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 placentation. As of 2009, the only successful treatment for preeclampsia is delivery. No definitive preventative 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 multital placentas 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 intrauterine growth restriction in a genetically isolated popula-
tions (12). Interestingly, uncontrolled maternal weight gain 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 $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg, and proteinuria ($\geq 0.3$ 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 otherinsidious 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-
sify 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-
eease 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 have hypertension but without proteinuria is uncertain, but close follow-up is prudent. This recommen-
dation 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 min-
imal 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 oncomic pressure is similar to healthy pregnant woman (49). Uncommon but serious

maternal complications of preeclampsia include acute renal failure, placental abruption, seizures, pulmonary edema, acute liver injury, hemolysis, and/or thrombo-
cytopenia. The latter three signs frequently occur together as part of the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Consider-
ed 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 $\sim 2\%$ of preeclampsia cases in the United States. Up to one-
third of these women develop eclampsia within 48 h after delivery (88). Complications affecting the devel-
of antigranulocyte and spontaneous prema-
aturity (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 conse-
quences. Approximately 20% of women with preeclampsia develop hypertension or microalbuminur-
ia 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 year
$\sim 20\%$ 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). 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 hyperten-
sion, 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-

148

er LDL cholesterol, triglycerides, increased BMI, fasting insulin, HOMA index, and urinary microalbu-

min/creatinine ratio. The increase in long-term cardio-

vascular 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 subhe vascular damage or persistent endothelial dysfunc-
tion 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 sFlt1 and soluble endoglin, produce systemic endothelial dysfunction, resulting in abnormal vascular tone, and the other systemic manifestations of preeclampsia (63, 96). The molecular basis for placental dysregulation of these angiogenic 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 preeclampsia with an extra-uterine pregnancy suggest that early detection, monitoring, and supportive care to the patient and the fetus.

Angiogenic factors are thought to be important in the regulation of placental vascular development (96). Fh1 (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 placentas of women with preeclampsia. Mice with these gene deletions have defective placental vascular development (96). sFlt1 accumulates in the maternal circulation by 10.220.33.4 on November 6, 2017 http://physiologyonline.physiology.org/ Downloaded from...
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).

![Diagram of placental development in normal and preeclamptic conditions](image)

**FIGURE 1. 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, 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 vasopressors 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 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 (73). This syndrome is called reversible posterior leukoencephalopathy (RPLS) or posterior reversible encephalopathy syndrome (PRES). This association supports the involvement of innate antiangiogenic 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 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, induced preeclampsia (63). sFlt1 antagonizes both VEGF and PLGF by binding them in the circulation and preventing interaction with their endogenous receptors (see FIGURE 3) (43).

There is mounting evidence that VEGF and TGF-β signaling is 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 pre-eclampsia, 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 prosta-cyclin, nitric oxide production, and release of procoagulant proteins. Figure adapted from Ref. 41.
In the setting of endogelinection (36) as well as cancer therapeutics (37), soluble posterior sFlt1, also called plGF receptor (PlGF) and sEng proteins (37), have abnormalities in preeclampsia. These proteins have been identified as being produced by the placenta (23), naturally occurring soluble form of Flk (VEGFR-2), has been shown to upregulate expression and secretion of angiogenic proteins by immunolocalization is altered in preeclampsia (37). 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).

Regurgitations in other angiogenic factors have also been observed. The other major VEGF receptor, a naturally occurring soluble form of Plk (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 (37). Soluble endostatin (sEnd), a truncated form of endostatin, which binds and antagonizes TGF-β (see FIGURE 3), is upregulated 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 are significantly increased in pregnant rats (51). Several factors may contribute to this increase in sEnd in women with preeclampsia. Levels of circulating pro-angiogenic proteins such as plGF, with structural homology to VEGF-A, are increased in smokers (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 Kanaasaki 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 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 who smoke (51). Circulating pro-angiogenic proteins such as plGF, with structural homology to VEGF-A, 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 Kanaasaki 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 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 who smoke (51). Circulating pro-angiogenic proteins such as plGF, with structural homology to VEGF-A, 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 Kanaasaki 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 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 who smoke (51). Circulating pro-angiogenic proteins such as plGF, with structural homology to VEGF-A, 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 Kanaasaki 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 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 who smoke (51). 

