Preeclampsia: The Role of Angiogenic Factors in Its Pathogenesis

Preeclampsia, a pregnancy-specific disorder characterized clinically by new onset of proteinuria and hypertension, is associated with significant morbidity and mortality to both mothers and fetuses. The pathogenesis of preeclampsia has been enigmatic; this review will focus on understanding the origins of this disorder. Preeclampsia originates in the placenta, starting with inadequate cytotrophoblast invasion and ending with widespread maternal endothelial dysfunction. Production of placental anti-angiogenic factors, specifically soluble fms-related tyrosine kinase 1 and soluble endoglin, have been shown to be upregulated in preeclampsia. These placental anti-angiogenic factors are released into the maternal circulation; their actions disrupt the maternal endothelium and result in hypertension, proteinuria, and other systemic manifestations of preeclampsia. The molecular basis for placental dysregulation of these pathogenic factors remains unknown, remains unknown. Hypoxia is likely an important regulator. Other factors such as alterations in the renin-angiotensin-aldosterone axis, immune maladaptation, excessive shedding of trophoblast debris, oxidative stress, and genetic factors likely contribute to the pathogenesis of the abnormal placentation. As of 2009, the only successful treatment for preeclampsia is delivery. No definitive preventive strategies have been identified. However, several of the recent observations related to phenotypic causality provide stimuli for the development of novel therapies.

Epidemiology and Risk Factors

The worldwide incidence of preeclampsia is 3–4% of all pregnancies (100b). Most cases of preeclampsia occur in healthynulliparous women, in whom the incidence of preeclampsia may be as high as 7.5% (108a). Multiparous women pregnant with a new partner have a similar preeclampsia risk as nulliparous women (95); this has been ascribed to factors associated with a change in paternity or increased interpregnancy interval (90). In addition, women with preeclampsia in a prior pregnancy continue to have a high risk of preeclampsia in subsequent pregnancies. Although most cases of preeclampsia occur in the absence of a family history, the presence of preeclampsia in a first-degree relative increases a woman’s risk of severe preeclampsia two- to fourfold (16). A history of preeclampsia in the father’s mother also confers an increased risk (27).

Several medical conditions are associated with increased preeclampsia risk, including chronic hypertension, diabetes mellitus, renal disease, obesity,
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 who develop preeclampsia even if present after delivery, are epidemiological studies suggesting that there may be long-term cardiovascular consequences. Approximately 20% of women with preeclampsia develop hypertension or microalbuminuria within 7 years 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 year ~20% of women have residual microalbuminuria.

In addition, the long-term risk of cardiovascular and cerebrovascular disease is doubled in women with 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 Viks 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 year postpartum, women who developed preeclampsia had increased blood pressure, total cholesterol, high-density lipoprotein, triglycerides, increased BMI, fasting insulin, HOMA index, and urinary microalbumin/creatinine ratio. The 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 angiogenic factors. These angiogenic factors, such as sFt1 and soluble endoglin, produce systemic endothelial dysfunction, resulting in both the uterine decidua and the other systemic 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 findings include acute atherosis, a lesion of diffuse vascular obstruction that includes fibrin deposition, and symptoms persisted until the placenta was delivered. Invasive 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 endothelial 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).

"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."

Angiogenic factors are thought to be important in the regulation of placental vascular development (96). sFt1 (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 VEGFR-1 (Flt-1); expression of these proteins by immunolocalization is altered in preeclampsia (115). sFt1 has been shown to decrease cytotrophoblast invasiveness in vitro (115), and circulating sFt1 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 vasocigenic 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 sFt1 accumulates in the maternal circulation, produces end-organ effects, and reflects the inflammatory state.
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).

Normal

Abnormal placentation in preeclampsia

In normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion adequate to sustain the growing fetus. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype, a process referred to as "pseudovasculogenesis" or "vascular mimicry" (top). In preeclampsia, cytotrophoblasts fail to adopt an invasive endothelial phenotype. Instead, invasion of the spiral arteries is shallow, and they remain small caliber, resistance vessels (bottom). Figure adapted from Ref. 50.
Target effects: maternal endothelial dysfunction

