Preeclampsia: The Role of Angiogenic Factors in Its Pathogenesis

Epidemiology and Risk Factors

The worldwide incidence of preeclampsia is 3–4% of pregnancies. Several medical conditions are associated with increased preeclampsia risk, including chronic hypertension, diabetes mellitus, renal disease, obesity, and prior preeclampsia. A genetic component is also considered in the pathogenesis of preeclampsia. Up to 30% of women with a history of preeclampsia in a prior pregnancy continue to have a high risk of preeclampsia in subsequent pregnancies. Although the majority of preeclampsia cases occur in healthy nulliparous women, in whom the incidence of preeclampsia may be as high as 7%, preeclampsia has also been observed in subsequent pregnancies. Another contributing factor is the maternal endothelium and result in hypertension, proteinuria, and the other systemic manifestations of preeclampsia. The molecular basis for the abnormal placentation remains unclear, but recent observations related to preeclampsia causality provide small for the development of novel therapies.
Clinical Features

The cardinal features of preeclampsia are de novo onset of hypertension (defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and proteinuria (>0.3 g in a 24-h urine specimen and/or protein to creatinine ratio of >0.30).

Historically, edema was part of the diagnostic triad for preeclampsia; however, edema was too nonspecific to be disease defining. Still, the sudden onset of severe edema, especially edema of the hands and face, is often the only change detectable by the patient in this otherwise insidious disease. Preeclampsia develops from 20 wk of gestation onward until term, although most cases are diagnosed preterm. In some cases, preeclampsia may even first present after delivery.

The spectrum of preeclampsia varies widely. For clinical purposes, it is classified as mild or severe, but such classifications may be misleading. Although the classification of severe preeclampsia serves to emphasize the more ominous features of the syndrome (see Table 1), some have suggested a more nuanced disease categorization (55a) or a classification of the disease based on the gestational age of presentation (98). The degree of proteinuria varies from minimal to nephrotic range; however, the amount of proteinuria does not appear to have an effect on maternal or fetal outcomes (106). The approach to pregnant women with hypertension but without proteinuria is uncertain, but close follow-up is prudent. This recommendation is supported by the observation that mild gestational hypertension that occurs remote from term may subsequently develop into preeclampsia (10). Ten percent of women with other clinical and/or histological manifestations of preeclampsia have minimal or no proteinuria (29), and 20% of women who develop eclampsia (seizures) have no proteinuria (88). Lafayette et al. showed that, in women with pre-eclampsia, the GFR is depressed, whereas the renal plasma flow and oncocytic pressure is similar to healthy pregnant women (49). Uncommon but serious maternal complications of preeclampsia include acute renal failure, placental abruption, seizures, pulmonary edema, acute liver injury, hemolysis, and/or thrombocytopenia. The latter three signs frequently occur together as part of the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Considered by many to be a severe variant of preeclampsia, HELLP syndrome is associated with a higher risk of maternal and neonatal adverse outcomes than preeclampsia alone. Eclampsia complicates ~2% of preeclampsia cases in the United States. Up to one-third of eclampsia cases occur up to 6 wk after delivery (88). Complications affecting the developing fetus include both iatrogenic and spontaneous preterm birth (111), intrauterine fetal growth restriction (IUGR), oligohydramnios, and increased risk of perinatal death.

Although the acute symptoms of preeclampsia will remit after delivery, there are epidemiological studies suggesting that there may be long-term cardiovascular consequences. Approximately 20% of women with preeclampsia develop hypertension or microalbuminuria within 7 yr of a pregnancy complicated by preeclampsia compared with only 2% among women with uncomplicated pregnancies (68). A study published by Smith et al. (91) reported that that at 1 yr ~20% of women have residual microalbuminuria.

