An Overview of Recent Advances in Pathogenesis and Diagnosis of Preeclampsia

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Preeclampsia is a serious complication of pregnancy, which is the cause of 60 000 maternal deaths annually worldwide. In addition to the well-known maternal risk factors such as hypertension, diabetes mellitus, antiphospholipid antibody syndrome, obesity, aging, and multiple pregnancies, recent studies have identified the role of genetic and immunological factors in the pathogenesis of preeclampsia. In particular, imbalance between angiogenic and anti-angiogenic factors, anti-angiotensin II type 1 receptor antibodies and dysregulation of oxygen supplies can cause preeclampsia. A group of biomarkers have been introduced for diagnosis of preeclampsia. Chief among them is the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor, which can be used in clinical practice. Recent studies have shown high specificity and sensitivity of these markers for early diagnosis of preeclampsia, which is critical for prevention of fetal and maternal complications.

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INTRODUCTION

Preeclampsia is a systemic complication of pregnancy, which presents with the onset of hypertension (arterial pressure exceeding 140/90 mmHg on at least 2 occasions, > 4 hours apart) and proteinuria (> 300 mg/dL/24 h) after 20 weeks of gestation, in a previously normotensive woman. When severe, preeclampsia can result in marked elevations of blood pressure and end-organ dysfunction. One of the specific variants of severe preeclampsia is the HELLP syndrome, which is a syndrome of hemolysis, elevated liver enzymes, and low platelets. Preeclampsia can be classified into 2 different entities, namely early-onset preeclampsia and late-onset preeclampsia. The early-onset preeclampsia tends to develop before 34 weeks of gestation, whereas the late-onset preeclampsia occurs beyond 34 weeks of gestation. Recent studies have identified a number of novel risk factors, biomarkers, and prognostic, genetic, and clinical features of preeclampsia. Early-onset preeclampsia is considered to be a consequence of fetal disorder, whereas the late-onset preeclampsia is generally caused by a maternal disorder.1–3

Incidence

Preeclampsia affects 3% to 5% of all pregnancies and is estimated to result in 60 000 maternal deaths annually worldwide.4 In the last report of the Ministry of Health of Iran, maternal mortality rate was estimated to be 22.18 per 100 000. Although this mortality rate is much lower than the prevailing rates in the other developing African and Asian countries,5,6 based on the reported data from the Fars Province, preeclampsia is the cause of 10.9% of maternal mortality in that region of the country.7

Risk Factors

Diabetes mellitus, obesity, family history of preeclampsia, mother’s age, history of chronic kidney disease, hypertension, antiphospholipid antibody syndrome, and multiple gestations are well-known risk factors for preeclampsia in the mother.8 In addition, history of preeclampsia in
the husband’s mother confers an increased risk of preeclampsia in the wife. This is not surprising since the placenta is a product of both mother and father.\(^9\) There is also considerable evidence for the role of immune maladaptation in the pathogenesis of preeclampsia. Nulliparous mothers have increased risk of preeclampsia in comparison to multiparous women. Protective effect of multiple pregnancies decreases by partner change, which shows that a long exposure to paternal antigens increases immune tolerance.\(^{10}\) Moreover, in ovum donation pregnancies, in which the fetus is a complete allograft, the incidence of preeclampsia is also very high (18.1%), reflecting the role of immune system in the pathogenesis of this disorder.\(^{11}\)

**PATHOPHYSIOLOGY OF PREECLAMPSIA**

Several pathophysiological mechanisms have been implicated in the pathogenesis of preeclampsia. Among them, alterations in the maternal immune response to the allogenic fetus and dysregulation of placental oxygen supplies have been most extensively studied. In a normal pregnancy, the placental cytotrophoblasts invade the maternal endothelium and extravillous trophoblasts acquire endothelial cell characteristics. They replace the spiral artery endothelial cells and destroy muscularis mucosa. These events are essential for maintaining a low resistance to blood flow in the placenta. Remodeling begins late in the course of the first trimester and is completed by 18 to 20 weeks of pregnancy.\(^{12,13}\) Impairment of trophoblast invasion is an early event in preeclampsia, but is not sufficient to account for all clinical features of preeclampsia by itself. In fact, as briefly described below, many of the pathophysiological features of preeclampsia are mediated by the defective angiogenesis, which is caused by dysregulation of several key angiogenic factors.

**Angiogenic Factors**

**Soluble vascular endothelial growth factor.** The role of the imbalance between angiogenic and anti-angiogenic factors in the pathogenesis of preeclampsia has gained the most attention in the past decade. Vascular endothelial growth factor (VEGF) has a key role in angiogenesis.\(^{14,15}\) It acts through 2 receptor tyrosine kinases, VEGF receptor-1 (also known as fms-like tyrosine kinase-1 [FLT-1]) and VEGF receptor-2 (kinase-insert domain region), which are selectively expressed on the vascular endothelial cell surface. The VEGF receptor-1 has 2 isoforms: a transmembrane isoform and a soluble isoform (sFLT-1). Placental growth factor (PGF) is another member of the VEGF family that is made predominantly in the placenta. It also binds to the VEGF receptor-1. The sFLT-1 is a circulating anti-angiogenic protein that binds to the VEGF and PGF, preventing interaction with their biologically active transmembrane receptor. Elevation of sFLT-1 occurs before the onset of clinical preeclampsia.

