Preeclampsia - the leading cause of maternal and neonatal mortality in the world - review of literature

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Abstract

**Background:** This review analyzes current knowledge on the pathophysiology, prevention and art of treatment of preeclampsia. Preeclampsia (known as EPH-gestosis) is nowadays the leading cause of maternal and neonatal mortality in the world. According to statistics it affects up to 5% of pregnant women. The symptoms are high blood pressure, edema, proteinuria. The scientists all over the world are trying their best to know the pathogenesis to devise a cure for the disease.
**Aim of study:** The goal of this article was to gather information about the pathophysiology and treatment of preeclampsia to prevent the risk of illness’ development.

**Materials and methods:** A review of the literature available in the “PubMed”, Google Scholar and Medline databases. The search was performed by using following keywords: “preeclampsia”, “ophthalmic artery doppler”, “PIGF”, “aspirin”, “placenta”.

**Results and conclusions:** In spite of the progress of science preeclampsia is still a serious threat for pregnant women all around the world. Thank to the advanced molecular and ultrasonographic techniques the doctors can estimate the risk of complications. The most important is screening, which helps the doctors to define the group of risk and then launch the treatment. That should decrease the amount of maternal and neonatal complications and deaths.

**Keywords:** preeclampsia, PIGF, placenta, ophthalmic artery doppler, aspirin

**Introduction**

Preeclampsia is a hypertension caused by pregnancy, which evolved after 20 weeks gestation and at least one of the following symptoms: proteinuria, acute kidneys injury, hepatic, hematological or neurological complications. It is worth to highlight that proteinuria or edema are not the obligatory for the diagnosis. We differentiate two types of the disorder: mild and severe. Mild is characterized by hypertension up to 140/90 mm Hg, proteinuria (≥0.3 g of protein in the 24-h collection of urine) and stable condition of the fetus. Any deterioration classifies the case as the severe one. The birth of placenta usually cures the disease, but the doctors must observe the patient, because the symptoms can continue or even intensify during the next 48 hours. The risk of pulmonary edema, kidneys injury oreclampsia rise. There is a syndrome called late postpartum preeclampsia-eclampsia. It is defined as the development of signs and symptoms for the first time at 48 hours but up to 4 weeks after
delivery (1). Couple researches have confirmed the existence of late postpartum preeclampsia-eclampsia (2), (3).

Pathogenesis

There are two stages: abnormal placentation and the development of the maternal syndrome (4). It starts with an inflammatory reaction, which is present in the beginning of each gestation (5). Especially important in this process is the nuclear factor kappa B (NFκB) increase. It takes part in the remodelling of maternal spiral arteries into wide and low-resistance vessels (6). But not only the NFκB is critical. The remaining inflammatory factors such as TNFα, IL6, thromboxane 2 increase in maternal blood as well (7). The consequence of incorrect transformation of uterine vessels is the loss of nutrients and oxygen in placental cells. That slows the angiogenesis and induces maternal endothelium dysfunction. Placental cells start do secrete factors: soluble fms-like tyrosine kinase 1 (sFlt-1) or soluble endoglin (sEng) into the maternal circulation. The growth of sFlt-1 reduces the bioavailability of vasodilatory nitric oxide (NO). That supports the hypertension and as a consequence - preeclampsia.

Risk factors

The scientists divide risk factors into the 3 groups: major, other and rare. Major are: prior preeclampsia, chronic hypertension, pregestational diabetes mellitus, multiple gestation, prepregnancy BMI >30, antiphospholipid syndrome. Other: systemic lupus erythematosus, history of stillbirth, prepregnancy BMI >25, nulliparity, prior placental abruption, assisted reproductive technology, chronic kidney disease, advanced maternal age >35. Rare: history of preeclampsia in family and trisomy 13 fetus (8,9), a single nucleotide polymorphism near the FLT1 locus on chromosome 13 (9). Study shows, that one of the risk factors of preeclampsia is race. It is more common problem in African-American population (10).

Prognostic factors
Ophthalmic artery Doppler (OAD) is nowadays the one of the test we must take to evaluate the risk of preeclampsia. It is used, because of the studies, which showed, that the PE is the consequence of cardiovascular and endothelial adaptations during the pregnancy (11). The advantage of OAD is the wide access to the method and easily accessible vessel to gain an information about intracranial circulation (12). Studies reported that in women with preeclampsia (PE), compared with normotensive pregnant women, there is a decrease in impedance to flow and an increase in velocities in the flow velocity waveforms from the ophthalmic arteries (13).

The Fetal Medicine Foundation proposed a Bayes theorem-based model to predict preterm PE using a combination of maternal characteristics, medical history, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor (PIGF) (14). PIGF is significant molecule in angiogenesis, plays a role in trophoblast growth and differentiation. When the levels of PIGF is lower and sFlt-1 are higher there is a huge risk of preeclampsia.