In addition, the long-term risk of cardiovascular and cerebrovascular disease is doubled in women with preeclampsia compared with age-matched controls (39, 76). This increase in subsequent cardiovascular disease is observed for both preeclampsia and gestational hypertension (76). Severe preeclampsia, preeclampsia with preterm birth, and preeclampsia with IUGR are most strongly associated with future adverse cardiovascular outcomes. A recent study by Vikse et al. showed that preeclampsia is also a marker for increased risk for subsequent end-stage renal disease (ESRD), although the absolute risk of ESRD in this population is low (97). Preeclampsia and cardiovascular disease share many common risk factors, including chronic hypertension, diabetes, obesity, renal disease, and metabolic syndrome. Smith et al. (91) showed that, by 1 yr postpartum, women who developed preeclampsia had increased blood pressure; total cholesterol, high-density lipoprotein cholesterol, triglycerides, increased BMI, fasting insulin, HOMA index, and urinary microalbumin/creatinine ratio. This increase in long-term cardiovascular mortality holds even for previously healthy women without any overt vascular risk factors who develop preeclampsia (20). Thus the increase in long-term cardiovascular events in women with a history of preeclampsia may either be the result of shared risk factors or the result of subtle vascular damage or persistent endothelial dysfunction caused by preeclampsia.
Pathogenesis

The first decade of this millennium has witnessed major advances in our understanding about the pathophysiology of preeclampsia. Historically known as the “disease of theories,” the mystery about the molecular pathogenesis of preeclampsia is beginning to be unraveled with a key discovery about alterations in placental angiogenic factors. These angiogenic factors, such as sFlt1 and soluble endoglin, produce systemic endothelial dysfunction, resulting in biochemical and morphological changes that are the typical manifestations of preeclampsia (63, 96). The molecular basis for placental dysregulation of these angiogenic proteins in early placental vascular development and trophoblast invasion is just beginning to be explored. Hypoxia is likely to be an important regulator. In addition, the renin-aldosterone-angiotensin II axis, excessive oxidative stress and syncytiotrophoblast debris, immune maladaptation, and genetic susceptibility may also all have roles in the pathogenesis of preeclampsia.

Role of the placenta

The placenta is central to preeclampsia. Preeclampsia only occurs in the presence of a placenta and almost always remits after its delivery. As in the case of the hydatidiform mole, the presence of a fetus is not necessary for the development of preeclampsia. Similarly, in a case of preeclampsia with an extra-uterine pregnancy, removal of the fetus alone was not sufficient, and symptoms persisted until the placenta was delivered (87). Cases of postpartum eclampsia have been associated with retained placental fragments, with rapid improvement after uterine curettage (62).

Severe preeclampsia is associated with pathological evidence of placental hypoperfusion and ischemia. Findings include acute atherosis, a lesion of diffuse vascular obstruction that affects both maternal and fetal vessels, intimal thickening, necrosis, atherosclerosis, and endothelial damage (82). Placental infarcts, likely due to occlusion of spiral arteries, are also common. Abnormal uterine artery Doppler ultrasound, consistent with decreased uteroplacental perfusion, is observed before the clinical onset of preeclampsia (69). The severity of the gross placental pathology appears to be correlated with the severity of the clinical disease, although these findings are not universal (82).

Abnormal placentation

Because of the necessity of the placenta in preeclampsia, there has been much scrutiny on how early abnormalities in placental vascular remodeling may play a role in the disease. Early in normal placental development, extravillous cytotrophoblasts replace the endothelial layer of the maternal spiral arteries, transforming them from small, high-resistance vessels to high-caliber capacitance vessels (see FIGURE 1) capable of providing adequate placental perfusion to sustain the growing fetus. In preeclampsia, this transformation is incomplete. Cytotrophoblast invasion of the spiral arteries is limited to the superficial decidua, and the myometrial segments remain narrow (65). Fisher et al. showed that in normal placental development the cytotrophoblasts assume an endothelium phenotype in a process called pseudovasculogenesis (114), in vascular mimicry, by downregulating the expression of adhesion molecules characteristic of their epithelial cell origin and adopting an endothelial cell surface adhesion phenotype. In preeclampsia, cytotrophoblasts do not undergo this switching of cell-surface molecules and thus are unable to adequately invade the myometrial spiral arteries (113).

