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Editorial

Pathogenesis of Preeclampsia

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Preeclampsia is a syndrome characterized by the onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation (Table 1). Additional signs and symptoms that can occur include visual disturbances, headache, epigastric pain, thrombocytopenia, and abnormal liver function. These clinical manifestations result from mild to severe microangiopathy of target organs, including the brain, liver, kidney, and placenta. Potential maternal sequelae include pulmonary edema, cerebral hemorrhage, hepatic failure, renal failure, and death. The fetal/neonatal burden of disease results from placental hypo perfusion and the frequent need for preterm delivery.

Table 1 — *Criteria for the diagnosis of preeclampsia*

Systolic blood pressure =140 mmHg or diastolic blood pressure =90 mmHg on two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient
If systolic blood pressure is =160 mmHg or diastolic blood pressure is =110 mmHg, confirmation within minutes is sufficient
and
Proteinuria =0.3 g in a 24-hour urine specimen or protein/creatinine ratio =0.3 (mg/mg)(30 mg/mmol)
Or dipstick =1+ if a quantitative measurement is unavailable
OR
Systolic blood pressure =140 mmHg or diastolic blood pressure =90 mmHg on two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient with the new onset of any of the following (with or without proteinuria):
Platelet count <100,000/microL
Serum creatinine >1.1 mg/dL (97.2 micromol/L) or doubling of the creatinine concentration in the absence of other renal disease
Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
Pulmonary edema
Cerebral or visual symptoms (eg, new-onset and persistent headaches not responding to usual doses of analgesics*; blurred vision, flashing lights or sparks, scotomata)

The pathophysiology of preeclampsia likely involves both maternal and fetal/placental factors. Abnormalities in the development of placental vasculature early in pregnancy may result in relative placental under perfusion/hypoxia/ischemia, which then leads to release of antiangiogenic factors into the maternal circulation that alter maternal systemic endothelial function and cause hypertension and other manifestations of the disease (hematologic, neurologic, cardiac, pulmonary, renal, and hepatic dysfunction). However, the trigger for abnormal placental development and the subsequent cascade of events remains unknown.

The current understanding of mechanisms causing the pathologic changes observed in preeclampsia is discussed here.

Abnormal Development of the Placenta :

The critical role of the placenta in the pathophysiology of preeclampsia is supported by epidemiologic and experimental data that show:

- Placental tissue is necessary for development of the disease, but the fetus is not
- Preeclampsia is always cured within days to weeks after delivery of the placenta

Examination of human placentas at various stages of gestation in women with normal pregnancies, as well as those with preeclampsia, has led to an understanding of normal placental morphology and pathologic changes in the uteroplacental circulation that are likely relevant to preeclampsia. It is clear that defects in spiral artery remodeling and trophoblast invasion, two related but separate processes, are characteristic of hypertensive disorders of pregnancy and fetal growth restriction[1]. These processes result in impaired placentation and placental ischemia, which are thought to be the primary events leading to placental release of soluble factors (sFlt)[2] that cause systemic endothelial dysfunction resulting in the preeclamptic phenotype.

It is not known why the normal sequence of events in development of the uteroplacental circulation does not occur in some pregnancies. Vascular, environmental, immunological, and genetic factors all appear to play a role.

Hypo perfusion, hypoxia, and ischemia — Hypo perfusion appears to be both a cause and a consequence of abnormal placental development.

Hypo perfusion, hypoxia, and ischemia is a critical component in the pathogenesis of preeclampsia because the hypo perfused, ischemic placenta elaborates a variety of factors into the maternal bloodstream that alter maternal endothelial cell function and lead to the characteristic systemic signs and symptoms of preeclampsia.

Immunologic Factors :

The focus on immunologic factors as a possible contributor to abnormal placental development was based, in part, upon the observation that prior exposure to paternal/fetal antigens appears to protect against preeclampsia[3].

Immunologic abnormalities, similar to those observed in organ rejection graft versus host disease, have been observed in preeclamptic women.

Increased Sensitivity to Angiotensin II :

Increased sensitivity to angiotensin II has been described in preeclampsia, and may be related to increased bradykinin (B2) receptor upregulation in preeclamptic patients[4].

Genetic Factors :

Although most cases of preeclampsia are sporadic, genetic factors are thought to play a role in disease susceptibility. Data suggests that both maternal and paternal contributions to fetal genes

may have a role in defective placentation and subsequent preeclampsia[5,6].

