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Angiogenic Factors and Preeclampsia

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Summary

Preeclampsia, a hypertensive disorder peculiar to pregnancy, is a systemic syndrome that appears to originate in the placenta and is characterized by widespread maternal endothelial dysfunction. Until recently, the molecular pathogenesis of phenotypic preeclampsia was largely unknown, but recent observations support the hypothesis that altered expression of placental anti-angiogenic factors are responsible for the clinical manifestation of the disease. Soluble Flt1 and soluble endoglin, secreted by the placenta, are increased in the maternal circulation weeks before the onset of preeclampsia. These anti-angiogenic factors produce systemic endothelial dysfunction, resulting in hypertension, proteinuria, and the other systemic manifestations of preeclampsia. The molecular basis for placental dysregulation of these pathogenic factors remains unknown, and as of 2010 the role of angiogenic proteins in early placental vascular development was starting to be explored. The data linking angiogenic factors to preeclampsia have exciting clinical implications, and likely will transform the detection and treatment of preeclampsia.

Keywords

Preeclampsia; angiogenic factors; hypertension in pregnancy; endothelial dysfunction; VEGF; sFlt1

Preeclampsia_[DVC3]_[DVC4]_[DVC5], a systemic syndrome manifested primarily by hypertension and proteinuria, presents mainly in the second half of pregnancy, and affects approximately 3% to 5% of pregnancies worldwide.¹ There have been recent advances in our understanding of the pathophysiology of preeclampsia, many reported this very decade, but as yet there is no specific cure, delivery of the placenta remaining the only definitive treatment. Thus, as of 2010 preeclampsia is still a leading cause of maternal mortality, preterm birth, and consequent neonatal morbidity and mortality. In developing countries, where access to safe, emergent delivery is less readily available, preeclampsia claims the lives of more than 60,000 mothers every year.¹

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This article describes recent discoveries concerning the pathogenesis of preeclampsia, with emphasis on the emerging role of angiogenic factors as potential mediators of the clinical signs and symptoms of preeclampsia. Also discussed are the potential use of angiogenic factors to predict preeclampsia, and the potential for prevention, and eventually treatment of the disease.

EPIDEMIOLOGY AND RISK FACTORS

Most cases of preeclampsia occur in women who commence their pregnancies as healthy nulliparas, among whom the incidence is approximately 7%.² The majority of these patients have no family history of the disorder; still, the presence of preeclampsia in a first-degree relative increases a woman's risk of severe preeclampsia by 2- to 4-fold,³ suggesting a genetic contribution to the disease. A history of preeclampsia in the father's mother also confers increased risk, recalling the fact that the placenta is a product of both mother and father.⁴

Several medical conditions are associated with increased preeclampsia risk, including chronic hypertension, diabetes mellitus, renal disease, obesity, and hypercoagulable states.⁵ Women with preeclampsia in a prior pregnancy also have a higher risk of developing preeclampsia in subsequent pregnancies. Conditions associated with increased placental mass, such as multifetal gestations and hydatidiform mole, also are associated with increased preeclampsia risk. Counterintuitively, smoking during pregnancy reduces the risk of preeclampsia.⁶ Although none of the earlier-noted risk factors is fully understood, they have provided insights into pathogenesis.

CLINICAL FEATURES

The new onset of hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) and proteinuria (≥ 300 mg/24 h) after 20 weeks' gestation are the cardinal features of preeclampsia. Although edema was historically part of the diagnostic triad for preeclampsia, it is also a common feature of normal pregnancy, diminishing its usefulness as a specific pathologic sign. Still, the sudden onset of severe edema—especially edema of the hands and face—can be an important presenting symptom in this otherwise insidious disease, and is sometimes the only change detectable by the patient.