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Angiogenic factors are thought to be important in the regulation of placental vascular development (96). Flt1 (VEGFR-1), VEGFR-2, Tie-1, and Tie-2 are essential for normal placental vascular development. Alterations in these pathways in early gestation may contribute to inadequate cytotrophoblast invasion observed in the placenta of women with preeclampsia. Mice with these gene deletions have defective placental vasculogenesis and early embryonic mortality (17a). Invasive cytotrophoblasts express vascular endothelial growth factor (VEGF), placental growth factor (PGF), and VEGFRI (Flt-1); expression of these proteins by immunolocalization is altered in preeclampsia (115). sFlt1 has been shown to decrease cytotrophoblast invasiveness in vitro (115), and circulating sFlt1 levels stay relatively low early in pregnancy and begin to rise in the third trimester. This may reflect a physiological anti-angiogenic shift in the placental milieu toward the end of pregnancy, corresponding to the completion of the vasculogenic phase of placental growth. Alterations in these angiogenic pathways in early gestation could contribute to the inadequate cytotrophoblast invasion seen in preeclampsia, thereby sparking a cycle of continued derangement in angiogenic balance, however, there is no definitive evidence for this hypothesis so far. By the third trimester, excess placental sFlt1 accumulates in the maternal circulation, produces end-organ effects, and reflects the
degree of placental ischemia. Similar to sFlt1, both monoclonal antibodies to endoglin and antisense endoglin oligonucleotides stimulated trophoblast outgrowth and migration in experiments using trophoblasts from 5 to 8 wk of gestation (14). Endoglin (CD105) is a cell surface receptor for TGF-beta. TGF-beta 1 and/or TGF-beta 3 inhibit trophoblast migration and invasion, endoglin may mediate this effect (14).

Therefore, it is possible that soluble endoglin produced by the placenta may be a compensatory mechanism to limit the effects of membrane-bound or surface endoglin. In preeclampsia, excessive production of surface endoglin leads to increased sEng in the maternal circulation. sEng together with sFlt1 may be responsible for the maternal endothelial dysfunction and the clinical manifestations of preeclampsia (see below).
Although preeclampsia appears to begin in the placenta, the target organ is the maternal endothelium (79). Many serum markers of endothelial activation and endothelial dysfunction are deranged in women with preeclampsia, including von Willebrand antigen, cellular fibronectin, soluble tissue factor, soluble E-selectin, platelet-derived growth factor, and endothelin. The incubation of serum taken from preeclamptic women with endothelial cells results in endothelial dysfunction (96). It has been hypothesized that circulating factors originating from the placenta are responsible for the profound effects on the cardiovascular, renal, and cerebral systems (80).

Hemodynamic changes. During normal pregnancy, there are physiological decreases in peripheral vascular resistance and arterial blood pressure, accompanied by increases in cardiac output and vascular compliance. Inversely, preeclampsia is characterized by widespread vasoconstriction, increased vascular resistance, and decreased cardiac output and vascular compliance. Some studies have suggested that cardiac output may be higher in preeclamptic subjects before the onset of overt signs and symptoms (16). This is particularly noted in women with higher BMI. There is also exaggerated sensitivity to vasoressors such as angiotensin II and norepinephrine (80). Women who go on to develop preeclampsia have impaired endothelium-dependent vasorelaxation (44) and subtle increases in blood pressure and pulse pressure before the onset of overt hypertension and proteinuria (22).

Renal pathology. Injury to maternal endothelium is most clearly visualized in the kidney, which reveals the characteristic pathological changes of preeclampsia. In 1959, Spargo et al. coined the term glomerular endotheliosis to describe the ultrastructural changes in renal glomeruli, including generalized swelling and vacuolization of the endothelial cells and loss of the capillary space (see FIGURE 2) (29). There are also deposits of fibrin within and under the endothelial cells. Electron microscopy shows loss of glomerular endothelial fenestrae (49). Unlike other nephrotic diseases, endothelial cells appear to be primarily injured, with modest damage to the podocyte foot processes. Although glomerular endotheliosis was once considered pathognomonic for preeclampsia, recent studies by Stevens et al. showed that mild glomerular endotheliosis also occurs in pregnancy without preeclampsia, especially in a subset of subjects with gestational hypertension (92). This suggests that the endothelial dysfunction of preeclampsia may be an exaggeration of a normal physiological process that occurs near the end of a term pregnancy.

