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Preeclampsia – long-term effects on mother and child

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Abstract

Preeclampsia (PE) is a pregnancy complication that affects 5% to 8% of all pregnancies. It is a leading cause of maternal mortality that contributes annually more than 60,000 maternal deaths all over the world. Data submitted so far by clinicians are still insufficient to completely understand the disease. Despite many researches, the prediction of patients suffering from PE remains difficult. Moreover therapeutic methods are also limited and concentrated on symptomatic treatment and early termination of pregnancy. The aim of the presented article is to review current research on the PE and its long-term effects on mother and child. PE is defined as a hypertension developing after 20 weeks of gestation with at least one of the following symptoms: proteinuria, maternal organ dysfunction or foetal growth restriction. Because initially patients may be completely asymptomatic, the diagnosis

is usually difficult. Untreated PE may lead to the death of both mother and neonate. In later life it predisposes woman and child to cardiovascular and metabolic diseases. Maternal consequences are related to increased risk of hypertension, stroke, thrombosis or chronic kidney disease, whilst offspring implications are directly correlated with hypertension, increased body mass index, hormonal changes and reductions in cognitive functions. In the future there is a need to develop more effective diagnostic methods of PE. Comprehensive understanding of the pathophysiology would allow to avoid many negative long-term effects and reduce its mortality rate.

Key words: Preeclampsia; hypertension; pregnancy; cardiovascular complications; biomarkers.

Introduction and purpose

During the last decade there has been observed a significant increase in the level of knowledge regarding hypertensive disorders of pregnancy. Recent researches are concentrated on the novel diagnostics and potential therapeutic methods of PE [1]. Despite the scientific progress, the clinical guidelines, that covers diagnosing and managing PE, are still insufficient. PE is a progressive disorder that is corelated with preterm delivery and many negative long-term implications both for mother and child. It is not only a main cause of perinatal morbidity and death, but also a leading cause of maternal mortality [2]. It contributes from 15 up to 20% of all preterm births [3]. The number of cases of PE tends to increase, especially in least developed countries [3,4]. Widely-ranged risk factors include maternal concomitant diseases such as chronic hypertension, obesity, prior PE, pregestational diabetes, prior placental abruption or chronic kidney disease [5,6]. PE is also associated with many foetal and neonatal implications: intra-uterine foetal growth restriction (IUGR), placental abruption, preterm delivery, neonatal respiratory distress syndrome, cerebral palsy, retinopathy and necrotizing enterocolitis. Moreover in pregnant woman the disease may affect central nervous system, respiratory system, urinary system and organs such as liver or cardiac muscle [7]. Heterogenous clinical presentation requires greater understanding of the mechanisms leading to multisystem organ failure [2]. This article reviews the data available in the literature on PE, as well as the latest discoveries regarding its long-term effects on mother and child. The informations used in the presented analysis were obtained from academic research databases: Google Scholar and PubMed. The strategy of searching is based on the following keywords: preeclampsia, hypertension, pregnancy, cardiovascular complications, biomarkers. The available articles have been selected in terms of their content value and thematic connection with this article.

Description of the state of knowledge

1. Pathogenesis

Data submitted so far by the researchers are still insufficient to understand completely the pathophysiology of PE [8]. The exact ethology remains unknown because of multifactorial character of the disease. However recent studies indicate abnormal placentation with coexisting ischemia as a major cause of PE [9]. Placental ischemia leads to T-helper cells

