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Angiogenic factors in preeclampsia: potential for diagnosis and treatment

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Abstract

Purpose of review—The review summarizes new observations of key roles for circulating angiogenic factors in diagnosing, managing, and treating preeclampsia.

Recent findings—Alterations in circulating angiogenic factors (soluble fms-like tyrosine kinase-1 and placental growth factor) in preeclampsia correlate with the diagnosis and adverse outcomes, particularly when the disease presents prematurely (<34 weeks). Measurement of these angiogenic biomarkers further helps differentiate preeclampsia and its complications from other disorders that present with similar clinical profiles. A ratio of soluble fms-like tyrosine kinase-1/placental growth factor greater than 85 appears ideal as the cut-off for both diagnosis and prognosis. There is also evidence that modulating these factors has therapeutic effects, suggesting a future role for angiogenic factors in treatment and prevention of preeclampsia.

Summary—Circulating angiogenic biomarkers help in diagnostic and prognostic profiling of preeclampsia and may facilitate better management of these patients.

Keywords

adverse outcomes; angiogenic factors; placental growth factor (PIGF); preeclampsia; soluble fms-like tyrosine kinase-1 (sFlt1)

INTRODUCTION

Preeclampsia is defined as new-onset hypertension and proteinuria occurring after 20 weeks' gestation. Other features of the preeclampsia syndrome include seizures (eclampsia), microangiopathic hemolytic anemia, elevated transaminases and thrombocytopenia (HELLP syndrome: hemolysis, elevated liver enzymes and low platelets), as well as pulmonary edema and renal failure [1]. Neonatal complications of preeclampsia include preterm delivery, fetal growth restriction, perinatal death, and long-term cardiovascular morbidity associated with low birth weight. Preeclampsia affects around 3–8% of all pregnancies, accounting for over 50 000 maternal deaths annually worldwide [2].

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Conflicts of interest

There are no conflicts of interest.

Although preeclampsia is mostly viewed as an acute disease and treated with delivery, data are accumulating that preeclampsia is associated with long-term maternal cardiovascular [3] and renal damage [4]. A population-based study from Norway suggested that women who had preeclampsia were at a four to five times increased risk of developing end-stage renal disease during a follow-up of 35 years [5]. Other studies have shown similar findings [6–8]. The exact mechanism of this increased risk is not known, but it is likely mediated by renal damage after primary renal injury during pregnancy.

Current diagnosis of preeclampsia depends solely on blood pressure (BP) monitoring ($\geq 140/90$) and detection of proteinuria (≥ 300 mg/24 h or a urine protein/creatinine ratio ≥ 0.3 mg/mg). However, neither hypertension nor proteinuria is specific to the pathophysiology of preeclampsia, which is characterized by glomerular endotheliosis, a classical histological lesion [9]. As a result, women with other conditions such as diabetes, lupus, or obesity that present with proteinuria and hypertension during pregnancy are often incorrectly classified as preeclampsia [9–13]. Moreover, current clinical and laboratory criteria fall short of an accurate assessment of severity of disease and risk to mother and her fetus [14,15]. Whereas some women with preeclampsia can be managed expectantly to nearly full term without complications, others may develop life-threatening complications [16]. This inability to accurately predict adverse outcomes greatly enhances costs in these patients. In 1992, approximately \$20 billion was spent in the United States to treat preeclamptic women and their neonates [17,18]. Simply establishing the diagnosis currently requires resource-intensive measures such as hospital admission with close observation of maternal BP, proteinuria, and laboratory trends.