Cerebral edema. Cerebral edema and intracerebral parenchymal hemorrhage are common autopsy findings in women who died from eclampsia, but there is considerable controversy in the literature on the finding of cerebral edema. The cerebral edema in

![FIGURE 2. Glomerular endotheliosis](image-url)
Eclampsia does not correlate with the severity of hypertension, suggesting that the edema may be secondary to endothelial dysfunction rather than a direct result of blood pressure elevation (84). Findings on head CT and MRI are similar to those seen in hypertensive encephalopathy, with vasogenic cerebral edema and infarctions in the subcortical white matter and adjacent gray matter, predominantly in the parietal and occipital lobes (88). An eclampsia-type syndrome with these characteristic MRI changes have been associated with other clinical scenarios, specifically acute hypertensive encephalopathy in the setting of renal disease or immunosuppression (36) as well as with the use of anti-angiogenic agents for cancer therapy (71). This syndrome is called reversible posterior leukoencephalopathy (RPLS) or posterior reversible encephalopathy syndrome (PRES). This association supports the involvement of innate angiogenic factors in the pathophysiology of preeclampsia/eclampsia, as detailed in the next section.

**Mechanisms of preeclampsia**

**Altered angiogenic balance.** Imbalance of endogenous angiogenic factors plays a key role in the pathogenesis of preeclampsia. Increased expression of soluble fms-like tyrosine kinase-1 (sFlt1), associated with decreased placental growth factor (PlGF) and VEGF signaling, were the first abnormalities described (3, 63). VEGF stabilizes endothelial cells in mature blood vessels and is particularly important in maintaining the endothelium in the kidney, liver, and brain. VEGF signals through two major receptors: Flk and Flt1. sFlt1 is a truncated splice variant of the membrane-bound VEGF receptor Flt1, also called VEGFR1. sFlt1 consisting of the extracellular ligand-binding domain without the transmembrane and intracellular signaling domains, is secreted by primarily synctiotrophoblasts into the maternal circulation (18). sFlt1 has also been found to be made in monocytes (75). sFlt1 antagonizes both VEGF and PlGF by binding them in the circulation and preventing interaction with their endogenous receptors (see FIGURE 3) (43).

Placental expression of soluble Flt1 is increased in preeclampsia and is associated with a marked increase in maternal circulating sFlt1 (63). Several investigators have confirmed that the increase in maternal circulating sFlt1 precedes the onset of clinical disease (52, 64, 105) and is correlated with disease severity (17, 52). In addition, in molar gestations, levels of sFlt1 are found to be elevated and may play a role in early onset preeclampsia reported in such pregnancies (47). In vitro effects of sFlt1 include vasocostriction and endothelial dysfunction. Exogenous sFlt1, delivered via an adenovirus vector to pregnant rats produced a syndrome resembling preeclampsia, including hypertension, proteinuria, and glomerular endotheliosis (63). Several variants of sFlt1 have been discovered, including a primate-specific variant that is designated sFlt-1-14 (43, 85). sFlt-1-14 is the predominant VEGF inhibitor produced by human nondendritic cells and in early studies appears to be the majority of the VEGF-neutralizing protein produced by the placenta in preeclamptic women (85).

VEGF is highly expressed by glomerular podocytes, and VEGF receptors are present on glomerular endothelial cells (58). Anti-VEGF therapies given to adult animals cause glomerular endothelial damage with proteinuria (93). In a podocyte-specific VEGF knockout mouse in renal disease glomerular endothelial injury is exacerbated, leading to proteinuria (102) and glomerulonephritis, which binds to human endothelial cells and sEng with brain edema and reversible posterior leukoencephalopathy. Levels of endogenous sFlt1 increases in maternal circulation increases in preeclampsia and is associated with a marked increase in maternal circulating sFlt1 (63). Several investigators have confirmed that the increase in maternal circulating sFlt1 precedes the onset of clinical disease (52, 64, 105) and is correlated with disease severity (17, 52). In addition, in molar gestations, levels of sFlt1 are found to be elevated and may play a role in early onset preeclampsia reported in such pregnancies (47). In vitro effects of sFlt1 include vasocostriction and endothelial dysfunction. Exogenous sFlt1, delivered via an adenovirus vector to pregnant rats produced a syndrome resembling preeclampsia, including hypertension, proteinuria, and glomerular endotheliosis (63). Several variants of sFlt1 have been discovered, including a primate-specific variant that is designated sFlt-1-14 (43, 85). sFlt-1-14 is the predominant VEGF inhibitor produced by human nondendritic cells and in early studies appears to be the majority of the VEGF-neutralizing protein produced by the placenta in preeclamptic women (85).

