Circulating Angiogenic Factors in the Pathogenesis and Prediction of Preeclampsia

Chun Lam, Kee-Hak Lim, S. Ananth Karumanchi

Abstract—Preeclampsia is a major cause of maternal, fetal, and neonatal mortality worldwide. Although the etiology of preeclampsia is still unclear, recent studies suggest that its major phenotypes, high blood pressure and proteinuria, are due in part to excess circulating soluble fms-like tyrosine kinase-1 concentrations. Soluble fms-like tyrosine kinase-1 is an endogenous antiangiogenic protein that is made by the placenta and acts by neutralizing the proangiogenic proteins vascular endothelial growth factor and placental growth factor. High serum soluble fms-like tyrosine kinase-1 and low serum free placental growth factor and free vascular endothelial growth factor have been observed in preeclampsia. Abnormalities in these circulating angiogenic proteins are not only present during clinical preeclampsia but also antedate clinical symptoms by several weeks. Therefore, this raises the possibility of measuring circulating angiogenic proteins in the blood and the urine as a diagnostic and screening tool for preeclampsia. The availability of a test to predict preeclampsia would be a powerful tool in preventing preeclampsia-induced mortality, especially in developing nations, where high-risk specialists are limited. This review will summarize our current understanding of the role of circulating angiogenic proteins in the pathogenesis and clinical diagnosis/prediction of preeclampsia. (Hypertension. 2005;46:1077-1085.)

Key Words: angiogenesis ▪ vasculature ▪ proteinuria ▪ hypertension, pregnancy ▪ preeclampsia

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Preeclampsia is characterized by new-onset hypertension, proteinuria, and edema after 20 weeks of gestation and can be complicated by renal failure, pulmonary edema, and coagulopathy.1-3 It can also progress to the HELLP (hemolysis, elevated liver functions, low platelets) syndrome and seizures (eclampsia). Preeclampsia occurs only in the presence of the placenta, with or without a fetus, as in the case of hydatidiform mole. Consequently, the only successful treatment is delivery of the placenta,4 which can involve significant morbidity and even death for the baby. Some describe preeclampsia as a 2-stage process:5-7; the first (placental) asymptomatic stage is marked by abnormal placentation, followed by placental elaboration of certain soluble factors that enter the maternal circulation and cause subsequent widespread endothelial dysfunction.6,7 The second (maternal) stage is characterized primarily by hypertension and proteinuria, the clinical picture known as the maternal syndrome. It has been recently hypothesized that an imbalance in circulating angiogenic factors may play a pathogenic role in preeclampsia.8,9 Although there has been marked progress toward understanding its pathogenesis, few inroads have been made in the areas of prediction and management of preeclampsia. Thus, preeclampsia remains a leading cause of maternal and fetal morbidity and mortality worldwide.10 We review the current data on circulating angiogenic factors and their roles in the pathogenesis of preeclampsia and in determining the risk of developing it.

