cardiovascular complications development

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Abstract**Introduction:**

The term “preeclampsia” (PE) refers to a multisystem disorder occurring after 20 weeks of pregnancy; it includes a new onset of hypertension and proteinuria and affects from 2 to 8% of all pregnancies. Cardiovascular disease (CVD) is a group of pathologies, which present significant mortality rate all over the world. The literature implicates that both disorders are linked in a sense of further cardiovascular complications in women who had preeclamptic pregnancy.

Purpose:

Evaluation of the relationship between pre-eclampsia and the risk of future potential maternal cardiovascular complications and proposal of the possible causes of this association.

Materials and methods:

We performed the database research using Pubmed, Springer Link and ResearchGate and we made review and meta-analysis of relevant studies. We searched for studies analyzing the relationship between preeclampsia and future maternal cardiovascular risk.

Results:

Systematic reviews and cohort studies qualified for the purpose of this review showed the relationship between preeclampsia and future cardiovascular diseases in mothers. The possible explanations include endothelium dysfunction enduring after delivery and the co-existence of common risk factors for both diseases.

Conclusions:

Preeclampsia is a risk factor predisposing to cardiovascular diseases and may lead to cardiac complications later in life. The course of pregnancies is very important for the future maternal health.

Key words: preeclampsia; pregnancy; hypertension; cardiovascular disease

Introduction:

Cardiovascular disease (CVD) encompasses many pathologies such as stroke, coronary artery diseases, peripheral arterial disease, heart failure, cerebrovascular disease, rheumatic heart diseases, venous thromboembolism, cardiomyopathy, congenital heart disease and others. CVD is a range of pathologies being the main cause of death worldwide; it is known to cause about 17.9 million deaths each year around the world and accounts for 31% of all deaths. It is also the primary cause of death among females globally. The number of risk factors predisposing to CVD is great. They involve both modifiable (physical inactivity, unhealthy diet, tobacco smoking, obesity thus hyperlipidemia and hypertension) and non-modifiable factors, such as family history, gender, age, genetic predisposition, diabetes mellitus, low socioeconomic status. They also include some sex-specific factors, for instance hormonal changes or disorders related to pregnancy, as there are differences in clinical presentation of CVD and therapy response between gender¹. Studies showed that the main CVD precursor is atherosclerosis. A very important factor of CVD risk is hypertension. Women can be affected by high blood pressure during pregnancy – there are four hypertensive disorders that can be recognized during pregnancy – preeclampsia, eclampsia, chronic hypertension and gestational hypertension. According to the World Health Organization, hypertensive disorders during pregnancy contribute to one-tenth of female deaths in Asia and Africa and to nearly one-quarter in Latin America. Nowadays, the mortality of preeclampsia still remains high, causing preeclampsia to be one of the major death causes among pregnant women.

Pre-eclampsia is a disorder of pregnancy, that most often begins after 20 weeks of gestation. However, it can occur also postpartum. Preeclampsia is characterized by an onset of hypertension ($\geq 140/90$ mm Hg) and significant proteinuria (loss of ≥ 300 mg of protein per day). There can be other manifestations occurring, as preeclampsia affects other organs. In case there is no onset of proteinuria, a condition is classified as preeclampsia if hypertension during pregnancy coexists with thrombocytopenia (hematological disorder), high levels of creatinine (renal dysfunction), increased activity of liver enzymes (hepatic damage) and hyperlipidemia. Alternative disorders may include complications in the central nervous system (CNS; blurred vision or headaches) or symptoms such as epigastric pain and pulmonary edema. The cause of preeclampsia is unknown, however many mechanisms are suggested. For a successful delivery, many physiological changes of the uterus are needed, some of them involve alterations in uterine vasculature to supply nutrients and oxygen to the fetus. In normal pregnancy, uterine spiral arteries undergo remodeling, thanks to the invasion of the trophoblast into the placental bed. Transformation includes loss of musculoelastic layers of arteries' walls, so spiral arteries become dilated vessels of low resistance that are less responsive to vasoconstrictors. This results in the increase of blood flow and enables fetus to receive enough oxygen and nutrients. Previously, preeclampsia was associated with impaired invasion of trophoblast, which results in the incomplete remodeling of spiral arteries, reduced perfusion of the placenta and placental ischemia. Nowadays, it is known that hypoxia of the placenta cannot be the only trigger to preeclampsia as the disorder can happen postpartum, when the placenta is absent, so pathogenesis of the disorder seems to be complex. Other suggested mechanisms involve oxidative stress, that contribute to the maternal release of proinflammatory cytokines, free radicals, oxidized lipids and other substances, leading to systemic endothelial dysfunction, vasoconstriction, and hypertension. The only remedy for placental preeclampsia is delivery. However, as preeclampsia is a multi-system disorder, clinical symptoms may disappear after delivery, but there is a risk of further complications persisting postpartum.

Purpose: Evaluation of the relationship between preeclampsia and the risk of future potential maternal cardiovascular complications on the basis of the available literature.

Materials and methods:

We performed the database research using Pubmed, Springer Link and ResearchGate and we made review and meta-analysis of relevant studies. We searched for studies analyzing the relationship between preeclampsia and future maternal cardiovascular risk.

Results:

The link between preeclampsia (generally hypertension during pregnancy) and CVD risk has been assessed in many studies. One of them, conducted in Taiwan, compared the risk of MACEs (major adverse cardiovascular events) and incidence of preeclampsia and eclampsia. The large cohort study reported that women suffering from preeclampsia or eclampsia were at greater risk of MACEs incidence (a 12.6-fold higher risk) and were more likely to die because of MACE-related deaths (the risk was 2.3-fold higher), compared to women who did not have preeclampsia or eclampsia during pregnancy².