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knockout mouse, heterozygosity for VEGF-A resulted in renal disease characterized by proteinuria and glomerular endotheliosis (26). In humans, anti-angiogenesis cancer trials with anti-VEGF antibodies have led to proteinuria, hypertension, and loss of glomerular endothelial fenestrae (25, 116). In experimental glomerulonephritis, VEGF is necessary for glomerular capillary repair (61, 70) and may be particularly important in maintaining the health of fenestrated endothelium (28). Fenestrated endothelium is found in the renal glomerulus, choroid plexus, and the bronchial and hepatic sinusoids, organs that are disproportionately affected in preeclampsia. Thus VEGF deficiency, whether induced by anti-VEGF antibodies, gene deletion, or excess sFlt1, is likely responsible for proteinuria and glomerular endotheliosis.

The physiological role of PlGF is less well understood than that of VEGF, but PlGF appears to stimulate angiogenesis under conditions of ischemia, inflammation, and wound healing (15) and may contribute to atherosclerosis (57). PlGF, with structural homology to VEGF-A, is a potent angiogenic growth factor that is thought to amplify VEGF signaling by displacing VEGF from the Flt1 receptor and allowing it to bind to the more potent KDR receptor instead. During pregnancy, inhibition of both PlGF and VEGF is necessary to produce preeclampsia-like changes in pregnant rats (63).

Derangements in other angiogenic factors have also been observed. The other major VEGF receptor, a naturally occurring soluble form of Flk (VEGFR-2), has been identified as being produced by the placenta (23), but its role in preeclampsia is unknown. Additionally, maternal serum levels of endostatin, an inhibitor of VEGF, are increased in preeclampsia (51). Soluble endoglin (slEnd), a truncated form of endoglin, which binds and antagonizes TGF-β (see Figure 3), is upregulated in preeclampsia in a pattern similar to that of sFlt1. Endoglin is expressed at high levels in the syncytiotrophoblast and invading cytotrophoblasts. Levels of endoglin are significantly lower in women with severe preeclampsia. The levels of COMT and 2-ME are also significantly lower in women with preeclampsia than in those without. Levels of circulating sFlt1 are increased in pregnant mice deficient in catechol-O-methyltransferase (COMT) (40), pregnant mice deficient in eotaxin-3 (TGF-β3), which has been shown to block cytotrophoblast invasion, is another HIF target. Hyposia has been shown to upregulate expression and secretion of soluble Flt1 protein in primary trophoblast cultures from first-trimester placentas (117). Paradoxically, cigarette smoking, an important risk factor for fetal growth restriction, is consistently associated with a reduced risk for preeclampsia (24). Levels of circulating sFlt1 and slEnd are significantly lower in women who smoke (51). Circulating pro-angiogenic proteins such as placental growth factor are increased in smokers (51).

Recent in vitro experiments in mice strongly suggest that placental hypoxia contributes to preeclampsia by upregulating soluble anti-angiogenic factors affecting the vasculature. In recent work by Kanasaki et al. (40), pregnant mice deficient in catechol-O-methyltransferase (COMT) also showed a preeclampsia-like phenotype resulting from an absence of 2-methoxyestradiol (2-ME), a natural metabolite of estradiol that is elevated during the third trimester of normal human pregnancy. The addition of 2-ME can improve placental growth factor phenotype resulting from an absence of 2-methoxyestradiol (2-ME) and its targeted delivery is common to both IUGR and preeclampsia. In addition, defective trophoblast invasion and inadequate maternal spiral artery remodeling is common to both IUGR and preeclampsia. Placental ischemia and hypoxia frequently go hand-in-hand. Women with preeclampsia have alterations in placental hypoxia-inhibitory factor (HIF) and its target genes (57). Women residing at high altitudes also have similar alterations in HIF and the rates of preeclampsia in this population are two- to fourfold higher (72). Common subjects of HIF-1 regulation include many angiogenic proteins, including Flt-1, VEGF, Tie-1, and Tie-2. Invasive cytotrophoblasts express several other angiogenic factors regulated by HIF, including VEGF, PlGF, and VEGFR-1; expression of these proteins by immunolocalization is altered in preeclampsia (115). Transforming growth factor beta-1 (TGF-β1), which has been shown to block cytotrophoblast invasion, is another HIF target. Hyposia has been shown to upregulate expression and secretion of soluble Flt1 protein in primary trophoblast cultures from first-trimester placentas (117). Paradoxically, cigarette smoking, an important risk factor for fetal growth restriction, is consistently associated with a reduced risk for preeclampsia (24). Levels of circulating sFlt1 and slEnd are significantly lower in women who smoke (51). Circulating pro-angiogenic proteins such as placental growth factor are increased in smokers (51).