Pathogenesis of Preeclampsia

Abnormal Placental Development

Normal placental development requires that cytotrophoblasts invade the maternal spiral arterioles. This remodeling of the spiral arterioles into low-resistance vessels begins in the late first trimester, ends by 18 to 20 weeks of gestation, and results in replacement of the endothelium and muscular tunica media (see Figure 1).11,12 Trophoblast invasion/differentiation entail changes in the expression of certain cytokines, adhesion molecules, extracellular matrix molecules, metalloproteinases, and the class Ib major histocompatibility complex antigen (HLA-G).13-15 Termed “pseudo-vasculogenesis,”16 the change represents a transformation from epithelial (eg, adhesion molecule expression of integrin α6β1, α2/β1, and E-cadherin) to endothelial (eg, integrin αv/β3, platelet and endothelial cell adhesion molecule, and VE-cadherin) characteristics. Its participation involves a considerable number of transcription factors, growth factors, and cytokines.17,18
In women destined to develop preeclampsia, cytotrophoblast endovascular invasion remains shallow, leading to a defective uteroplacental circulation and subsequent placental ischemia (Figure 1). This is evident in the gross and microscopic description of placentas from preeclamptic patients. Biopsy specimens from preeclamptic placentas also show narrow and constricted vessels as a result of insufficient trophoblast invasion of maternal decidual arterioles. Not unexpectedly, individuals with predispositions to vascular insufficiency, such as diabetes mellitus, thrombophilias, systemic lupus erythematosus, and chronic hypertension, are at higher risk for preeclampsia. Women with an increased placental mass and comparatively less placental blood flow are also at elevated risk. Moreover, disruption of uterine blood flow resulting in placental insufficiency and preeclampsia has been demonstrated in animal models. In vitro and in vivo studies have shown that trophoblasts from preeclamptic placentas do not undergo adhesion molecule alteration and pseudovasculogenesis. Although many etiologies of insufficient trophoblast invasion have been proposed, including environmental, genetic, and immunologic factors, the principal cause of shallow cytotrophoblast invasion remains elusive. Extensive studies from the laboratories of Dr Fisher suggest that variations in oxygen tension may regulate cytotrophoblast invasiveness. More recently, hypoxia-inducible transcription factors have been shown to be selectively increased in preeclamptic placentas. Furthermore, gene expression profiles of preeclamptic placentas seem to mimic those from villous explants exposed to hypoxia and placentas obtained from women who delivered at high altitudes. Although hypoxia may be present in preeclamptic placentas, it remains debated whether this is a primary or secondary phenomenon. The abnormal placentation and accompanying hypoxia are thought to lead to the elaboration of soluble factors that act on the maternal vasculature to induce endothelial dysfunction and the clinical symptoms of preeclampsia.

**Systemic Endothelial Dysfunction**

Data from many studies have indicated that generalized endothelial dysfunction is the cause of the clinical abnormalities in preeclampsia. Specifically, the loss of endothelial control of vascular tone leads to hypertension, increased glomerular vascular permeability causes proteinuria, and disturbed endothelial expression of coagulation factors results in coagulopathy. In addition, vasoconstriction and ischemia
arising from endothelial injury can bring about liver dysfunction. Renal biopsy samples from preeclamptic patients show a characteristic, diffuse, glomerular endothelial cell swelling, known as “glomerular endotheliosis.”35 Sera of preeclamptic women have been found to have increased levels of markers of endothelial cell injury, such as fibronectin, factor VIII antigen, and thrombomodulin.56–38 In vitro studies with human umbilical vein endothelial cells have shown that preeclamptic serum induces endothelial cell activation.99 Arterial vessel endothelial dysfunction of patients with preeclampsia has been suggested by an increased pressor sensitivity and abnormal flow-induced vasodilation, even before onset of the disease.40–42 Increased vascular sensitivity to angiotensin II and increased generation of endothelins, as well as diminished production of endothelium-derived vasodilators, such as prostacyclins, have also been reported in women with preeclampsia.43–45

The search for circulating factors mediating this generalized endothelial dysfunction has been the subject of much ongoing research. Variations in the levels of tumor necrosis factor-α, interleukin (IL)-6, IL-1α, IL-1β, Fas ligand, oxidized lipid products, neurokinin B, and asymmetric dimethylarginine have been reported in preeclampsia, although there is no convincing evidence that these molecules cause the clinical syndrome.3,42–46,48 Heterodimerization of bradykinin (B2) receptors and angiotensin II type I receptors (AT1) occurs in the setting of upregulation of B2 in preeclampsia; in vitro, these heterodimers have been shown to increase responsiveness to angiotensin II.49 Women with preeclampsia have also been found to have circulating agonistic autoantibodies against the angiotensin receptor-1 (AT1-AAs).50 It is thought that these autoantibodies may enhance angiotensin II sensitivity by activating the AT1 receptor.50,51 In addition, AT1 receptor activation by AT1-AAs has been shown to induce the production of reactive oxygen species and to diminish human cytostrophoblast invasiveness in vitro.52,53 Recently, in a transgenic rat model of preeclampsia, AT1-AAs were reported to be elevated.54 Although these data are provocative, AT1-AAs have not been temporally correlated to or definitively shown to directly cause the clinical characteristics of preeclampsia. More recent studies have demonstrated increased placental expression and secretion of soluble fms-like tyrosine kinase-1 (sFlt-1), a naturally occurring, circulating, vascular endothelial growth factor (VEGF) antagonist, in patients with preeclampsia.8 Notably, sFlt-1 overexpression in rats has been shown to be sufficient to induce a preeclampsia-like illness.8