activation. That stimulates the production of inflammatory cytokines, autoantibodies against angiotensin II type 1 receptor (AT1-AA), endothelin 1 (ET-1) and soluble vascular endothelial growth factor receptor 1 (sFlt-1). On the other hand there is an observable reduction of nitric oxide (NO) synthesis. In that pathway, by maternal vascular endothelial dysfunction, develops hypertension and uterine growth restriction (IUGR). Additionally pre-existing maternal risk factors, such as diabetes or obesity, implicate improper function of the ischemic placenta and predispose to the development of PE [8]. Oxidative stress, inflammation and shallowed trophoblast invasion of the uterine spiral arterioles also play a crucial role in the pathophysiology of PE. Reduced blood flow to the foetus results in intrauterine growth restriction [10]. The sources of oxidative stress include multiple types of cells such as trophoblast or endothelial cells. Oxidative stress leads to an accumulation of free radicals which can be manifested by remodelling of the maternal spiral arteries. Oxidative stress is also highly correlated with the term of inflammation. Endothelial dysfunction and hypertension are the implications of a systemic inflammatory response that is released by a reactive oxygen species produced by hypoxemic placenta [11]. PE is also characterised by an elevated levels of sFlt-1 and decreased concentration of placental growth factor (PlGF). The level of sFlt-1 significantly increases approximately 5 weeks before the disease onset and PlGF level declines even earlier [12]. Currently, both of them can be seen to have a great potential in the diagnosis of PE and detection of placental dysfunction. As angiogenic and antiangiogenic factors, PlGF and SFlt-1 can provide the early suspicion based on these biochemical markers [9]. Moreover increased sFlt-1/PlGF ratio may be useful in the confirmation of the diagnosis. Due to researches its negative predictive value is estimated on 99.3% in women with suspected PE and sFlt-1/PlGF ratio ≤ 38. Therefore sFlt-1/PlGF ratio in the future might be useful in the screening tests of pregnant women with uncertain diagnosis. Moreover this tool would eliminate an unnecessary hospitalization and reduce the costs of a diagnostic process [13].

2. Symptoms

The clinical picture of PE depends on its subtype. Two different types of PE can be distinguished: early onset (<34 weeks of gestation) and late onset (>34 weeks of gestation). Some components such as ethology or main complications differentiate these two types of PE (Table 1) [14,15]. The course of PE usually remains asymptomatic. In severe cases predominant maternal symptoms include headache, blurred vision, nausea, vomiting or epigastric pain. There are also observable epileptic seizures, stroke, reversible ischemic neurologic deficit or posterior reversible encephalopathy syndrome. Other possible manifestations like liver failure, kidney dysfunction or cardio-respiratory complications such as myocardial infarction and pulmonary oedema, may be noted. Some women can develop HELPP syndrome which is characterised by haemolysis, elevated liver enzymes and low platelet count. Moreover co-existing signs and symptoms are hypertension, proteinuria and peripheral oedema [16]. Hypertension is defined as a systolic blood pressure of ≥ 140 mm Hg and/or diastolic blood pressure of ≥ 90 mm Hg in two separate measurements at least 4h apart. Otherwise proteinuria is a state in which in 24 hour urine collection there is detected ≥ 300 mg of the protein [17]. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), PE can be diagnosed after 20 weeks of gestation in conditions of gestational hypertension accompanied by proteinuria and/or one of other maternal organ

dysfunction. The researches confirm that multiple maternal risk factors are associated with the development of PE. Among them there are not only advanced maternal age, previous history of PE, assisted reproduction, family history of PE, obesity, Afro-Caribbean and South-Asian ethnicity, but also persisting other co-morbidities such as hyperglycaemia in pregnancy, pre-pregnancy obesity, multiple pregnancy, pre-existing chronic hypertension, renal disease and autoimmune diseases (like systemic lupus erythematosus and anti-phospholipid syndrome) are medical conditions that also predispose women to develop PE [18]. Recent studies suggests that higher levels of vitamin D, measured by the 35-hydroxyvitamin D test, reduce the risk of PE [19]. Consequently, supplementation of vitamin D may be useful in the prevention for PE [20].