**Soluble endoglin.** Endoglin is the coreceptor for transforming growth factor-β. This receptor is highly expressed on the cell membranes of the endothelial cells and syncytiothrophoblasts. A placenta-derived soluble form of endoglin (sEng), which is an anti-angiogenic protein, has been found in the plasma of patients with preeclampsia. The plasma concentration of sEng positively correlates with severity of the disease and falls after delivery. Its addition to the culture medium inhibits capillary tube formation in cultured endothelial cells in vitro, and its administration to pregnant rats causes hypertension and increased vascular permeability. The effect of sEng in the pregnant rats is markedly amplified by co-administration of the sFLT-1, leading to severe preeclampsia and HELLP syndrome.\(^{16}\) Clinical studies have shown that measurements of both sEng and sFLT-1 may be a better predictor of preeclampsia than either alone. Stephan and colleagues\(^{17}\) have shown that measurements of sEng and sFLT-1 can predict early-onset preeclampsia with a sensitivity of 100% and a specificity of 93.3%. Some studies have shown elevated levels of sEng, especially in early-onset preeclampsia.

**Immunological Mediators**

There is considerable evidence pointing to the role of maternal immune response in the pathogenesis of preeclampsia. Preexisting autoimmune diseases, changes of sexual partner prior to the next pregnancy, and short exposure time to paternal semen all increase the risk of preeclampsia.\(^{8,18,19}\) Auto-antibodies to angiotensin II type 1 (AT1) receptor have been detected in some women with preeclampsia. In fact, injection of the AT1 receptor antibody together with angiotensin-2 in rats has been shown to cause hypertension, proteinuria, fetal growth retardation, activation of hypoxia...
inducible factor-1α, and increased production of reactive oxygen species. It has been suggested that by causing cell death and shedding of paternal antigens, hypoxia can promote immune response to paternal antigens, demonstrating a link between hypoxia and immune reactivity.

**Dysregulation of Oxygen Supply**

There is considerable evidence that conditions associated with vascular disease or reduced blood supplies such as hypertension, systemic lupus erythematosus, diabetes mellitus and twin pregnancy increase the risk of preeclampsia. Several experimental models have been used to show the role of hypoxia and ischemia-reperfusion injury in the pathogenesis of preeclampsia. In pregnant rat models, hypoperfusion of the ovarian artery results in proteinuria, increased concentrations of sFLT-1 and inflammatory cytokine, interleukin-6; reduced levels of PGF; and fetal growth restriction. Impaired placentation causes intermittent disruption of placental perfusion, ischemia-reperfusion type injury, oxidative stress, and systemic inflammatory response.

**DIAGNOSIS OF PREECLAMPSIA**

**Screening Tests for Early Prediction of Preeclampsia**

The PGF/sFLT-1 ratio has been shown to be a predictive marker for preeclampsia. Verlohren and coworkers demonstrated in a multicenter clinical study that the PGF/sFLT-1 ratio had a 82% detection rate for preeclampsia with a false-positive rate of 5%. This ratio had no predictive value in the first trimester of pregnancy, but for early-onset preeclampsia, the detection rate was 89%. Recently, 2 automated immunoassays, the Alere Triage PLGF assay (Alere, Waltham, MA, USA) and Elecsys sFLT/PIGF Ratio (Roche, Basel, Switzerland) have become available for clinical use. In contrast to the enzyme-linked immunosorbent assay method, these methods are fast, standardized, and inexpensive. Benton and colleagues performed a study to compare these commercially available immunoassays. In this case-control study of 44 patients with preeclampsia and 84 matched controls, they utilized Triage PLGF assay and Elecsys sFLT/PIGF Ratio assays. Both assays had discriminatory power in diagnosis of early onset preeclampsia with greater than 95% specificity. The Triage assay had higher sensitivity.

**Uterine Artery Velocimetry**

The impedance to blood flow in the uterine arteries steadily declines with progression of normal pregnancy. However, due to defective differentiation of trophoblast and impaired invasion of spiral arteries, the resistance to the blood flow is increased in preeclampsia. By using bedside ultrasound technique, changes in fetal growth, placentation, flow waveform ratio, and diastolic notching can be determined as a screening test for predicting preeclampsia. A systematic review of 74 studies has shown that uterine artery notching plus pulsatility index has a reliable predictive value during the second trimester of pregnancy. However, some studies have shown a high false-positive rate with this method. Espinoza and colleagues showed that a combination of uterine Doppler ultrasound and PGF was associated with odds ratios of 43.8 for occurrence of early-onset preeclampsia and 37.4 for late-onset preeclampsia.

**PREVENTION OF PREECLAMPSIA**

Several studies have explored the efficacy of various interventions in preventing preeclampsia. Since low-dose acetylsalicylic acid inhibits synthesis of thromboxane to a greater extent than prostacyclin (and as such may protect against vasoconstriction, platelet activation, and thrombosis in the placenta), several studies have explored its effect on prevention of preeclampsia. The meta-analyses of the data from these studies have shown a trend towards lower incidence of preeclampsia in moderate- to high-risk pregnancies when the drug was prescribed at the end of the first trimester. The meta-analysis of the available data on the effects of fish oil has revealed insufficient evidence to support the efficacy of their routine use during pregnancy in reducing the risk of preeclampsia. Likewise, vitamin C and vitamin E supplementation have shown no benefits in preeclampsia prevention. However, calcium supplements may be effective in lowering the incidence of preeclampsia, particularly in women with high-risk pregnancies and low dietary calcium intake.

**CONFLICT OF INTEREST**

None declared.
REFERENCES


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