Circulating Angiogenic Factors

VEGF is a potent angiogenic and mitogenic factor for endothelial cells. It exerts its effects principally via the 2 receptors, VEGFR-1 and VEGFR-2, also known as fms-like tyrosine kinase-1 (Flt-1) and the kinase domain region (Flk/KDR), respectively.55 A soluble and endogenously secreted form of Flt-1 is produced by alternative splicing and contains the extracellular ligand-binding domain but not the transmembrane and cytoplasmic portions.56,57 sFlt-1 is able to block the effects of VEGF by inhibiting interaction with its receptors. Similarly, sFlt-1 also inhibits placental growth factor (PIGF), a member of the VEGF family of growth factors, which is produced chiefly by the placenta.

Increased sFlt-1 during preeclampsia is associated with decreased free VEGF and free PIGF in the blood. In vitro studies have indicated that the antiangiogenic state in preeclampsia induced by excess placental production of sFlt-1 could be “rescued” by giving VEGF and PIGF.6 Exogenous gene transfer of sFlt-1 into pregnant rats via an adenoviral vector resulted in hypertension, proteinuria, and glomerular endotheliosis, the classic pathologic renal lesion of preeclampsia.8 That this was also seen in nonpregnant animals suggested that the effects of sFlt-1 on the maternal vasculature were direct and not dependent on the presence of the placenta. When pregnant rats were given a soluble form of VEGF receptor-2 antagonist (sFlk-1), which does not antagonize PIGF, they did not develop a preeclamptic phenotype, indicating that antagonism of both VEGF and PIGF was necessary to bring about the maternal syndrome.8 These data led to the conclusion that excess sFlt-1 made by preeclamptic placentas results in a paucity of VEGF and PIGF, thereby creating an antiangiogenic state and the characteristic hypertension and proteinuria seen in the maternal syndrome of preeclampsia.

VEGF is well known for its proangiogenic and vasodilatory properties, the latter of which occur via increased production of nitric oxide and prostacyclin, signaling molecules that are decreased in preeclampsia.98 In genetically modified mice, even a 50% reduction of renal VEGF production results in glomerular endotheliosis and proteinuria.59 Furthermore, a large percentage of patients receiving VEGF signaling antagonists for treatment of cancer develop hypertension and proteinuria.60,61 Therefore, by neutralizing VEGF and PIGF, excess sFlt-1 may have a contributory role in the pathogenesis of the maternal syndrome of preeclampsia. The hypothesis that excessive production of sFlt1 may play a causal role in preeclampsia is supported by recent clinical studies that reported a link between trisomy 13 pregnancies and circulating angiogenic protein concentrations during the first and second trimesters. The genes for sFlt1 and Flt-1 are carried on chromosome 13. Fetuses with an extra copy of this chromosome should theoretically produce more of these gene products than their normal counterparts. The incidence of preeclampsia in mothers who carry fetuses with trisomy 13 is in fact greatly increased, when compared with all other trisomies or with control pregnant patients.62 The ratio of circulating sFlt1 to PIGF was recently shown to be significantly increased in these women, thus accounting for the increased risk of preeclampsia noted in these patients.61

What remains unclear, however, are the specific mechanisms that lead to excess sFlt-1 production by the placenta, the role that sFlt-1 plays in normal placental development and pseudovasculogenesis, and the relation between sFlt-1, PIGF, and VEGF and the known risk factors for preeclampsia. Because coagulopathy, liver dysfunction, and brain abnormalities (eclampsia) have not been reported in sFlt-1–treated animals, it is still unknown whether sFlt-1 plays a causal role in the pathogenesis of the HELLP syndrome and eclampsia. If a threshold exists for the sFlt-1 level, below which normal pregnancy proceeds and above which preeclampsia develops,
then it could be hypothesized that this threshold might be lower in women with risk factors, rendering them more “susceptible” and resulting in the maternal syndrome at a level that ordinarily would permit a normal pregnancy to progress. It is also probable that additional, heretofore unidentified, synergistic factors generated by the placenta play a role in the pathogenesis of the generalized endothelial dysfunction of preeclampsia and that these factors could conceivably serve as useful biomarkers in the prediction of preeclampsia.