Uncommon but serious complications of preeclampsia can include acute renal failure, seizures (eclampsia), pulmonary edema, acute liver injury, hemolysis, and/or thrombocytopenia. The latter three signs frequently occur together, as part of the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, a severe preeclampsia variant. Seizures (eclampsia) occur in approximately 2% of women with preeclampsia in the United States. Although eclampsia most often occurs in the setting of hypertension, proteinuria, and evidence of central nervous system involvement (such as headache and hyperreflexia), it can occur without these warning signs.

Complications affecting the developing fetus and neonate include prematurity (both induced for maternal indications and spontaneous⁷) fetal growth restriction, oligohydramnios, and placental abruption. Although the exact pathogenesis of these complications is unknown, impaired uteroplacental blood flow or placental infarction are likely to contribute.

MATERNAL AND NEONATAL MORTALITY

Approximately 500,000 women die in childbirth each year worldwide. Hypertensive disorders of pregnancy are estimated to account for 16% of maternal deaths in developed countries, and 9% of maternal deaths in Africa and Asia.⁸ Maternal death most often is

caused by eclampsia, cerebral hemorrhage, renal failure, hepatic failure, or the HELLP syndrome. Adverse maternal outcomes often can be avoided with timely delivery; hence, in the developed world the burden of morbidity and mortality falls on the neonate. Worldwide, preeclampsia is associated with a perinatal and neonatal mortality rate of 10%.⁹ Neonatal death most commonly is caused by premature delivery undertaken to preserve the health of the mother, but also can result from placental abruption or intrauterine fetal death.

THE ROLE OF PLACENTAL ISCHEMIA

Observational evidence suggests the placenta has a central role in preeclampsia. Preeclampsia only occurs in the presence of a placenta—although not necessarily a fetus, as in the case of hydatidiform mole—and almost always remits quickly after delivery of the placenta. In this respect there have been cases of postpartum eclampsia associated with retained placental fragments, with rapid improvement only after uterine curettage.¹⁰ In severe preeclampsia, there is pathologic evidence of placental hypoperfusion and ischemia, including acute atherosclerosis, intimal thickening, necrosis, atherosclerosis, and endothelial damage, and placental infarction. Although these findings are not universal, they appear to correlate with severity of clinical disease.¹¹

Abnormal uterine artery Doppler ultrasound, consistent with decreased uteroplacental perfusion, may be observed before the clinical onset of preeclampsia. Unfortunately, this finding is nonspecific, so it is not diagnostically useful if used alone. In women residing at high altitude, among whom the incidence of preeclampsia is increased 2- to 4-fold,¹² there are alterations in placental hypoxia-inducible factor and its targets similar to those seen in preeclampsia^{13,14} (see later). Hypertension and proteinuria can be induced by constriction of uterine blood flow in pregnant primates and other mammals.^{15,16} These observations suggest that placental hypoxia and/or ischemia may be an early event in preeclampsia.

However, evidence that placental ischemia causes preeclampsia remains circumstantial, and several observations call the hypothesis into question. For example, the animal models based on uterine hypoperfusion fail to induce several of the multiorgan features of preeclampsia, including seizures and the HELLP syndrome. In most cases of preeclampsia, there is no evidence of growth restriction or fetal intolerance of labor, expected consequences of placental ischemia. Conversely, cases of fetal growth restriction, in which placental insufficiency is the rule, often occur without preeclampsia. Hence, overt placental ischemia may be neither universal nor specific for preeclampsia, but instead may be an important secondary event observed in severe cases.

PLACENTAL VASCULAR REMODELING

Early in normal placental development, extravillous cytotrophoblasts invade the uterine spiral arteries of the decidua and myometrium. These invasive fetal cells replace the endothelial layer of the uterine vessels, transforming them from small resistance vessels to flaccid, high-caliber capacitance vessels. This vascular transformation allows the increase in uterine blood flow needed to sustain the fetus through the pregnancy. In preeclampsia, this transformation is incomplete. Cytotrophoblast invasion of the arteries is limited to the superficial decidua, and the myometrial segments remain narrow and undilated.¹⁷ In normal placental vasculogenesis, invasive cytotrophoblasts down-regulate the expression of adhesion molecules characteristic of their epithelial cell origin and adopt an endothelial cell-surface adhesion phenotype, a process dubbed *pseudovasculogenesis*.¹⁸ In preeclampsia, cytotrophoblasts do not undergo this switching of cell-surface integrins and adhesion molecules, and fail to adequately invade the myometrial spiral arteries.¹⁹