Another cohort study in UK showed that toxemia in pregnancy (preeclampsia) increased the risk of vascular problems later in life, such as angina pectoris, chronic ischemic heart disease or venous thromboembolism³. Also, the correlation between preeclampsia and further cardiovascular complications was confirmed in a study conducted by Bellamy including > 3 million women. It displayed that the risk of stroke, ischemic heart disease, venous thromboembolism and cardiovascular-related death was higher for women with history of preeclampsia⁴. The risk of subsequent cardiovascular events in women suffering from hypertensive disorders during pregnancy is high in lot of reviews. The odds were doubled when compared to women not affected by PE. Hypertensive disorders such as preeclampsia and eclampsia were related to the risk of cardiac disease according to the severity of the condition (for mild: RR, 2.00; 95% CI, 1.83–2.19; for moderate: RR, 2.99;95% CI, 2.51–3.58 and for severe: RR, 5.36; 95% CI, 3.96–7.27, $P<.0001$)⁵. The risk of cardiac disease was elevated for women with preeclampsia of an early-onset, preeclampsia that required preterm delivery or women with recurrent PE. The risk was from 4 to 8 times higher comparing to normotensive pregnancies⁵. The calcium scoring with multislice CT of the coronary artery showed that the frequency of coronary artery calcium score was increased by 17% in preeclamptic women, comparing to the general population. The coronary artery calcium score of 95th percentile or higher was assumed for the general population of age 45 to 55 years. Preeclamptic events can accelerate atherosclerosis of coronary artery, as 47% of women with a history of PE had atherosclerotic plaques and 4% suffered from stenosis of this artery⁶. The age of women with pregnancies complicated by preeclampsia, HELLP syndrome, or placental abruption was lower at the onset of stroke comparing to the age of stroke patients with a history of normotensive pregnancies⁶.

Discussion:

The precise cause of preeclampsia is complex and unknown – many pathomechanisms are proposed, such as incomplete remodeling of spiral arteries and oxidative stress. However, numerous risk factors for preeclampsia are known – such as preexisting diseases (chronic hypertension, antiphospholipid syndrome, diabetes mellitus, chronic kidney diseases), history of preeclampsia, obesity, multiple pregnancy and mental stress.

As we know, preeclampsia shares some of the predisposing factors with cardiovascular disease – they include hypertension, diabetes mellitus, and body mass index. A predominant feature of all these conditions, usually with systemic inflammation, is endothelial dysfunction, which characterizes preeclampsia and obesity as well. As preeclampsia is a multi-system disorder, clinical symptoms may disappear after delivery, but there is a risk of further complications persisting postpartum, including endothelial disorder. Obesity is often related

to endothelial dysfunction and can be associated with some comorbidities, such as hypertension, insulin resistance or dyslipidemia⁷. Any aberration in serum lipids or hypercholesterolemia can induce endothelial dysfunction, which, in turn, can develop into atherosclerosis⁸. Also, hypertension can be a risk factor of atherosclerosis⁹, which is considered as a major CVD trigger. Similarly for preeclampsia - high blood pressure before pregnancy and improper levels of serum lipids (triglycerides, cholesterol and LDL) are factors predisposing to preeclampsia¹⁰. High body mass index before pregnancy is significantly correlated with pressure of the blood, so the risk of pregnancy hypertensive disorders is increased by the pre-pregnancy obesity, as study conducted by Gaillard R et al.¹¹ showed. Also, women with diabetes (both pre-gestational and gestational) are more likely to suffer from preeclampsia¹². The common risk factors of PE and CVD are included in metabolic syndrome – a group of conditions including obesity, hypertension, dyslipidemia and sometimes insulin resistance that increase the risk of atherosclerosis, type 2 diabetes mellitus and their cardiovascular complications. The relationship between metabolic syndrome and any placental dysfunction (manifested mostly as hypertensive disorders in pregnancy) was assessed by Ray et al.¹⁰. A large cohort of women was studied and it was stated that the risk of any placental dysfunction is greater for those who suffered from any component of the metabolic syndrome before the pregnancy¹⁰.

Interestingly, the size of cardiac chambers during pregnancy increases and then decreases after giving birth, as echocardiographic studies demonstrated. In preeclampsia, the afterload and cardiac output are elevated and thus myocardial remodeling do not occur quickly and can persist for a long-term. A study performed by Ray et al.¹⁰ demonstrated increased rates of heart failure and dysrhythmias. Persisting myocardial abnormality can predispose to cardiovascular and cerebrovascular conditions later in life, as study from Finland¹³ has shown. Thus, a high risk for future hypertension persisting after hypertensive disorders of pregnancy such as PE can be explained by prepregnancy risk factors.

Conclusions:

To conclude, many studies showed the evidence relationship between hypertension in pregnancy and cardiovascular complications later in life. Preeclampsia was identified as a risk factor predisposing to cardiovascular disease. Both conditions – preeclampsia and cardiovascular disease share risk factors, including high blood pressure, obesity and diabetes mellitus. These states, in turn, have a common feature which is the endothelium dysfunction. It plays a key role in atherosclerosis development, vasoconstriction and hypertension. The possible cardiovascular risks for women affected by preeclampsia are rather long term, thus preeclampsia should be taken into consideration during assessment of CVD risk. As women with history of preeclampsia are predisposed to heart and blood vessels diseases, they should be aware of the risk. Preventive strategies to manage predisposing factors properly should be undertaken, for instance healthy diet, control of body mass index, smoking cessation. Also, health care providers should be aware of the potential subsequent cardiac disease complications.

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