**Diagnosis and Prediction of Preeclampsia**

The pursuit of safe, reliable, and cost-effective screening tests for the prediction of preeclampsia has been the goal of researchers for many decades, with the aim of improving maternal and fetal surveillance, despite the fact that the only current effective treatment remains delivery. To date, however, no specific tests have been proven to be effective and appropriate screening tests for preeclampsia.64 This is partly attributable to the wide range of terminology used for hypertensive disorders in pregnancy, to the varying criteria for the diagnosis of these complex disorders, and to differences in measures of outcome. Many candidates have been examined, including serum β-human chorionic gonadotropin, fibronectin, uric acid, urinary kallikrein, and urinary calcium, among others, but none has proven to be specific and sensitive enough to be of clinical value.65 More recently, however, a number of studies have concentrated on examining the potential utility of sFlt-1 and PlGF as biomarkers in the diagnosis and prediction of preeclampsia.

**sFlt-1**

Recent investigations have all supported the finding that placental expression8,66,67 and serum levels8,67–74 of sFlt-1 in preeclamptic women are increased during active disease compared with normal pregnancies. In 1 study, average serum sFlt-1 levels during clinical disease in the various patient subgroups were as follows: normal-term pregnancy, 1.50±0.22 ng/mL; mild preeclampsia, 3.28±0.83 ng/mL; and severe preeclampsia, 7.64±1.5 ng/mL.5 Postpartum, sFlt-1 levels decrease dramatically in women with both normal and preeclamptic pregnancies,8,68,72 A number of studies have confirmed that the sFlt-1 concentration is positively correlated with gestational age and that after ≈35 weeks, a more dramatic rise occurs.69,72,73 In 1 cross-sectional analysis of sera collected at 4- to 5-week gestational intervals from 8 to 12 weeks to 25 to 35 weeks, sFlt-1 levels were unchanged until 33 to 36 weeks, after which they rose until delivery.69 In women who eventually developed preeclampsia, sFlt-1 levels began to rise at 20 weeks of gestation.69 Several studies have also examined serum sFlt-1 concentrations at 10 to 11, 4 to 14, and 15 to 25 weeks of gestation and have confirmed that before 20 weeks, no significant difference in sFlt-1 concentrations is discernible between those destined to develop preeclampsia and those who ultimately have normal pregnancies, although 1 study did find a difference that approached statistical significance.72,75,76 Clinically, sFlt-1 levels have been observed to be directly proportional to the severity of proteinuria but inversely correlated with platelet count, gestational age, and neonatal birth weight adjusted for gestational age.73 In women with preeclampsia, sFlt-1 concentrations are higher in those with earlier onset (before 37 weeks),69,73 more severe disease,8,69,73 and small-for-gestational-age (SGA) infants.69,77 Comparison of gestational age–matched women with active preeclampsia and those with normal pregnancies in a large cross-sectional study revealed significantly higher concentrations in the former group. Only within 5 weeks of onset of hypertension and proteinuria were sFlt-1 levels significantly increased.69 Among various subgroups, no distinctions in sFlt-1 concentrations have been noted between nulliparous and multiparous women with or without preeclampsia, although women with prior histories of preeclampsia appear to have higher levels than those without a previous history.73 Recently, however, 1 group showed sFlt-1 levels to be higher in first pregnancies compared with second pregnancies in the same women, offering a possible reason for the increased risk of preeclampsia in nulliparous women.79 In nonpreeclamptic women with SGA infants, including the subgroup with fetal growth restriction, serum concentrations of sFlt-1 at term were similar to those of matched controls.77 This finding is in contrast to that from another study that reported a modest elevation in sFlt-1 in the SGA group when compared with matched controls; however, when compared with sFlt-1 levels in preeclamptic women, the SGA groups had significantly lower concentrations.67 A study that included women with chronic and gestational hypertension showed that sFlt-1 levels in such groups are not significantly higher than those of normal controls70; however, that study had a small number of patients, and it is therefore difficult to draw definitive conclusions.