MATERNAL ENDOTHELIAL DYSFUNCTION

Although preeclampsia appears to originate in the placenta, the tissue affected most is the maternal endothelium. The clinical manifestations of preeclampsia reflect widespread endothelial dysfunction, with vasoconstriction and end-organ ischemia. Exposure of endothelial cells to serum from women with preeclampsia results in endothelial dysfunction; hence, it has been hypothesized that circulating factors, probably originating in the placenta, are responsible for the manifestations of the disease.²⁰ Dozens of 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.

HEMODYNAMIC CHANGES

The decrease in peripheral vascular resistance and arterial blood pressure that occur during normal pregnancy are usually absent or reversed in preeclampsia. Systemic vascular resistance is high and cardiac output is low during overt disease, owing to widespread vasoconstriction. There is exaggerated sensitivity to vasopressors such as angiotensin II and norepinephrine.²⁰ Some women destined to develop preeclampsia have been shown to manifest impaired endothelium-dependent vasorelaxation²¹ and subtle increases in blood pressure and pulse pressure⁵ before onset of definitive hypertension and proteinuria, suggesting that changes in endothelial function are present early in the course of the disease.

Renal Pathology

The renal pathology of preeclampsia is described elsewhere in this issue^[DVC6]. Briefly, in 1959, Spargo^[DVC7] et al coined the term *glomerular endotheliosis* to describe ultrastructural changes in renal glomeruli, including generalized swelling and vacuolization of the endothelial cells and loss of the capillary space (Fig. 1). There is often subendothelial fibrin deposition and loss of glomerular endothelial fenestrae. The primary injury appears to be to the endothelial cells because the podocyte foot processes are intact early in disease, a finding atypical of other nephrotic diseases. Glomerular endotheliosis is characteristic but not pathognomic for preeclampsia because it has been described periodically in case reports of placental abruption in hypertensive pregnancies without proteinuria, and even in normal gestations.²² However, in virtually all these instances the changes are borderline to mild, and it is only in preeclampsia that a simultaneous increase in glomerular volume accompanies the endothelial swelling. Still, the observation of some endotheliosis in mild de novo hypertensive patients and perhaps in normal gestation suggests the endothelial dysfunction of preeclampsia may in fact be an exaggeration of a process present near term in many normal pregnancies.

CEREBRAL EDEMA

Intracerebral parenchymal hemorrhage, ranging in magnitude from microscopic to overt bleeding, is a common autopsy finding in eclampsia. Cerebral edema also often is observed, and when noted radiologically the presence of cerebral edema in eclampsia correlates with markers of endothelial damage but not the severity of hypertension,²³ suggesting the edema is secondary to endothelial dysfunction rather than a direct result of blood pressure increase. Findings on head computed^[DVC8] tomography and magnetic resonance imaging may be similar to those described in hypertensive encephalopathy, with vasogenic cerebral edema and infarctions in the subcortical white matter and adjacent gray matter, predominantly in the parieto-occipital lobes.²⁴ A syndrome that includes these characteristic magnetic resonance imaging changes, together with headache, seizures, altered mental status, and hypertension, has been described in patients with acute hypertensive encephalopathy in the

setting of renal disease, eclampsia, or immunosuppression. This syndrome, termed *reversible posterior leukoencephalopathy*, subsequently has been associated with the use of anti-angiogenic agents for cancer therapy.²⁵ This association supports the involvement of innate anti-angiogenic factors in the pathophysiology of preeclampsia/eclampsia, as detailed in the next section.

