# Preeclampsia: Pathogenesis, Prevention, and Long-Term Complications

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**Summary:** Preeclampsia continues to afflict 5% to 8% of all pregnancies throughout the world and is associated with significant morbidity and mortality to the mother and the fetus. Although the pathogenesis of the disorder has not yet been fully elucidated, current evidence suggests that imbalance in angiogenic factors is responsible for the clinical manifestations of the disorder, and may explain why certain populations are risk. In this review, we begin by demonstrating the roles that angiogenic factors play in pathogenesis of preeclampsia and its complications in the mother and the fetus. We then continue to report on the use of angiogenic markers as biomarkers to predict and risk-stratify disease. Strategies to treat preeclampsia by correcting the angiogenic balance, either by promoting proangiogenic factors or by removing antiangiogenic factors in both animal and human studies, are discussed. We end the review by summarizing status of the current preventive strategies and the long-term cardiovascular outcomes of women afflicted with preeclampsia.
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Preeclampsia continues to elude physicians and scientists as an enigma, or a "disease of theories". Significant progress, however, has been made in the last 15 years in our understanding of their pathogenesis, which gives hope to early identification and rational treatments to come. In this review, we will describe the pathogenesis, prevention, and current treatment options. It is meant to shed a little more light onto this intriguing entity.

## PATHOGENESIS

The pathogenesis of preeclampsia, though not fully elucidated, is generally believed to be initiated by placental ischemia followed by placental release of antiangiogenic factors into the circulation. In normal pregnancy, invasion of uterine arteries transforms cytotrophoblasts from an epithelial to an endothelial phenotype, a process called pseudovasculogenesis.[1] This remodeling is meant to increase the supply of oxygen and nutrients to the fetus.[2] In doing so, the cytotrophobasts upregulate expression of molecules that are important to uterine invasion such as those from the vascular endothelial growth factor (VEGF) family (e.g., VEGF-A, VEGF-C, placental growth factor [PlGF]).[3] In preeclampsia, however, pseudovasculogenesis is incomplete, thus resulting in placental ischemia and the triggering of hypoxia inducible factors and other placenta-derived factors. Similarly, expression of the important VEGF family of molecules is downregulated, yet its inhibitor (see below) is upregulated.[4]

Some of these placenta-derived factors have been characterized in the last decade. Several groups have demonstrated that the soluble fms-like tyrosine kinase 1 (sFlt-1) is upregulated in placentae of preeclamptic women.[5–7] sFlt-1 is a circulating decoy receptor that binds to PlGF, preventing their interaction with cell surface receptors on endothelial cells and leading to endothelial dysfunction.[8] Early studies showed that sFlt-1 levels were elevated in the sera of preeclamptic women throughout their pregnancies and that their upregulation was associated with decreased levels of circulating free VEGF and free PlGF.[5,9,10] Experimental studies also suggested that sFlt-1 made by preeclamptic villous tissue induced an antiangiogenic state that was reversed by removal of sFlt-1.[11] When sFlt-1 was administered to pregnant rats, it induced the hallmark features of preeclampsia: hypertension, glomerular endotheliosis, and proteinuria.[5] VEGF induces nitric oxide formation that neutralizes reactive oxygen species and vasoconstrictor signaling. In the presence of excess sFlt-1, lack of endothelial nitric oxide leads to vasoconstrictor sensitivity and hypertension.[12] As an example in modern medicine, VEGF antagonists used as chemotherapy for solid tumors have occasionally produced a preeclampsia-like phenotype of severe hypertension and proteinuria as well as an eclampsia picture of reversible posterior leukoencephalopathy.[13–15] VEGF inhibitors in cancer patients have been associated with impaired nitric oxide production, suggesting that impaired nitric oxide signaling may be a final common pathway that mediates hypertension.[16]