Many of the studies mentioned have looked statistically at sFlt-1 as a potential predictor of preeclampsia.69,70,76,79 Examining odds ratios, sensitivity, and specificity for various sFlt-1 cutoff values in different trimesters has yielded the conclusion that the higher the sFlt-1 level, the more predictive it is of preeclampsia (see Table 1 for details). Despite the extensive data indicating a strong correlation between higher sFlt-1 levels and the risk and presence of preeclampsia, however, some preeclamptic women undoubtedly have sFlt-1 levels well within the normal range and vice versa60; hence, the utility of serum sFlt-1 concentration as a screening test remains investigational at present.

**PlGF**

In numerous studies, PlGF has been demonstrated to be diminished in preeclamptic serum,8,67,69,71,81–87 This is most likely because of its binding with elevated levels of circulating sFlt-1 rather than decreased production of PlGF by the preeclamptic placenta. The expected trend of PlGF concentrations in normal pregnancy is a steady increase during the first 2 trimesters, a peak at 29 to 32 weeks, and a consistent decline thereafter.69,83 Its decrease is thought to be a result of sFlt-1 concentrations from 33 to 36 weeks of gestation through the end of pregnancy and indeed, is the reciprocal of sFlt-1: the higher the sFlt-1 concentration, the lower the PlGF level.69 Numerous studies have documented that beginning in the early second trimester and as early as 10...
to 11 weeks of gestation, PIGF concentrations are lower than those of normotensive controls.69,75,81,83,88–93 In 1 large randomized, controlled study, serum PIGF levels at 21 to 32 weeks of gestation were lower in earlier-onset preeclampsia (<37 weeks) versus later onset; in severe versus mild preeclampsia; and in preeclampsia associated with an SGA rather than an appropriate-size-for-gestational-age (AGA) infant.69 One report found that at 12 weeks of gestation, women with low serum levels of both PIGF and sex hormone–binding globulin (of which low levels indicate insulin resistance) have an extremely high risk of preeclampsia.84 Other studies, however, did not confirm the reduction in PIGF concentrations in preeclamptic serum86,89: this discrepancy may have arisen from differing population characteristics, varying severity of preeclampsia, or failure to adjust for gestational age at the time of blood collection, among other reasons. In 1 such study, samples were stored at −20°C rather than −70°C, which might have hastened deterioration of the specimens.85

In preeclampsia, PIGF concentrations begin to decrease 9 to 11 weeks before the appearance of hypertension and proteinuria, with considerable diminution during the 5 weeks before the onset of disease. More than 5 weeks preceding occurrence of the maternal syndrome, the difference in PIGF levels between normotensive controls and those who later developed preeclampsia was less marked.69 Serum PIGF levels in normotensive women with SGA infants were significantly lower than gestational-age-matched controls with AGA infants at 33 weeks, but not at 17 or 25 weeks.86 The disparity in serum PIGF concentrations between preeclamptic women and normotensive women with SGA infants is therefore, less pronounced but still present. In another study, women were divided into those with normal Doppler flow velocity waveforms who delivered AGA infants (controls) and those with abnormal Doppler flow velocity waveforms who had SGA infants or subsequent preeclampsia. Blood collected at intervals of 4 weeks between 20 and 36 weeks revealed that PIGF levels were highest in the controls, typically intermediate in the SGA group, and lowest in the preeclamptic group. Interestingly, the PIGF value in the SGA group was significantly lower than that in normotensive controls earlier in pregnancy—at 24 and 32 weeks of gestation—but not at 20, 28, and 36 weeks.80 One longitudinal study examined 4 different groups: normotensive controls with uncomplicated pregnancies, normotensive women with SGA infants, preeclamptic women with AGA infants, and preeclamptic women with SGA infants. As has been observed in other trials, it was noted that PIGF levels were lower at 35 weeks in normotensive women with SGA infants compared with normotensive controls with uncomplicated pregnancies.83 Unlike other studies, however, this difference was not seen earlier in pregnancy; no significant differences were found between controls and normotensive women with SGA infants at 15 to 19 weeks, 21 to 25, 27 to 30, and 35 to 38 weeks. In contrast, women with preeclampsia had significantly lower levels starting at 15 to 19 weeks for those with SGA infants and at 21 to 25 weeks for those with AGA infants.83 Another study found higher levels in normotensive, nonproteinuric controls at 10 to 11 weeks than in normotensive women with an SGA infant, women who developed gestational hypertension without preeclampsia, and women with subsequent preeclampsia. After adjusting for gestational age, PIGF concentrations were predictive of preeclampsia but not of SGA or gestational hypertension.75