ANTIANGIOGENIC FACTORS IN PREECLAMPSIA

There is a topic^[DVC9] of literature that has grown almost logarithmically since 2003 suggesting that circulating angiogenic factors play a key role in the pathogenesis of preeclampsia. Increased expression of soluble fms-like tyrosine kinase-1 (sFlt1), together with decreased placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) signaling, were the first abnormalities described.^{26,27}

sFlt1: A CIRCULATING ANTAGONIST TO VEGF AND PLGF

sFlt1 results from alternative splicing of Flt1, an endothelial receptor for VEGF and PlGF. sFlt1 consists of the extracellular ligand-binding domain of Flt1, but lacks the transmembrane and intracellular signaling domain. Hence, it is secreted into the circulation where it binds and antagonizes VEGF and PlGF²⁸ (Fig. 2). The extensive literature on sFlt1 in preeclampsia, discussed later, assumes the form originally described by Kendall and Thomas^{28[DVC10]} derived from an endothelial cell line. However, more recent studies have identified a second sFlt1 splice form expressed in cytotrophoblasts, which differs in its c-terminus and also appears to be up-regulated in preeclampsia.^{29–32} The biologic significance of the different sFlt1 variants with regard to anti-angiogenic activity and their role in the pathogenesis of preeclampsia is a subject of ongoing study.

Placental expression of sFlt1 is increased in preeclampsia and is associated with a marked increase in the levels of maternal circulating sFlt1.²⁶ Circulating levels of sFlt1 and PlGF are altered several weeks before the onset of clinical disease and are correlated with severity of disease.^{33–35} sFlt1 levels normalize within several days after delivery, coinciding with improvement in proteinuria and hypertension.

In vitro effects of sFlt1 include vasoconstriction and endothelial dysfunction. Increasing circulating sFlt levels in gravid mice and rats, either by direct infusion of the protein by injecting adenovirus expressing the sFlt messenger RNA, produces a syndrome resembling human preeclampsia, including hypertension, proteinuria, and glomerular endotheliosis^{26,36} (Fig. 1). Animal models of preeclampsia based on reduced uterine perfusion pressure in both rats and primates are characterized by increased circulating and placental sFlt1.^{15,37} Thus, sFlt1 overexpression is a key mechanism linking placental dysfunction with maternal endothelial dysfunction.

SOLUBLE ENDOGLIN: A CIRCULATING ANTAGONIST TO TRANSFORMING GROWTH FACTOR- β

Soluble endoglin (sEng) is another anti-angiogenic biomarker that is up-regulated in preeclampsia in a pattern similar to sFlt1. sEng is a truncated form of endoglin (CD105), a cell surface receptor for transforming growth factor- β (TGF- β), which binds and antagonizes TGF- β (Fig. 3). sEng amplifies the vascular damage mediated by sFlt1 in pregnant rats, inducing a severe preeclampsia-like syndrome with features of the HELLP syndrome.³⁸ As with sFlt1, circulating sEng levels are increased weeks before preeclampsia onset,^{39–41} and increased sEng levels are observed in the reduced uterine perfusion pressure rat model of preeclampsia.⁴² Cultured placental trophoblasts from women with

preeclampsia show increased sEng and sFlt1 expression, both at normoxic conditions and in response to hypoxia, as compared with normal placental trophoblasts.⁴³ The similarity in gestational patterns of circulating sFlt1 and sEng suggest they may be regulated by a common upstream signaling pathway.