Environmental Factors :

Calcium intake — A possible role for low dietary intake of calcium as a risk factor for preeclampsia is suggested by epidemiologic studies linking low calcium intake with increased rates of preeclampsia and prevention of preeclampsia with calcium supplementation in high-risk women.

Body mass index — A prospective study demonstrated a linear relationship between increasing body mass index and increasing risk of developing preeclampsia.

Systemic Endothelial Dysfunction :

All of the clinical features of preeclampsia can be explained as clinical responses to generalized endothelial dysfunction[7]. As an example, hypertension results from disturbed endothelial control of vascular tone, proteinuria and edema are caused by increased vascular permeability, and coagulopathy is the result of abnormal endothelial expression of procoagulants. Headache, seizures, visual symptoms, epigastric pain, and fetal growth restriction are the sequelae of endothelial dysfunction in the vasculature of target organs, such as the brain, liver, kidney, and placenta.

Observations suggest a major role for sFlt-1 and related angiogenic factors in the pathogenesis of at least some features of preeclampsia[8].However, the trigger for increased sFlt-1 production by the placenta is unknown. The most likely trigger is placental ischemia.

Soluble endoglin

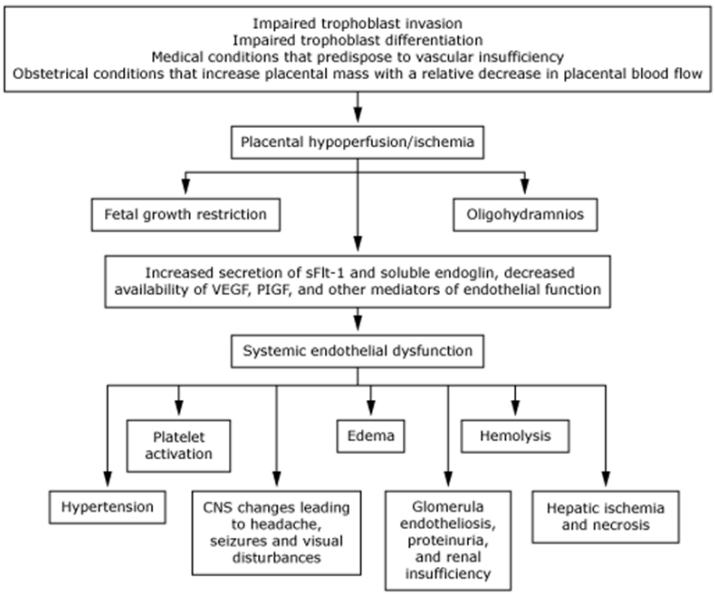
It is likely that synergistic factors elaborated by the placenta other than sFlt-1 also play a role in the pathogenesis of the generalized endothelial dysfunction noted in preeclampsia.

Eng is a coreceptor for transforming growth factor (TGF)-beta and is highly expressed on cell membranes of vascular endothelium and syncytiotrophoblasts. A novel placenta-derived soluble form of Eng, referred to as soluble endoglin (sEng), is an anti-angiogenic protein that appears to be another important mediator of preeclampsia. Although the precise relationship of sEng to sFlt-1 is unknown, it appears that both sEng and sFlt-1 contribute to the pathogenesis of the maternal syndrome through separate mechanisms[9].

Inflammation/Infection :

Signs of maternal inflammation, which appear to be present in normal pregnancies at term, are exaggerated in preeclampsia. Circulating syncytiotrophoblast debris has been hypothesized to contribute to maternal inflammation and some of the features of the maternal syndrome[10]. Placental DNA released into the maternal circulation could play a role in driving the systemic inflammatory response of preeclampsia. Placental hypoxia increases placental necrosis and apoptosis, which releases cell-free DNA into the maternal circulation. As early as 17 weeks of gestation, women who develop preeclampsia appear to have higher levels of trophoblast cell-free DNA compared with controls, with a sharp rise three weeks before clinical signs of preeclampsia become apparent. Fetal DNA rise correlates with sFlt1 rise and syncytial micro particles that carry the fetal DNA are loaded with sFlt1 and other toxic syncytial proteins. It is likely that the inflammatory state may also increase the vascular endothelial sensitivity to toxic factors such as sFlt1 and sEng, although definitive evidence is lacking.

Model for pathogenesis of preeclampsia



Summary: Overall, our understanding of preeclampsia has changed significantly and the future holds promise for mechanism-based novel diagnostics and therapeutics.

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