As with sFlt-1, various studies have investigated PIGF in the first or second trimester as a possible predictor of preeclampsia69,75,83,87,88,90,92,93 (see Table 2 for details). These studies have found that, converse to the pattern of sFlt-1, PIGF concentrations are low in preeclampsia and predict disease with relative risks, receiver operator characteristic curves, and odds ratios to a similar accuracy as sFlt-1 concentrations. One cross-sectional and longitudinal study found that PIGF levels were decreased as early as 15 to 19 weeks in preeclampsia with SGA pregnancies and in the third trimester in SGA, preeclamptic, and preeclamptic with SGA pregnancies compared with controls. As seen in other studies, levels were inversely proportional to disease severity.83 Current evidence suggests, therefore, that low levels of serum PIGF in early and possibly mid-pregnancy may distinguish women who subsequently develop preeclampsia from those who remain normotensive during pregnancy but who deliver an SGA infant. It is also likely that a metric that uses PIGF in combination with other markers such as sFlt1 and/or sex hormone–binding globulin may be a better screening tool than when used alone.75,84

Recently, urinary PIGF was explored as another possible screening test for the diagnosis of preeclampsia. Although sFlt-1 is too large a molecule to be filtered by the healthy kidney into the urine, PIGF is a considerably smaller protein and was indeed, found to be decreased in the urine of women

### Table 1. Results of Tests Used for Detection/Prediction of Preeclampsia (PE)

<table>
<thead>
<tr>
<th>Author</th>
<th>Serum sFlt1, pg/mL</th>
<th>GA, wk</th>
<th>Study Size, N</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>Levine et al69</td>
<td>&gt;1131*</td>
<td>21–32</td>
<td>240</td>
<td></td>
<td></td>
<td>5.1 (for PE &lt;37 wk)</td>
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<tr>
<td></td>
<td>&gt;2191*</td>
<td>33–41</td>
<td></td>
<td></td>
<td></td>
<td>6.0 (for term PE)</td>
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<tr>
<td>Hertig et al70</td>
<td>957</td>
<td>25–28</td>
<td>23</td>
<td>80</td>
<td>100</td>
<td></td>
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<tr>
<td>Chaiworapongsa et al70</td>
<td>1560</td>
<td>24–28</td>
<td>88</td>
<td>16.7 (for PE at 29–34 wk)</td>
<td>97.4 (for PE at 29–34 wk)</td>
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<td>1575</td>
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<td>95 (for PE at 32–34 wk)</td>
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<td>2164</td>
<td>32–36</td>
<td>70 (for PE &gt;37 wk)</td>
<td>97 (for PE &gt;37 wk)</td>
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</table>

Abbreviations are as defined in text.