VEGF SIGNALING AND ENDOTHELIAL CELL HEALTH

There is additional experimental evidence that supports the hypothesis that interference with VEGF/PlGF signaling could mediate endothelial dysfunction in preeclampsia. VEGF is important in the stabilization of endothelial cells in mature blood vessels. VEGF is particularly important in the health of the fenestrated and sinusoidal endothelium found in the renal glomerulus, brain, and liver⁴⁴—organs severely affected in preeclampsia. VEGF is highly expressed by glomerular podocytes, and VEGF receptors are present on glomerular endothelial cells.⁴⁵ Anti-VEGF therapies given to adult animals cause glomerular endothelial damage with proteinuria.^{46,47} In a podocyte-specific VEGF knock-out mouse, heterozygosity for VEGF-A_[DVC11] resulted in renal disease characterized by proteinuria and glomerular endotheliosis.⁴⁸ The most striking experimental illustration of the effect of VEGF antagonism in human beings comes from anti-angiogenesis cancer trials, in which anti-VEGF antibodies produce proteinuria, hypertension, and loss of glomerular endothelial fenestrae.^{49,50} This suggests that VEGF deficiency, induced by excess sFlt1, can produce the characteristic renal manifestations of preeclampsia.

The physiologic 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, and may contribute to atherosclerosis.⁵¹ Blockade of both VEGF and PlGF is required to produce preeclampsia-like changes in pregnant rats,²⁶ signifying that PlGF blockade may be important in the pathogenesis of sFlt1-induced endothelial dysfunction.

ANGIOGENIC SIGNALS IN PLACENTAL VASCULAR DEVELOPMENT

Angiogenic factors are likely to be important in the regulation of placental vasculogenesis. VEGF, PlGF, and Flt1 are highly expressed by invasive cytotrophoblasts, and their expression is altered in preeclampsia.¹⁹ Mice deficient in these receptors have defective placental vasculogenesis and die in utero.⁵² sFlt1 decreases cytotrophoblast invasiveness in vitro.¹⁹ Circulating sFlt1 and sEng levels are relatively low early in pregnancy, and begin to increase in the third trimester. It is intuitive to hypothesize that placental vascular development might be regulated by a local balance between proangiogenic and anti-angiogenic factors, and that local alterations in early gestation could contribute to inadequate cytotrophoblast invasion in preeclampsia. By the third trimester, excess placental sFlt1 is detectable in the maternal circulation producing end-organ effects. In this case, placental ischemia may not be causative, but rather reflective of the derangement of angiogenic balance.

INSIGHTS FROM PREECLAMPSIA RISK FACTORS

Altered angiogenic factor expression is seen with several preeclampsia risk factors. Higher sFlt1 levels have been noted in first versus second pregnancies,⁵³ twin versus singleton pregnancies,⁵⁴ hydatidiform mole,^{55,56} and pregnancies with fetuses having trisomy 1357—all established risk factors for preeclampsia. Conversely, decreased levels of sFlt1 in pregnant smokers^{58,59} may explain the protective effect of smoking in preeclampsia. Cigarette smoke extract appears to directly diminish sFlt1 production in placental villous explants.⁶⁰

Several preeclampsia risk factors, including chronic hypertension, diabetes mellitus, and obesity, probably are related to underlying maternal endothelial dysfunction, which may increase susceptibility of the vasculature to the effects of circulating anti-angiogenic factors. If so, the manifestations of preeclampsia might be produced at a lower threshold of circulating sFlt1 than in previously healthy women. Indeed, sFlt1 levels are lower in obese versus normal-weight women with preeclampsia.⁶¹ Whether other vascular risk factors, such as chronic hypertension and diabetes mellitus, have a similar pattern remains to be seen.

PREECLAMPSIA AND INTRAUTERINE GROWTH RESTRICTION: SHARED CLINICAL AND PATHOPHYSIOLOGIC FEATURES

Preeclampsia and intrauterine growth restriction (IUGR) share many clinical and pathologic features. IUGR is a common complication of preeclampsia, and abnormal uterine blood flow by Doppler ultrasound in early pregnancy is associated with an increased risk for both disorders. Why some women with placental insufficiency manifest the systemic syndrome of preeclampsia, whereas others have IUGR without preeclampsia, is unknown. Data are mixed regarding alterations in angiogenic factors in IUGR alone: some studies report alterations in sFlt1, sEng, and/or PlGF in patients with IUGR similar to those seen in preeclampsia,^{62,63} whereas others have not found such changes.^{64,65} Alterations in angiogenic factors in IUGR without preeclampsia, when detected, are less pronounced than in preeclampsia. The two conditions may share common pathophysiologic underpinnings, at least at the level of insufficient placental vascular development, but the discordant literature on this subject is beyond the scope of this review. Variability in clinical phenotype may be attributable to individual environmental and genetic differences that alter the maternal response to the placental disease.