In summary, the role of trophoblast invasion is seen in preeclampsia is a consequence or cause of placental ischemia/hypoxia. In pregnant primates and other mammals, constriction of uterine blood flow (32, 46) has been shown to induce hypertension and proteinuria. However, in these animal models, uterine ischemia does not lead to seizures or HELLP syndrome. In addition, in most cases of preeclampsia, there are minimal downstream fetal consequences expected from placental ischemia, with no evidence of fetal growth restriction or fetal intolerance of labor. Conversely, cases of fetal growth restriction secondary to placental insufficiency frequently occur without preeclampsia. In addition, defective trophoblast invasion and inadequate maternal spiral artery remodeling is common to both IUGR and preeclampsia. Placental ischemia and hypoxia frequently go hand-in-hand. Women with preeclampsia have alterations in placental hypoxia-inhibitory factor (HIF) and its target genes (57). Women residing at high altitudes also have similar alterations in HIF and the rates of preeclampsia in this population are two- to fourfold higher (72). Common subjects of HIF-1 regulation include many angiogenic proteins, including Flt-1, VEGF, Tie-1, and Tie-2. Invasive cytotrophoblasts express several other angiogenic factors regulated by HIF, including VEGF, PlGF, and VEGFR-1; expression of these proteins by immunolocalization is altered in preeclampsia (115). Transforming growth factor beta-1 (TGF-β1), which has been shown to block cytotrophoblast invasion, is another HIF target. Hyposia has been shown to upregulate expression and secretion of soluble Flt1 protein in primary trophoblast cultures from first-trimester placentas (117). Paradoxically, cigarette smoking, an important risk factor for fetal growth restriction, is consistently associated with a reduced risk for preeclampsia (24). Levels of circulating sFlt1 and slEnd are significantly lower in women who smoke (51). Circulating pro-angiogenic proteins such as placental growth factor are increased in smokers (51).
clearly critical to successfully supporting a pregnancy, but overt placental ischemia and hypoxia may not be the causative factor in preeclampsia but rather an important secondary event.

Renin-angiotensin-aldosterone. In addition to altered angiogenic balance and failed cytotrophoblast invasion, the renin-angiotensin-aldosterone axis is also perturbed in preeclampsia. In normal pregnancy, renin, aldosterone, and angiotensin are increased. These hormones are suppressed relative to normal pregnancy in preeclampsia. Women with preeclampsia have increased vascular responsiveness to angiotensin II and other vasoconstrictive agents. Angiotensin II is a well recognized octapeptide mediator of elevated blood pressure that signals arterial vasoconstriction after binding to the angiotensin II type 1 (AT1) receptor. Angiotensin II hypersensitivity in preeclampsia may also be due to heterodimerization of AT1 receptors with bradykinin receptors (1).

Studies have identified agonistic (AT1) receptor autoantibodies in women with preeclampsia (99). These AT1 receptor autoantibodies, like angiotensin II itself, could lead to the production of tissue factor by endothelial cells. Xia et al. found that AT1 receptor autoantibodies decreased invasiveness of immortalized human trophoblasts in an in vitro invasion assay (109). Studies from Zhou et al. indicate that AT1 receptor autoantibodies recovered from the circulation of women with preeclampsia can replicate the key features of preeclampsia in pregnant mice and increase both sFlt1 and sEng in pregnant mice (112). The effects of these antibodies can be blocked with losartan, a pharmacological AT1 receptor antagonist, or by an antibody-neutralizing peptide (30). However, AT1 receptor autoantibodies appear to be increased as well in malignant renovascular hypertension and vascular rejection (30). These autoantibodies may account for the increased angiotensin II sensitivity for preeclampsia. In summary, AT1-AA may be one of several insults that can contribute to the placental damage that is proximally linked to the production of anti-angiogenic factors (see FIGURE 4).