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Similarly, a second placenta-derived protein, soluble endoglin (sEng), was later found to be upregulated in preeclampsia.[17] sEng is an inhibitory factor that binds to transforming growth factor beta (TGF-β) in circulation, disallowing its binding to the in situ TGF-β receptor. Inactivation of both VEGF and/or TGF-β signaling have led to impaired endothelium-mediated vasodilation and vascular autoregulation by demonstrating elevated surface adhesion molecule expression and increased leukocyte adhesion.[18] Indeed, the administration of both sEng and sFlt-1 has been shown to induce signs of severe preeclampsia in pregnant rats consisting of liver necrosis and hemolysis, all of which is consistent with the phenotype of HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome and fetal growth restriction. Because receptors for VEGF and TGF-β have been found on the choroid plexus of the brain, blockade of VEGF and TGF-β have shown to result in loss of fenestrae on the choroid plexus, causing endothelial cell instability and periventricular edema.[19] Clinically, this may manifest as seizures and the reversible posterior leukoencephalopathy syndrome on magnetic resonance imaging. Elevated levels of sFlt-1 and sEng in preeclampsia in humans have been subsequently replicated by other groups.[5,11,20–22] To demonstrate whether preeclampsia and eclampsia share similar pathophysiology, the derangements of sFlt-1, sEng, and PlGF were similar to those with severe preeclampsia, suggesting that they share a common pathogenic pathway.[23] Recent work suggests that sFlt-1 and sEng are largely expressed in syncytial knots in the placenta and released into maternal circulation as syncytial microparticles.[24]

The etiology of the abnormal placentation is still being debated. Various pathways have been proposed to have key roles in inducing placental disease, including deficient heme oxygenase expression, impaired corin expression, placental hypoxia, genetic factors, autoantibodies against the angiotensin receptor, oxidative stress, inflammation, altered natural killer cell signaling, and deficient catechol-*O*-methyl transferase (Fig. 1).[25,26] Interestingly, most of these were shown to increase placental production of the antiangiogenic factors in vitro or in vivo rodent studies. Still, the underlying events that induce placental disease activating the cascade of placental damage and antiangiogenic factor production in humans remain unknown.

More recently, preeclampsia and endothelial dysfunction have been reported in mothers without placental disease (maternal preeclampsia).[27] This form of preeclampsia presents at term with usually milder features of the disease. We have argued that increased vascular sensitivity (from pre-existing maternal risk factors such as obesity or chronic hypertension) to circulating sFlt-1 that increases prior to delivery in all women may contribute to term disease; however, definitive evidence is still lacking.

## EPIDEMIOLOGIC STUDIES

The risk factors for preeclampsia have been well described and are summarized in Table 1. Again, altered angiogenic factors may explain the mechanism

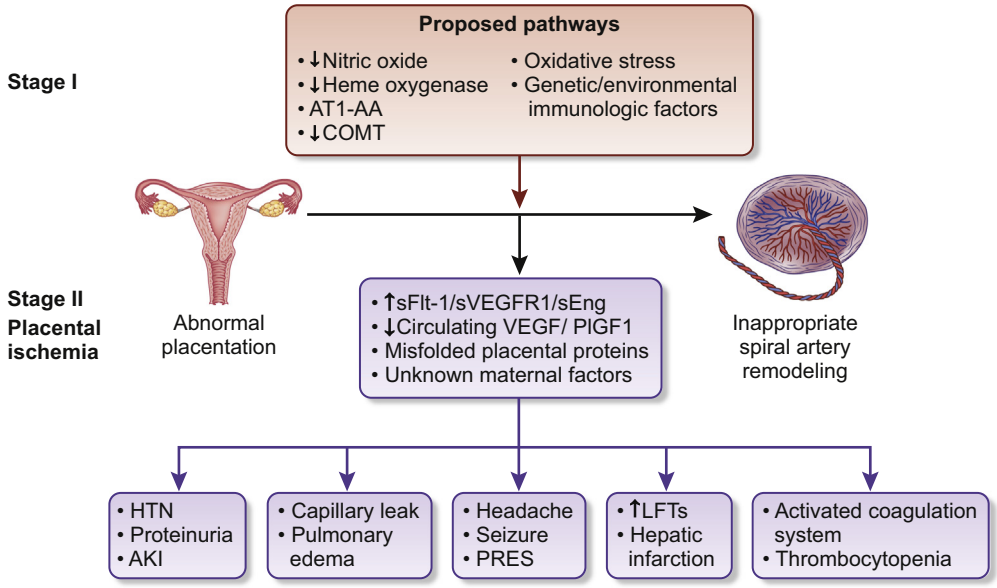


**Figure 1.** Pathogenesis for preeclampsia: two-stage model. AKI, acute kidney injury; AT1-AA, autoantibodies to angiotensin receptor 1; COMT, catechol-*O*-methyltransferase; HTN, hypertension; LFT, liver function test; PlGF1, placental growth factor 1; PRES, posterior reversible encephalopathy syndrome; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase 1; sVEGFR1, soluble vascular endothelial growth factor receptor 1; VEGF, vascular endothelial growth factor. Reprinted with permission from Bramham et al.[126]