Placental ischemia/hypoxia is not understood whether the cytotoxic trophoblast invasion leading to incomplete remodeling of the uterine spiral arteries seen in preeclampsia is a consequence or cause of placental ischemia/hypoxia. In pregnant primates and other mammals, constriction of uterine blood flow (32, 40) 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 is 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 pre-eclampsia. In addition, defective trophoblast invasion and inadequate maternal spiral artery remodeling is common to both RIGR and preeclampsia. Placental ischemia and hypoxia frequently go hand-in-hand. Women with preeclampsia have alterations in placental hypoxia-inducible factor (HIF) and its target (57). Women residing at high altitudes also have similar alterations in HIF and the rates of preeclampsia in this population are two- to four-fold higher (72). Common subjects of HIF-1 regulation include many angiogenic proteins, including Flk-1, VEGF-B, Tie-1, and Tie-2. Invasive cytotrophoblasts express several other angiogenic factors regulated by HIF, including VEGF, PlGF, and VEGF-B-1, expression of these proteins by immunolocalization is altered in preeclampsia (115). Transforming growth factor beta-1 (TGF-B1), which has been shown to block cytotrophoblast 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 (167). 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).
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 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 (108). 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 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. 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 (96), or with long interpregnancy interval (96). In addition, women using barrier contraceptive methods have higher risk of preeclampsia. Despite this, the nature of the immunological intolerance has not been clear. Several studies have suggested that maternal immune system is primed before pregnancy begins. Unfortunately, it has been difficult to study these observations in humans, and most studies have been in animal models. In a small study, women who were already pregnant at the time of their pregnancy were included, and these women had a threefold increased risk of preeclampsia (16). If a woman was already carrying a baby in her womb, her immune system was already primed for pregnancy (96).

Genetics. SNP in the VEGF gene in both the maternal and paternal lineages were associated with increased risk for preeclampsia (1). The SNPs in the VEGF gene showed an additive maternal effect (1). The VEGF gene was associated with increased risk for preeclampsia even after controlling for maternal age, maternal height, and maternal weight. This suggests that VEGF is a major susceptibility gene for preeclampsia (49). However, in another study, VEGF gene was not associated with preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101). There are many other SNPs that may contribute to risk for preeclampsia (116). The exact role of these SNPs in preeclampsia is not clear, but they may play a role in the development of preeclampsia (101).
normal pregnancy, a condition with an enhanced systemic inflammatory response, becomes markedly exaggerated in preeclampsia (77). There is evidence of increased circulating fetal DNA and syncytiotrophoblast debris in the maternal circulation in women with preeclampsia (38, 78, 83). These debris, consisting of syncytiotrophoblast membrane micro particles and cytotrophoblast debris, are inflammatory and a likely cause for increased oxidative stress.

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-NNAME (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 preeclamptic placenta (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 was also found 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 antioxidant therapies in preeclampsia.

Inflammation remains a key driver of the genetic hypersensitivity reactions that lead to the clinical symptoms of preeclampsia. Women in whom preeclampsia develops appear to be more sensitive to placental oxidative stress and increased circulating fetal DNA (77). Antioxidant supplementation in women at high risk of preeclampsia may already reduce the risk of preeclampsia (86). Although there is not yet any definitive therapeutic or preventative strategy for preeclampsia, early identification of high-risk women and implementation of preventive strategies may reduce maternal and fetal morbidity and mortality.

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, FH1 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 seizures prophylaxis, anti-hypertensive medications and bedrest, and expedited 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 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 (PREG) 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 (31).

Other than delivery of the placenta, there is no known cure. After delivery, symptoms typically resolve within 48–72 h. Potential 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 sFlt-1-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
using DIGIBIND, a digoxin antibody that binds digital-is-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, maritubogin (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 home oxygenase-1 (HO1) 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 con-traindicated 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 antiangiogenic 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 are needed to determine the importance 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 is supported by a Clinical Scientist Award from the Burroughs Wellcome Foundation and an Established Investigator Grant from the American Heart Association. S. Rana is supported by an NIH-K12 and an Established Investigator grant from the American Heart Association.

References

1. AbdAlla S, Lother H, el Massiery A, Quitterer U. Increased Abbott Diagnostics. to Johnson & Johnson, Roche, Beckman Coulter, and patents filed by the Beth Israel Deaconess Medical Center career development award. S. A. Karumanchi is a consultant for the use of angiogenic proteins for the diagnosis and prevention 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.


REVIEWs