Immunological intolerance and inflammation/oxidative stress. Immune maladaptation remains an intriguing explanation about the pathogenesis of preeclampsia. Normal placentation requires the development of immune tolerance between the fetus and the mother. Preeclampsia occurs more often in first pregnancies, after a change in paternity (94), or with long interpregnancy interval (95). In addition, women using barrier contraceptive methods that reduce maternal exposure to sperm have increased incidence of preeclampsia (46). Women who conceived via intracytoplasmic sperm injection (ICSI) in which sperm was surgically obtained from the male had a threefold increased risk of preeclampsia compared with ICSI cases where sperm was obtained by ejaculation (102). These observations suggest that preeclampsia may involve an abnormal maternal immune response to novel paternally derived fetal antigens. Women with untreated HIV have a very low incidence of preeclampsia, but the incidence returns to normal in HIV-positive women who are on antiretroviral therapy (108).

Natural killer (NK) cells at the maternal/fetal interface are also thought to play an important role in the pathogenesis of preeclampsia. They are thought to be important in modulating immune tolerance required for normal placentation development as well as the induction of angiogenic factors and vascular remodeling (33). Recent genetic studies have suggested that the susceptibility to preeclampsia may be influenced by polymorphic human leukocyte antigen C (HLA-C) ligands and the killer immunoglobulin receptors (KIRs) present. NK-cell signal transduction and cytokine secretion may change with pregnancy (103, 104). KIRs have a high degree of polymorphism, and there is considerable variation in NK-cell recognition of human HLA-C ligands. Still others believe genetic factors influence from
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Endothelial dysfunction in preeclampsia has also been attributed to placental oxidative stress, the excess production of damaging reactive oxygen species (77). A key animal model of preeclampsia is produced by infusion of an inhibitor of nitric oxide (NO) synthesis called L-NAMe (L-nitroarginine methyl-ester), into pregnant rats, which produces hypertension, proteinuria, and thrombocytopenia (110). In preeclampsia, there is decreased production of enzymatic antioxidants (100, 103, 117). Markers of high oxidative stress are also detectable in preeclampsic patients (77), with increased superoxide generation (89, 104), placental levels of lipid peroxidation (101), and production and secretion of isoprostanes (101). There have been a few human clinical trials looking for benefit of antioxidants in preeclampsia. In a small study, treatment with the antioxidant lycopene was also found to reduce the risk of preeclampsia (86). Unfortunately, in randomized controlled studies, supplementation with vitamin C and E during pregnancy has not been shown to reduce the risk of preeclampsia in nulliparous women, intrauterine growth restriction, and other adverse fetal outcomes (13, 74, 81). In summary, although oxidative stress is present in preeclampsia, more work will be needed to design and test specific antioxidants that ameliorate the placental secretion of toxic factors but at the same time promote vascular endothelial health.

Genetics. Although most cases of preeclampsia occur in women without a family history, the presence of preeclampsia in a first-degree relative increases a woman’s risk of severe preeclampsia two- to fourfold (16). If a woman becomes pregnant by a man who has already fathered a preeclamptic pregnancy in a different woman, her risk of developing preeclampsia is almost doubled (55). These studies implicate a strong paternal (thus fetal) component to the genetic predisposition and support a single-gene inheritance model that requires homozygosity for the same recessive gene in both mother and fetus (56). Others have hypothesized a role for genomic imprinting. STOX1 has been extensively studied, with inconsistent findings about its association with preeclampsia (11, 45). Still others believe that preeclampsia is polygenic with influence from multiple susceptibility genes. Other candidate genes that have been studied include prothrombin, lipoprotein lipase, superoxide dismutase, nitric oxide synthetase, and apolipoprotein E (107).