UPSTREAM PATHWAYS OF ANGIOGENIC FACTOR DYSREGULATION IN PREECLAMPSIA

The factors regulating sFlt1 and sEng expression in preeclampsia are just beginning to be described (Fig. 3). Heme oxygenase-1 (HO-1), an anti-inflammatory enzyme with antioxidant properties, attenuates VEGF-induced and proteinase-activated receptor-2–induced sFlt1 expression.^{66,67} Diminished activity of HO-1 has been observed in women with preeclampsia,⁶⁸ and may mediate increased placental sFlt1 and sEng expression. Indeed, HO-1–deficient mice have defective placental vasculogenesis, increased circulating sFlt1 levels, and hypertension in pregnancy.⁶⁹ These observations are particularly exciting because they suggest a potential use of statins, which induce HO-1 production, in the treatment of preeclampsia. Unfortunately, statins currently are contraindicated for use in human pregnancy (Food and Drug Administration category X).

A potential role for agonistic autoantibodies to the angiotensin II type-1 receptor in the pathogenesis of preeclampsia has developed over recent years, as described in detail elsewhere in this issue of *Seminars in Nephrology* (see the article by Xia^[DVC12]). In a series of elegant studies, Zhou et al^{70,71} showed that angiotensin II type-1 receptor autoantibodies derived from the serum of women with preeclampsia produce a preeclampsia-like syndrome in pregnant rats, and induce placental sFlt1 and sEng expression. Hence, angiotensin II type-1 receptor autoantibodies may be a key regulator of pathogenic sFlt1 and sEng up-regulation in preeclampsia.

2-Methoxyestradiol is a metabolite of estradiol and is generated by catechol-O-methyltransferase. Recently, catechol-O-methyl-transferase–deficient mice were shown to have a preeclampsia-like phenotype, which was rescued by administration of 2-

methoxyestradiol, possibly via inhibition of hypoxia-inducible factor 1- α and downstream targets such as sFlt1.⁷² 2-Methoxyestradiol appears to mediate cytotrophoblast invasiveness under hypoxic conditions, suggesting a role in normal placental vasculogenesis.⁷³

OTHER ANGIOGENIC BIOMARKERS IN PREECLAMPSIA

Other proteins with angiogenic activity also have been linked to preeclampsia. Angiopoietin-1 and its endogenous inhibitor, angiopoietin-2, are involved in implantation and placental vasculogenesis. Several studies suggest plasma levels of angiopoietin-1 and angiopoietin-2 are altered before the onset of overt preeclampsia.^{74–76}

Adiponectin, an adipocyte-derived hormone with angiogenic properties, is decreased in obesity, type 2 diabetes, hypertension, atherosclerosis, and other conditions of endothelial dysfunction. The association of both maternal obesity⁵ and excess maternal weight gain⁷⁷ with preeclampsia has led to the hypothesis that low adiponectin may contribute to preeclampsia risk. This has been supported by several^{78–80} but not all^{81,82} clinical studies. Thus, the role of adiponectin in preeclampsia remains obscure.