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, placenta-derived growth factor, and endotelin. 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...
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 (80). An eclampsia-type syndrome with these characteristic MRI changes has 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 syncytiotrophoblasts 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 nongestational 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 vasoconstriction and endothelial dysfunction. Exogenous sFlt1, delivered via an adenovirus vector to pregnant rats, induced 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 sFlt1-14 (43, 85). sFlt1-14 is the predominant VEGF inhibitor produced by human nonendometrial 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 (83). In a podocyte-specific VEGF knockout mouse in renal disease, glomerular endotheliosis caused by VEGF inhibition led to proteinuria, glomerulosclerosis, and hypertension (11). Anti-VEGF antibodies in humans have been associated with severe proteinuria (93). In a podocyte-specific VEGF knockout mouse in renal disease, glomerular endotheliosis caused by VEGF inhibition led to proteinuria, glomerulosclerosis, and hypertension (11). Anti-VEGF antibodies in humans have been associated with severe proteinuria (93). In a podocyte-specific VEGF knockout mouse in renal disease, glomerular endotheliosis caused by VEGF inhibition led to proteinuria, glomerulosclerosis, and hypertension (11). Anti-VEGF antibodies in humans have been associated with severe proteinuria (93). In a podocyte-specific VEGF knockout mouse in renal disease, glomerular endotheliosis caused by VEGF inhibition led to proteinuria, glomerulosclerosis, and hypertension (11). Anti-VEGF antibodies in humans have been associated with severe proteinuria (93).
in the setting of preeclampsia (36) as well as placentation and cancer therapy. sFlt1 prevents receptor tyrosine kinase activation by interfering with the binding of its ligand, PlGF, and thereby inhibits vascular invasion by trophoblast cells (59). Thus, sFlt1 is an important inhibitor of PlGF, a proangiogenic factor, and abnormality in the gene encoding sFlt1, is a cause of the human nonen- donostatin, a truncated form of endostatin, is elevated in preeclampsia (37). Maternal serum levels of endostatin, an inhibitor of angiogenesis, are elevated in preeclampsia (37). Soluble endoglin (sEng), a truncated form of endoglin, which binds and antagonizes TGF-β, 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 major VEGF receptor, a naturally occurring soluble form of Flk (VEGFR-2), has been shown to upregulate expression and secretion of pro-angiogenic factors affecting trophoblast invasion, is another HIF target. Hypoxia has been shown to upregulate expression and secretion of soluble Flt1 protein in primary trophoblast cultures from first-trimester placentas (67). 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 sEng are significantly lower in women who smoke (51). Circulating pro-angiogenic proteins such as placental growth factor are increased in smokers (51).

Recent in vivo 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 preeclampsia-like features without toxicity in the Comt(−/−) pregnant mice. In addition, 2-ME has been shown to suppress placental hypoxia, hypoxia-inducible factor-1alpha expression, and sFlt1 elevation. The levels of Comt and 2-ME are also significantly lower in women with severe preeclampsia. More work is needed to better assess the role of this pathway in human disease. In summary, the role of trophoblast invasion is
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 cytrophoblast invasion, the renin-angiotensin-aldosterone axis is also perturbed in preeclampsia. In normal pregnancy, renal, aldosterone, and angiotensin are the circulating factors (such as sFlt1 and sEng) and other inflammatory mediators to induce angio-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 AT1 receptor autoantibodies (110). In a small study, natural killer (NK) cells at the maternal/fetal interface and sEng were increased in preeclampsia (102). These AT1 receptor autoantibodies, like angiotensin II 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.

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 (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 do not give explanation for the suppression of aldosterone production noted in preeclampsia (42). Present not only during pregnancy, AT1 receptor autoantibodies appear to be increased as well in malignant renovascular hypertension and vascular rejection (30). These AT1 receptor autoantibodies do not give explanation 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 AT1 receptor autoantibodies (110). In a small study, natural killer (NK) cells at the maternal/fetal interface and sEng were increased in preeclampsia (102). These AT1 receptor autoantibodies, like angiotensin II 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 AT1 receptor 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.

In normal pregnancy, AT1 receptor autoantibodies appear to be increased as well in malignant renovascular hypertension and vascular rejection (30). These AT1 receptor 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 AT1 receptor autoantibodies (110). In a small study, natural killer (NK) cells at the maternal/fetal interface and sEng were increased in preeclampsia (102). These AT1 receptor autoantibodies, like angiotensin II or by an antibody-neutralizing peptide (30). However, AT1 receptor autoantibodies do not give explanation for the suppression of aldosterone production noted in preeclampsia (42). Present not only during pregnancy, AT1 receptor autoantibodies appear to be increased as well in malignant renovascular hypertension and vascular rejection (30). These AT1 receptor 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 AT1 receptor autoantibodies (110). In a small study, natural killer (NK) cells at the maternal/fetal interface and sEng were increased in preeclampsia (102). These AT1 receptor autoantibodies, like angiotensin II or by an antibody-neutralizing peptide (30). However, AT1 receptor autoantibodies do not give explanation for the suppression of aldosterone production noted in preeclampsia (42). Present not only during pregnancy, AT1 receptor autoantibodies appear to be increased as well in malignant renovascular hypertension and vascular rejection (30). These AT1 receptor 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).
As a helpful assistant, I can provide a plain text representation of the document. Please note that I will focus on summarizing the key points and important information from the text you provided.

**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 seizures 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 to sEng to PlGF 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 PlGF) for the prediction of preeclampsia are promising (53). Placental protein 13 (PP13) 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 (34). Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potentially novel pharmacological 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...
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 its 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 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.

S. A. Karumanchi is an investigator of the Howard Hughes Medical Institute and a supported by a Clinical Investigator Award from the Burroughs Wellcome Foundation and is supported by a Clinical Scientist Award from the Burroughs Wellcome Foundation.
soluble vascular endothelial growth factor, a protein that mediates the recruitment of leukocytes and induces angiogenesis, plays a significant role in the pathogenesis of preeclampsia.

In summary, preeclampsia is a complex disease that involves multiple factors, including genetic susceptibility, placental abnormalities, and maternal physiology. Further research is necessary to better understand the underlying mechanisms and develop effective preventive strategies.

References:


[2]lished 2017 http://physiologyonline.physiology.org/ Downloaded from