Subtype	Early onset preeclampsia	Late onset preeclampsia
Other name	Placental	Maternal
Beginning	<34weeks of gestation	>34 weeks of gestation
Ethology	Abnormal placentation after hypoxemic conditions with higher levels of sFlt-1 and lower PlGF	Interaction between a normal placenta and maternal factors associated with endothelial dysfunction
Main complications	Foetal growth restriction and adverse maternal or neonatal implications	Generalized vasoconstriction and reduced blood to multiple organs
Percentage of all cases	5-20%	80-95%

Table 1. Subtypes of preeclampsia

3. Consequences for mother

Due to the following data women with previous PE are more exposed to a long term risk of mortality and developing cardiovascular diseases. Consequently, the American Heart Association recognizes PE as a significant part of evaluation of the cardiovascular risk. Especially the onset of the disease before 34 week of gestation is related to an eight to nine fold increase of that risk [1]. PE predisposes to chronic hypertension, heart failure, stroke, coronary heart disease and cardiovascular mortality [21]. Moreover renal disease and metabolic disorders may occur. Early-onset PE is combined with more severe multiorgan complications both for mother and child [15]. Nearly half of women with a history of PE (suffered from hypertension) were hypertensive after 10 years following the past episode. Researches revealed that this group of patients is also 60% more prone to develop an ischemic stroke. In accordance with World Health Organization increased risk of haemorrhagic stroke and venous thromboembolism are also connected with previous history of PE. Furthermore all clinical conditions mentioned above may contribute to growth of the mortality and morbidity rate of women even many years after hypertensive disorders identified in pregnancy. The development of end-stage kidney disease in the mother is described as a result of PE. Another symptom of the urinary system is reduced glomerular filtration rate occurring 12 months

postpartum [22]. Conducted observational studies highlight the protective influence of PE on cancer. The explanation of that phenomena leans on the crucial role of the immune system in the pathogenesis of that complication. Not only long-term maternal consequences endanger the health of women, but also there are many significant short-term implications such as eclampsia, hepatic failure, renal dysfunction as well as preterm delivery and placental abruption. High risk of recurrence in subsequent pregnancies (approximately 25 to 65%) is also observable [23].

4. Consequences for child

In developing countries, approximately one quarter of stillbirths and neonatal deaths have connection with PE. The reason of this phenomenon is the fact that PE is associated with many complications such as foetal growth restriction and preterm birth. Both of them may lead to neonatal deaths and multiple implications for future life [3]. The group of neonatal complications includes clinical sepsis, bronchopulmonary dysplasia, intracranial haemorrhage, periventricular leukomalacia, necrotizing enterocolitis and patent ductus arteriosus [24]. Due to the researches preterm infants are more prone to respiratory problems: respiratory distress syndrome, transient tachypnoea of the new born, persistent pulmonary hypertension and respiratory failure. They also much more often require supplemental oxygen or assisted ventilation than infant born on time. As a result of decreased uteroplacental blood flow and ischemia, complication called intrauterine growth restriction (IUGR) may develop. That process is reflected in the reduced foetal weight below the 10^{th} percentile. Furthermore it remarkably increases the risk of mortality of the child. A separate issue is neonatal thrombocytopenia that occurs in the course of maternal PE. Its severity is individually variable and the therapeutic process requires additional studies [2]. Another problem is retinopathy of prematurity, which is highly correlated with gestational age at birth. In advanced cases it can cause retinal detachment or even irreversible blindness. On the other hand some extremely early neonates in their school-age are affected by cerebral palsy connected for instance with moderate disability [18,25]. In addition PE predisposes children to behavioural problems and cardiovascular diseases in their future life, what emphasizes the necessity of better understanding relationship between ischemic placenta and the development of foetal complications [8].

Summary

PE is a specific multifactorial disorder that requires further studies to reveal the potential future therapies and the exact mechanisms that lays at the basis of its pathophysiology [3]. Despite the multiple maternal, foetal and neonatal consequences, there is a need to improve multidisciplinary healthcare in order to prolong the pregnancy and ensure the safety of both mother and child [2]. Prophylaxis of PE is just as important as the treatment and leads to reduction in number of long-term complications in the future life [26]. Analysis shows that high frequency of incidences of PE in the global society should prompt to conduct screening tests for all pregnant women. That would allow to reduce costs of hospitalisation and therapy related to pre-term delivery [18].

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