*Compared with all other quartiles.
with preeclampsia compared with those with normal pregnancies. In a large cross-sectional analysis examining urine samples at gestational intervals of 4 to 5 weeks, urinary PIGF concentrations were discovered to parallel those of the serum, ie, a rise in the first 2 trimesters with a more dramatic increase after 21 to 24 weeks of gestation, a peak at 29 to 32 weeks, and a steady decline thereafter. In preeclampsia, the pattern was similar but at substantially lower levels at 3 points: 25 to 28, 29 to 32, and 33 to 36 weeks. These differences were most pronounced within 5 weeks of onset of hypertension and proteinuria, as they were in the serum. Furthermore, as with serum PIGF, urine levels were lowest in the preeclamptic group with active disease regardless of gestational age at the time of onset of symptoms (29 to 32, 33 to 36, and 37 to 42 weeks). The same report also examined urinary sFlt-1 concentrations in normotensive controls, normotensive women with SGA infants, women with gestational hypertension alone, and preeclamptic women with disease onset before 37 weeks. No differences among the groups were found except for the lowest PI GF concentrations in the preeclamptic group. Based on this finding, it was concluded that urinary PI GF concentrations during mid-pregnancy were not affected by the presence of an SGA infant or by the development of gestational hypertension but were low only in the setting of preeclampsia. Finally, when urinary PI GF was combined with a serum sFlt1/PI GF (ratio >10, suggestive of preeclampsia), all of the cases destined to develop preeclampsia within the following 5 weeks were able to be distinguished from the control pregant women. Thus, a 2-step approach of initial urinary screening followed by serum sFlt1/PI GF in those women who have low urinary PI GF levels may be a cost-effective approach for the screening of preeclampsia. In a more recent article, urinary angiogenic markers were measured in women with clinical preeclampsia. During active disease, because of the disruption in the glomerular barrier leading to proteinuria, a small amount of circulating sFlt-1 spills into the urine. In that report, urinary sFlt-1 was found to be significantly increased in women with preeclampsia when compared with normal pregnant women (145 versus 15.6 pg/mL, P<0.001). Urinary PI GF was also significantly decreased in preeclamptic women when compared with normal pregnant women (19.2 versus 65.7 pg/mL, P<0.001). When urinary angiogenic factors were used as a ratio during active disease, the logarithmically transformed urinary sFlt-1 to PI GF ratio had an 88.2% sensitivity and 100% specificity in differentiating preeclamptic women from normal controls.

**VEGF**

As described earlier, VEGF plays a very important role in the pathogenesis of preeclampsia. Although total VEGF has been shown to be modestly elevated in preeclampsia, VEGF is bound by sFlt-1 in preeclampsia. Similar to PI GF, this leads to low circulating levels of free or bioactive VEGF during active preeclampsia. However, because VEGF binds sFlt1 with a higher affinity than PI GF, it is more significantly reduced in the sera of pregnant women, leading to extremely low circulating concentrations of free VEGF. Typical circulating concentrations are <30 pg/mL and are mostly below the detection limit of currently available ELISA kits. Although 1 study has reported serum VEGF to be a promising marker in the prediction of early-onset preeclampsia, most studies found undetectable levels. Therefore, serum VEGF is unlikely to serve as a useful screening marker until ELISA kits that are sensitive enough to detect single-digit picogram concentrations with high reliability become available.

**Conclusions**

Despite a remarkable decline in morbidity and mortality from preeclampsia in the last half century, attributable to improvements in obstetric and perinatal care chiefly in the developed world, there have been no revolutionary advances in the treatment of preeclampsia. Unfortunately, the promising early data of the preventive utility of various supplements, such as aspirin and calcium, have not been borne out in large, randomized, controlled trials. Although preeclampsia is thought to be a 2-stage process of abnormal placentation followed by the maternal syndrome, much of the pathogenesis of both stages remains to be elucidated (see Figure 2 for summary). Recent evidence points to excessive levels of circulating anti-endothelial factors produced by the diseased placenta, such as sFlt-1, as a cause of the generalized endothelial dysfunction so prominent in the maternal syn-
drome, but the origins of abnormal placentation and its specific role in preeclampsia are still not well understood. Future studies to characterize the circulating proteins released by preeclamptic placentas and clarify their relation with currently known mediators of endothelial dysfunction, such as sFlt-1, should help shed light on the pathologic mechanisms of the maternal syndrome. In light of the recent developments in our understanding of the pathogenesis of preeclampsia, treatment strategies aimed at rescuing the endothelial dysfunction with agents such as VEGF, PI GF, and prostacyclins could be explored in women with severe disease. From a diagnostic standpoint, the discovery of soluble angiogenic markers used either alone or in combination with other markers offers tremendous promise in the diagnosis and screening of preeclampsia. Although there is a significant and growing body of evidence supporting the diagnostic use of such markers, virtually all of the data are retrospective. Prospective longitudinal investigations are necessary to further study the various circulating angiogenic factors to more reliably identify women at high risk of preeclampsia, as well as more definitively diagnose the disease.

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References


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