Prevention

Aspirin (acetylic acid, ASA) is nonsteroidal anti-inflammatory drug, which irreversible inactivates the cyclooxygenase (COX) enzyme and as a result suppress the production of prostaglandins and thromboxanes.

That is one of possible explanations for using aspirin in preeclampsia prevention (15). There are other theories of drug using, which are considered by scientists: (1) improvement in the placentation process, which is supported by the fact that early initiation of therapy indicates a more prominent reduction in the risk of preeclampsia and (2) inhibition of platelet aggregation and its antithrombotic effect, thereby leading to lower levels of placental infarct. Aspirin is highly effective in preventing preterm preeclampsia when administered to high-risk women at doses up to 150 mg and initiated before 16 weeks of gestational age, reducing its incidence by more than 60% (16). It should be taken everyday, in the evening (17). Of course we have to be aware of possible side effects like: gastrointestinal discomfort (18), sporadic cases of intracranial hemorrhage in immature infants (19). The literature indicates no significant association between low-dose aspirin treatment and premature closure of the arterial canal or neonatal bleeding (20).
But what we are supposed to do when the pregnant woman is allergic to ASA or cannot take the drug because of other contraindications like bleeding disorders, asthma? Then aspirin using is forbidden. High-risk patients who cannot take aspirin may benefit from LMWH or calcium supplementation in specific cases, and these interventions should be considered on an individual case basis following adequate counselling and evaluation of risks and benefits (21).

**Treatment**

One of the dimensions is anticonvulsive preventive therapy. Magnesium sulfate (MgSO4) is the drug of choice for preventing eclampsia, and the only drug with proven preventive effects against eclamptic seizures. MgSO4 should be used during labor, prior to cesarean section, or whenever there are signs/symptoms consistent with imminent eclampsia. If there is severe PE or eclampsia it should be used up to 24 hours postpartum (22).

**Dosage:**
- **Attack dose:** 4g of MgSO4 (8 mL of 50% MgSO4 7H2O diluted in 12 mL of distilled water) IV in 5–10 minutes
- **Maintenance dose IV:** 0.6–2g/h IV (dilute10mL of50% MgSO4 7H2O in 240 mL of saline solution and infuse at a rate of 50 mL/hour (1 g/hour) or 100 mL/hour (2 g/hour) continuously. Every 120 minutes, check if diuresis is preserved (> 25 mL/hour) and if tendon reflexes are present.

The second drug used in treatment is low molecular weight heparin (LMWH). It improves endothelial function more than the anti-coagulant effect. LMWH plays a role in inflammation modulating circulating levels of angiogenic factors such as PLGF and sFLT1 and inflammatory cytokines such as IL-8, IL-6 and TNF-a (23).
LMWH is able to inhibit leukocyte adhesion to damaged tissue and reduce complement activation (24). It has been demonstrated that LMWH improves endothelium-dependent relaxation in pregnant women at risk of PE and increases circulating levels of PLGF [81].

**Maternal and neonatal consequences**
Unfortunately preeclampsia is not only the problem during the pregnancy. Multiple clinical studies of women with preeclampsia show an increased risk of developing cardiovascular diseases later in life (25). In a study using fibroscan, an increase in fibrosis was observed in preeclamptic patients when compared with normotensive controls (26). As a result of transition in lipid metabolism, steatosis has also been discovered in liver biopsy. Oxidative stress disturbs the natural redox state of all cellular components while cell death occurs under severe conditions. Experimental hepatic microvascular steatosis causes mitochondrial dysfunction and oxidative stress in hepatic subcellular organelles (27). These have been established in preeclamptic patients (28).

Studies showed, that the infants born to mothers with early-onset PE were more likely to develop IRDS, with 62% of infants affected versus 50% in the control group, which is in accordance with others (29). The postnatal course of early-onset PE neonates was more often complicated by sepsis (43% vs. 30%) compared to non-PE neonates (30). The increased risk of IRDS could at least be partially related to the higher frequency of cesarean delivery (66% vs. 35%, p<0.001) in women with PE (31), despite the treatment of ante partum corticosteroids in 81% of cases.

**Conclusion**

Preeclampsia is extremely dangerous disorder which has serious consequences for pregnant woman as well as for fetus. The scientists still are not hundred percent sure about the pathogenesis of the syndrome. The work on solution of the problem base on different theories of development. Nowadays, in developed countries we have methods to find patients from high-risk groups and treat them according to international’s scientific societies guidelines. It is the main challenge to improve the methods to low the risk of maternal and neonatal deaths.

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