Endostatin, a potent anti-angiogenic factor primarily derived from endothelial cells, is increased in the serum of women who later develop preeclampsia beginning in the early second trimester.⁸³

CLINICAL IMPLICATIONS FOR SCREENING AND PREDICTION OF PREECLAMPSIA

As noted, preventive and definitive therapeutic strategies in the management of preeclampsia have remained elusive. Nevertheless, early detection, monitoring, and supportive care are considered both important and beneficial in improving outcomes for both the patient and the fetus. Reliable prediction of preeclampsia would allow closer prenatal monitoring, early diagnosis, and timely intervention with steroids to enhance fetal lung maturity, magnesium for seizure prophylaxis, antihypertensive medications, bed rest, and, when indicated, expeditious delivery. Furthermore, a robust biomarker for preeclampsia would enable targeted studies of therapies and preventive strategies for preeclampsia, including existing (eg, antiplatelet agents), controversial (calcium, antioxidants), and novel approaches. Although no screening test has yet proven accurate enough for widespread clinical use, research evaluating combinations of biomarkers shows promise.^{84,85}

Results from many independent studies have confirmed that maternal levels of PlGF, sFlt1, and/or sEng are significantly different before the onset of preeclampsia compared with women whose gestations proceed normally.^{33,39,40,86–94} Changes in PlGF are recorded by the first^{92,93,95,96} or early second^{33,87,88} trimester, whereas reproducible alterations in sFlt1 and sEng are noted in the mid- to late-second trimester onward. The discrimination of sFlt1 for preeclampsia has been reported as high as 96%,⁹⁷ although sensitivity and specificity appear to be much lower for late-onset preeclampsia, especially when sampled early in pregnancy.⁹⁸ Maternal sFlt1 levels are particularly increased in severe preeclampsia, early onset preeclampsia, and IUGR.^{33,99} Urinary PlGF is lower in women with preeclampsia before the onset of symptoms,¹⁰⁰ and may prove useful in screening and diagnosis, especially in early onset and severe disease.¹⁰¹

The timing, source (ie, serum versus urinary), and combination of biomarkers and other tests that will prove most predictive of preeclampsia and its complications are now being explored. For example, the combination of ultrasonographic changes and angiogenic biomarkers in the second trimester may be more predictive of preeclampsia than angiogenic

markers alone.¹⁰² Combining biomarkers into a single angiogenic index appears to be more predictive than any single marker, and some of these combinations meet the likelihood ratios and other criteria required for a prediction test to be clinically useful.^{39,84,86,94,103,104} Changes in angiogenic factor levels with advancing gestation may be more predictive of preeclampsia than levels at any single timepoint.^{40,86,90,94}

DIAGNOSIS AND RISK STRATIFICATION

Angiogenic proteins may prove useful in establishing the diagnosis of preeclampsia in challenging, ambiguous, or atypical cases. For example, angiogenic biomarkers may distinguish preeclampsia from other causes of hypertension in pregnancy in patients with pre-existing renal disease,¹⁰⁵ other causes of gestational thrombocytopenia such as idiopathic thrombocytopenic purpura,¹⁰⁶ or in cases of gestational hypertension or proteinuria before 20 weeks' gestation.¹⁰⁷ The observation that derangements in circulating angiogenic biomarkers appear to correlate with severity of preeclampsia^{35,39} and complications such as placental abruption¹⁰⁸ and IUGR^{33,64} has suggested they might be useful for risk stratification. There are several ongoing studies in progress that probe the utility of angiogenic biomarkers in the clinical arena.

NOVEL TREATMENT STRATEGIES

Currently, the only definitive treatment for preeclampsia is delivery of the fetus and placenta. Preeclampsia occurring in the late second and early third trimester, which frequently requires delivery to preserve the health of the mother, can result in significant neonatal morbidity and mortality owing to severe prematurity. The identification of sFlt1 and sEng as a key pathogenic link between placental pathology and maternal endothelial damage provides hope that these biomarkers also may be effective therapeutic targets. Potential therapies may be directed at restoring normal angiogenic balance in the maternal circulation, that is, the biologic activity of proangiogenic factors such as VEGF, PlGF, and TGF- β relative to anti-angiogenic factors such as sFlt1 and sEng. For example, both VEGF^{109,110} and PlGF⁹¹ diminished hypertension and ameliorated the proteinuria in rodent and murine models of sFlt1-induced preeclampsia, without apparent harm to the fetuses. Other strategies include the use of monoclonal antibodies to sFlt1 or sEng, small-molecule inhibitors of sFlt1 or sEng action, or agents that enhance endogenous VEGF, PlGF, or TGF- β production. Such therapies may transform the way preeclampsia is managed; an intervention that allows clinicians to safely postpone delivery for even a few weeks could have a tremendous impact on neonatal morbidity and mortality in select cases.

