Angiogenic Factors and Preeclampsia

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Summary: Preeclampsia, a hypertensive disorder peculiar to pregnancy, is a systemic syndrome that appears to originate in the placenta and is characterized by widespread maternal endothelial dysfunction. Until recently, the molecular pathogenesis of phenotypic preeclampsia was largely unknown, but recent observations support the hypothesis that altered expression of placental anti-angiogenic factors are responsible for the clinical manifestations of the disease. Soluble Flt1 and soluble endoglin, secreted by the placenta, are increased in the maternal circulation weeks before the onset of preeclampsia. These anti-angiogenic factors produce systemic endothelial dysfunction, resulting in hypertension, proteinuria, and the other systemic manifestations of preeclampsia. The molecular basis for placental dysregulation of these pathogenic factors remains unknown, and as of 2011 the role of angiogenic proteins in early placental vascular development was starting to be explored. The data linking angiogenic factors to preeclampsia have exciting clinical implications, and likely will transform the detection and treatment of preeclampsia.

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Preeclampsia, a systemic syndrome manifested primarily by hypertension and proteinuria, presents mainly in the second half of pregnancy, and affects approximately 3% to 5% of pregnancies woldwide.[1] There have been recent advances in our understanding of the pathophysiology of preeclampsia, many reported this very decade, but as yet there is no specific cure, delivery of the placenta remaining the only definitive treatment. Thus, as of 2011 preeclampsia is still a leading cause of maternal mortality, preterm birth, and consequent neonatal morbidity and mortality. In developing countries, where access to safe, emergent delivery is less readily available, preeclampsia claims the lives of more than 60,000 mothers every year.[1]

This article describes recent discoveries concerning the pathogenesis of preeclampsia, with emphasis on the emerging role of angiogenic factors as potential mediators of the clinical signs and symptoms of preeclampsia. Also discussed are the potential use of angiogenic factors to predict preeclampsia, and the potential for prevention, and eventually treatment of the disease.

EPIDEMIOLOGY AND RISK FACTORS

Most cases of preeclampsia occur in women who commence their pregnancies as healthy nulliparas, among whom the incidence is approximately 7%.[2] The majority of these patients have no family history of the disorder; still, the presence of preeclampsia in a first-degree relative increases a woman's risk of severe preeclampsia by 2- to 4-fold,[3] suggesting a genetic contribution to the disease. A history of preeclampsia in the father's mother also confers increased risk, recalling the fact that the placenta is a product of both mother and father.[4]

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Several medical conditions are associated with increased preeclampsia risk, including chronic hypertension, diabetes mellitus, renal disease, obesity, and hypercoagulable states.[5] Women with preeclampsia in a prior pregnancy also have a higher risk of developing preeclampsia in subsequent pregnancies. Conditions associated with increased placental mass, such as multifetal gestations and hydatidiform mole, also are associated with increased preeclampsia risk. Counterintuitively, smoking during pregnancy reduces the risk of preeclampsia.[6] Although none of the earlier-noted risk factors is fully understood, they have provided insights into pathogenesis.

CLINICAL FEATURES

The new onset of hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) and proteinuria (≥300 mg/24 h) after 20 weeks' gestation are the cardinal features of preeclampsia. Although edema was historically part of the diagnostic triad for preeclampsia, it is also a common feature of normal pregnancy, diminishing its usefulness as a specific pathologic sign. Still, the sudden onset of severe edema—especially edema of the hands and face—can be an important presenting symptom in this otherwise insidious disease, and is sometimes the only change detectable by the patient.

Uncommon but serious complications of preeclampsia can include acute renal failure, seizures (eclampsia), pulmonary edema, acute liver injury, hemolysis, and/or thrombocytopenia. The latter three signs frequently occur together, as part of the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, a severe preeclampsia variant. Seizures (eclampsia) occur in approximately 2% of women with preeclampsia in the United States. Although eclampsia most often occurs in the setting of hypertension, proteinuria, and evidence of central nervous system involvement (such as headache and hyperreflexia), it can occur without these warning signs.

Complications affecting the developing fetus and neonate include prematurity (both induced for maternal indications and spontaneous[7]) fetal growth restriction, oligohydramnios, and placental abruption. Although the exact pathogenesis of these complications is unknown, impaired uteroplacental blood flow or placental infarction are likely to contribute.

MATERNAL AND NEONATAL MORTALITY

Approximately 500,000 women die in childbirth each year worldwide. Hypertensive disorders of pregnancy are estimated to account for 16% of maternal deaths in developed countries, and 9% of maternal deaths in Africa and Asia.[8] Maternal death most often is caused by eclampsia, cerebral hemorrhage, renal failure, hepatic failure, or the HELLP syndrome. Adverse maternal outcomes often can be avoided with timely delivery; hence, in the developed world the burden of morbidity and mortality falls on the neonate. Worldwide, preeclampsia is associated with a perinatal and neonatal mortality rate of 10%.[9] Neonatal death most commonly is caused by premature delivery undertaken to preserve the health of the mother, but also can result from placental abruption or intrauterine fetal death.

THE ROLE OF PLACENTAL ISCHEMIA

Observational evidence suggests the placenta has a central role in preeclampsia. Preeclampsia only occurs in the presence of a placenta—although not necessarily a fetus, as in the case of hydatidiform mole—and almost always remits quickly after delivery of the placenta. In this respect there have been cases of postpartum eclampsia associated with retained placental fragments, with rapid improvement only after uterine curettage.[10] In severe preeclampsia, there is pathologic evidence of placental hypoperfusion and ischemia, including acute atherosis, intimal thickening, necrosis, atherosclerosis, and endothelial damage, and placental infarction. Although these findings are not universal, they appear to correlate with severity of clinical disease.[11]

Abnormal uterine artery Doppler ultrasound, consistent with decreased uteroplacental perfusion, may be observed before the clinical onset of preeclampsia. Unfortunately, this finding is nonspecific, so it is not diagnostically useful if used alone. In women residing at high altitude, among whom the incidence of preeclampsia is