Currently in progress in Great Britain is a large study called The Genetics of Preeclampsia Collaborative (GOPEC) study that is collecting genomic information from 1,000 women with preeclampsia, along with the proband’s parents, child, and partner to explore both maternal and fetal contributions to preeclampsia risk. From an evolutionary perspective, F-H1 variants may confer increased fetal fitness in sub-Saharan Africa from placental malaria and may be under natural selection in a malaria endemic area (86).

Clinical implications Although there is not yet any definitive therapeutic or preventative strategy for preeclampsia, clinical experience suggests that early detection, monitoring, and supportive care are beneficial to the patient and the fetus. Reliable prediction of preeclampsia would allow closer prenatal monitoring and timely intervention with steroids to enhance fetal lung maturity, magnesium for seizure prophylaxis, anti-hypertensive medications and bedrest, and expedient delivery as necessary. Furthermore, a robust biomarker for preeclampsia would provide a clear endpoint to simplify human studies of novel therapies and preventative strategies for preeclampsia. However, no screening test has yet proven accurate enough for widespread clinical use (19).

Because alterations in circulating levels of angiogenic factors occur weeks before the clinical onset of preeclampsia, they represent promising biomarkers for screening and/or diagnosis. Significant elevations in maternal sFlt1 and sEng are observed from mid-gestation onward (73, 105) and appear to rise 5–8 wk before onset of disease (34, 51). The ratio of sFlt1 and sEng to PIGF is a better marker for the diagnosis/prognosis of preeclampsia than any measure alone (51). Retrospective studies demonstrating the feasibility of a urine screening test (PIGF) followed by a confirmatory blood test for circulating angiogenic proteins (sFlt1 and PIGF) for the prediction of preeclampsia are promising (53). Placental protein 11 (PP113) has been reported to be a robust first trimester biomarker for predicting preeclampsia. The biological role of PP13 and its relationship with angiogenic factors remain unknown (31). Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potentially novel interventional treatment strategies may include restoration of normal angiogenic balance in the maternal circulation. One example would be VEGF-121. VEGF-121 was shown to diminish hypertension and proteinuria and prevent extensive renal pathology in a rat model of sFlt1-induced preeclampsia, without apparent harm to the fetus (54). Any intervention that could delay delivery and prolong fetal gestation could have a tremendous impact on neonatal morbidity and mortality. Studies
Our understanding about the pathogenesis of preeclampsia has significantly evolved (see FIGURE 4). Although the initiating events in preeclampsia are still not known, research about the role of circulating angiogenic factors and their regulation will have exciting clinical implications and are likely to transform the detection and treatment of preeclampsia in the future. But many challenges need to be met before findings from this discovery can be applied to disease prevention and treatment. Prospective longitudinal studies examining both urine and serum samples throughout gestation for alterations in angiogenic factors are needed to determine the relevance of these markers for the early identification of preeclampsia and the prediction of its severity. More work is also needed to further define the regulation of placenta vascular development and expression of these factors in normal and diseased pregnancies and to further explore the mechanisms responsible for the variability in maternal response.

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Summary and Future Directions

Our understanding about the pathogenesis of preeclampsia has significantly evolved (see FIGURE 4). Although the initiating events in preeclampsia are still not known, research about the role of circulating angiogenic factors and their regulation will have exciting clinical implications and are likely to transform the detection and treatment of preeclampsia in the future. But many challenges need to be met before findings from this discovery can be applied to disease prevention and treatment. Prospective longitudinal studies examining both urine and serum samples throughout gestation for alterations in angiogenic factors are needed to determine the relevance of these markers for the early identification of preeclampsia and the prediction of its severity. More work is also needed to further define the regulation of placenta vascular development and expression of these factors in normal and diseased pregnancies and to further explore the mechanisms responsible for the variability in maternal response.

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S. A. Karumanchi is listed as a co-investigator on multiple patents filed by the Beth Israel Deaconess Medical Center for the use of angiogenic proteins for the diagnosis and therapy of preeclampsia. S. A. Karumanchi is a consultant to Johnson & Johnson, Roche, Beckman Coulter, and Abbott Diagnostics.

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PHYSIOLOGY


