Preeclampsia: The Role of Angiogenic Factors in Its Pathogenesis

Preeclampsia, a pregnancy-specific disorder characterized 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 the 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 placenta. 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 (108b). Most cases of preeclampsia occur in healthy nulliparous 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, and...
hypercoagulable states, such as antiphospholipid syndrome and factor V Leiden. Advanced maternal age is also an independent risk factor for preeclamp-
sia (22). Conditions associated with increased
placental mass, such as multifetal gestations and hydatidiform mole also predispose women to
preeclampsia. There seems to be no clear association
between consanguinity and the incidence or severity
of preeclampsia (9), however, there are reports of
familial aggregation of preeclampsia and intraterine
growth restriction in a genetically isolated popula-
tions (12). Interestingly, unosculating a pregnant
woman appears to reduce the risk of preeclampsia (24).
Although none of these epidemiological risk factors
are well understood, they have helped to provide
insight into the pathogenesis of preeclampsia.

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 speci-
men 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 empha-
size the more ominous features of the syndrome (see
Table 1), some have suggested a more nuanced dis-
case categorization (55a) or a classification of the dis-
ease based on the gestational age of presentation (98).
The degree of proteinuria varies from minimal to
nephrotic range; however, the amount of proteinuria
within 7 years of a pregnancy complicated by
preeclampsia compared with only 2% among women
with uncomplicated pregnancies (68). A study pub-
lished 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
disease is doubled in women with preeclampsia and gestational hypertension (76). This increase in subsequent cardiovascular disease is observed for both preeclampsia and gestational hypertension (76). A recent study by Viike 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 hyperten-
sion, 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-
er LDL cholesterol, triglycerides, increased BMI,
fasting insulin, HOMA index, and urinary microalbu-
min/creatinine ratio. The increase in long-term car-
diovascular mortality holds even for previously
healthy women without any overt vascular risk fac-
tors 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 subdi-
ately vascular damage or persistent endothelial dysfunc-
tion caused by preeclampsia.
Pathogenesis

The first decade of this millennium has witnessed major advances in our understanding of 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 antiangiogenic factors, such as sFlt1 and soluble endoglin, produce systemic endothelial dysfunction, resulting in homocysteinemia, and the other systemic manifestations of preeclampsia (63, 96). The molecular basis for placental dysregulation of these pathogenic factors remains unknown, and the role of 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-angiotensin-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 leaves fibrin deposits, 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).

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 pseudovascularization (47), or 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). F81 (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 (PlGF), and VEGFR-1 (Flt-1); expression of these proteins by immunolocalization is altered in the placentas of women with 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).

Hemodynamics

There are physical, mechanical, and humoral changes occurring in the placenta, maternal vascular bed, and systemic circulation leading to generalized vasoconstriction and increased systemic vascular resistance. Inversely, pre-existing generalized vasodilation in the smaller vessels decreases systolic blood pressure and increases renal perfusion and glomerular filtration rate.

Receptor Function

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, 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 vaso pressors 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 (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 VEGFRI. 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 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 vasoconstriction and endothelial dysfunction. Exogenous sFlt1, delivered via an adenovirus vector to pregnant rats, induces preeclampsia-like disease in early onset preeclampsia reported in such pregnancies (47).

**Soluble endoglin**

Soluble endoglin (sEng) is another circulating antiangiogenic factor and is thought to amplify the effects of sFlt1. Levels of endoglin increase in maternal circulation during pregnancy (27). In vitro, sEng inhibits both Flt1 and VEGFR1. sEng binding domain without the transmembrane and intracellular signaling domains, is secreted by primarily syncytiotrophoblasts into the maternal circulation. There is mounting evidence that VEGF and TGF-β1 are required to maintain endothelial health in several tissues, including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signaling in the vasculature. In preeclampsia, excess placental secretion of sFlt1 and sEng (two endogenous circulating anti-angiogenic proteins) inhibits VEGF and TGF-β1 signaling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased proliferation, nitric oxide production, and release of procoagulant proteins. Figure adapted from Ref. 41.

**Normal**

![Diagram showing normal endothelial function with VEGF and TGF-β signaling](image)

**Preeclampsia**

![Diagram showing endothelial dysfunction with sFlt1 and sEng](image)