SUMMARY AND FUTURE DIRECTIONS

The past decade has brought exciting advances in our understanding of the pathogenesis of preeclampsia. Although the initiating events in preeclampsia are still not known, recent work suggests that excess circulating anti-angiogenic factors link the placental disease and the systemic maternal manifestations. The implications for the management of preeclampsia may be profound. More work is needed to further define the regulation of placental vascular development and expression of these factors in normal pregnancy and in preeclampsia, and the mechanisms responsible for variability in the maternal response.

There remain significant challenges to the development of new treatments for preeclampsia, and it is unclear if these novel therapies will prove to be safe and effective. Nevertheless, it is exciting to witness advances in our understanding of the pathophysiology of preeclampsia that have the potential to lead to treatment options for this challenging disease.

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Figure 1.

Glomerular changes in preeclampsia. Comparison between a rat model induced with anti-angiogenic proteins and the human disease. (A) Normal human glomerulus (hematoxylin-eosin). (B) Glomerular changes in preeclampsia (hematoxylin-eosin). A 33-year-old woman with twin gestation and severe preeclampsia at 26 weeks' gestation with a urine protein/creatinine ratio of 26 at the time of biopsy. (C) Glomerular changes in preeclampsia (electron microscopy). Note occlusion of capillary lumen cytoplasm and expansion of the subendothelial space with electron dense material. Podocytes show protein resorption droplets and relatively intact foot processes. Original magnification, 1,500 $\times$. (D) Animal model of preeclampsia: control rat glomerulus (hematoxylin-eosin). Note normal cellularity and open capillary loops. (E) Animal model of preeclampsia: sFlt1-treated rat glomerulus (hematoxylin-eosin). Note occlusion of capillary loops by swollen cytoplasm with minimal increase in cellularity. (F) Animal model of preeclampsia: sFlt1-treated rat glomerulus (electron microscopy). Note occlusion of capillary loops by swollen cytoplasm with relative preservation of podocyte foot processes. Original magnification, 2,500 $\times$. All light micrographs were taken at an identical original magnification of 40 $\times$. Reproduced with permission from Karumanchi et al.¹¹¹[DVC13]

Figure 2.

sFlt1 and sEng cause endothelial dysfunction by antagonizing VEGF and TGF- β 1 signaling. Under physiologic conditions, and during normal pregnancy, VEGF and TGF- β 1 maintain endothelial health by interacting with their endogenous endothelial receptors. In preeclampsia, excess placental secretion of sFlt1 and sEng inhibit VEGF and TGF- β 1 signaling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins. Reproduced with permission from Karumanchi and Epstein.¹¹²

Figure 3.

Hypothetical framework for the pathogenesis of preeclampsia. Placental dysfunction, triggered by poorly understood mechanisms—including genetic, immunologic, and environmental—plays an early and primary role in the development of preeclampsia. Alterations in regulatory factors including HO, catechol-o-methyltransferase(COMT)/2-methoxyestradiol (2ME), and angiotensin type 1 agonistic autoantibodies (AT1AA) lead to excess placental secretion of angiogenic factors into the maternal circulation. These factors lead to impaired VEGF/PlGF and TGF- β signaling, resulting in systemic endothelial cell dysfunction mediated by a variety of factors, as shown. Endothelial dysfunction, in turn, results in the systemic manifestations of preeclampsia. Reproduced with permission from Maynard and Thadhani.¹¹³[DVC14]