**FIGURE 3.** sFlt1 and sEng cause endothelial dysfunction by antagonizing VEGF and TGF-β signaling

There is mounting evidence that VEGF and TGF-β1 are required to maintain endothelial health in several tissues, including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signaling in the vasculature. In preeclampsia, excess placental secretion of sFlt1 and sEng (two endogenous circulating anti-angiogenic proteins) inhibits VEGF and TGF-β1 signaling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased proliferation, nitric oxide production, and release of procoagulant proteins. Figure adapted from Ref. 41.
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 fenestrations (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 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 acts 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 angiogenesis, are elevated in preeclampsia in a pattern similar to that of sFlt1. Endostatin is expressed at high levels in the syncytiotrophoblast and invading cytotrophoblasts. Levels of endostatin and VEGF in the sera of pregnant women with severe preeclampsia are significantly lower in women who smoke (37). Soluble endoglin (sEng), 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 synecytium of trophoblasts and invading cytotrophoblasts. Levels of sEng are significantly increased in women with severe preeclampsia (94). Several studies in humans and animals have demonstrated that sEng levels are higher in women who smoke, which is associated with increased risk for preeclampsia (24). Levels of circulating 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 all preeclampsia-like features without toxicity in the pregnant mouse. In addition, 2-ME has been shown to suppress placental hypoxia, hypoxia-inducible factor-1 alpha expression, and sFlt1 elevation. The levels of CMNT and 2-ME are also significantly lower in women with severe preeclampsia (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 cytrophoblast 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 medi-ator 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 the AT1 receptor autoantibodies recovered from the circulation of women with preeclampsia can replicate the key features of preeclampsia in pregnant mice (12). 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 (36). 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 placentalation 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 concieved 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 placental 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 secretion of cytotoxic mediators, and other inflam- matory mediators are thought to be increased in women with preeclampsia (109). Normal pregnancy is characterized by an exaggerated systemic inflammatory response, and this response is exaggerated in preeclampsia, and this is also reflected in increased cytokine and chemokine production by placental syncytiotrophoblasts (101). There is evidence that high oxidative stress may be a contributory factor in preeclampsia. In a study by Zhou et al. (110), invasiveness of immortalized human trophoblasts in an in vitro invasion assay was decreased by 10% in preeclampsia compared with normal pregnancy. This was thought to be due to an increased concentration of reactive oxygen species (77).

Genetics. It is increasingly clear that preeclampsia occurs in women with certain genetic abnormalities. Enzymatic studies have been shown to have an inherited component (89, 104). Different species (77). A strong association with preeclampsia has been found in nulliparous women (101), and pro-B-cell interleukin (IL)-1 receptor antagonist (IL-1Ra) deficiency has been identified in women with preeclampsia (103). The presence of pro-B-cell IL-1Ra deficiency has been associated with increased oxidative stress in preeclampsia (101). There is evidence that high concentrations of enzymatic protective effects on women with preeclampsia (101).

FIGURE 4. Summary of the pathogenesis of preeclampsia

Immune factors (such as AT1-AA), oxidative stress, NK cell abnormalities, and other factors may cause placental dysfunction, which in turn leads to the release of anti-angiogenic factors (such as sFlt1 and sEng) and other inflammatory mediators to induce hypertension, proteinuria, and other complications of preeclampsia.
AA may be one inflammatory explanation for the circulatory remodeling that occurs during pregnancy (112). However, other explanations for increased oxidative stress are also detectable in preeclampsia (77). A key animal model of preeclampsia is produced by infusion of an inhibitor of nitric oxide (NO) synthesis called L-NAMe (L-nitrosoglutathione 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 preeclamptic placentas (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.

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 maternal/fetal component to the genetic predisposition. Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potentially novel pharmacological treatments 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 sFlt-1-induced preeclampsia, without apparent harm to the fetus (54). Current pregnancy outcomes suggest that the first trimester biomarker for predicting preeclampsia (PP13) has been reported to be a robust first trimester biomarker for predicting preeclampsia (53). Placental protein 13 (PP13) has been shown to be a robust first trimester biomarker for predicting preeclampsia (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 remains unknown (31). Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potentially novel pharmacological treatments 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 sFlt-1-induced preeclampsia, without apparent harm to the fetus (54). Current pregnancy outcomes suggest that the first trimester biomarker for predicting preeclampsia (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 remains unknown (31). Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potentially novel pharmacological treatments 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 sFlt-1-induced preeclampsia, without apparent harm to the fetus (54). Current pregnancy outcomes suggest that the first trimester biomarker for predicting preeclampsia (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 remains unknown (31). Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potentially novel pharmacological treatments 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 sFlt-1-induced preeclampsia, without apparent harm to the fetus (54). Current pregnancy outcomes suggest that the first trimester biomarker for predicting preeclampsia (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 remains unknown (31). Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potentially novel pharmacological treatments 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 sFlt-1-induced preeclampsia, without apparent harm to the fetus (54).
using DIGIBIND, a digoxin antibody that binds digitalis-like cardiac steroids (CTS), have been given to women with severe and early preeclampsia to try to prolong gestation since there have been previous trials that have noted that the drug can lower blood pressure in hypertensive gravidas (2). Of interest in this respect is that the levels of a digitalis-like cardiac steroid with vasoconstrictor properties, maritominogenin (MBG), are increased fourfold in patients with severe preeclampsia (5). Statins have also been proposed as a potential therapeutic agent for preeclampsia through their effects on heme oxygenase-1 (HO-1) activity and lowered sR1 production (21). Of note, however, is that these suggestions come from animal studies, and the use of statins in human pregnancy is currently contraindicated because of potential teratogenic effects.

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 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 placental 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-inventor 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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