The past decade has seen new insights into pathogenesis of preeclampsia, most notably the role of antiangiogenic proteins in producing preeclampsia phenotypes in pregnant rodents and elevated levels in women with preeclampsia [19]. Specifically, soluble fms-like tyrosine kinase-1 (sFlt1) levels were shown to be elevated in women with preeclampsia compared to normotensive gravidas [19,20]. In contrast, the free circulating levels of vascular endothelial growth factor and placental growth factor (VEGF and PlGF, respectively) were significantly reduced [21–24]. Overwhelming evidence suggests that sFlt1 plays a major role in causing preeclampsia by inhibiting VEGF signaling in the endothelium. Humans exposed to VEGF inhibitors used as part of cancer chemotherapy develop a preeclampsia-like syndrome [25]. In addition, increased plasma sFlt1 and decreased PlGF has been shown to correlate with preeclampsia phenotypes and adverse maternal and fetal outcomes [21,26,27].

In this review, we will discuss important papers published over the past 2 years highlighting the use of these angiogenic biomarkers for diagnosis and prognosis of preeclampsia, along with their role for risk stratification and in clinical management.

IMPAIRED VASCULAR ENDOTHELIAL GROWTH FACTOR SIGNALING IN PREECLAMPSIA

Glomerular endotheliosis with proteinuria is one of the classical renal manifestations of preeclampsia. Previous studies with glomerular-selective deletion of VEGF-A in mice have shown worsening proteinuria and endotheliosis [28]. This seems plausible as VEGF-A is highly expressed in podocytes that make up a major portion of the barrier between the blood and urinary spaces. sFlt1 overexpression is sufficient to recapitulate hypertension, proteinuria, and glomerular endotheliosis in rodents [19]. These data suggest that excess sFlt1 of placental origin causes proteinuria in women with preeclampsia by inhibiting VEGF signaling in the glomerulus.

The human counterpart of this study has been seen in patients who are treated with anti-VEGF antibody for inhibition of tumor-related vasculogenesis or agents inhibiting signaling through receptor tyrosine kinases such as VEGF receptor. Glusker *et al.* [29] in a case report showed occurrence of reversible posterior leukoencephalopathy (that resembles eclampsia) directly attributable to bevacizumab (Avastin), a recombinant, humanized, monoclonal IgG1 antibody that binds and inhibits VEGF. Cross *et al.* [25] in a more recent study reported the whole spectrum of changes resembling preeclampsia (hypertension, proteinuria, central nervous system irritability, liver enzymes elevation, and reversible posterior encephalopathy on MRI) in two patients treated with bevacizumab. These changes reversed to normal after discontinuation of bevacizumab therapy. Similarly, case series by Patel *et al.* [30] and Eremina *et al.* [31] has demonstrated that patients exposed to VEGF receptor tyrosine kinase inhibitors or bevacizumab may develop a preeclampsia-like syndrome characterized by hypertension, proteinuria, and renal thrombotic micro-angiopathy.

ROLE OF SOLUBLE FMS-LIKE TYROSINE KINASE-1 AND PLACENTAL GROWTH FACTOR AS BIOMARKERS IN THE DIAGNOSIS AND PREDICTION OF PREECLAMPSIA

Over the past decade, numerous cross-sectional and longitudinal studies have shown that high sFlt1 and low PlGF are present during preeclampsia and prior to clinical disease [21–24,32–35]. In addition, the recent availability of automated platforms has allowed researchers to validate these biomarkers in several cohorts. Several studies have demonstrated the ability of the ratio of sFlt1 and PlGF to distinguish women with and without preeclampsia, using newly developed automated assays with sensitivities and specificities above 95% for preterm preeclampsia [36–39].

Unfortunately, and despite an initial enthusiasm, the results have shown that the ability of these factors to predict preeclampsia when measured early in pregnancy failed to achieve sufficient likelihood ratios and the positive and negative predictive values required for clinical use [40–42], though prediction appeared more reliable for early-onset (<34 weeks) preeclampsia [34]. However, a number of studies recently have shown that when measured late in pregnancy, these proteins can predict development of adverse outcomes with very high sensitivity and specificity. These were triage studies designed to separate patients unlikely to experience severe complications and who can be managed conservatively from patients who are at higher risk of developing adverse outcomes and therefore need close surveillance as well as lower threshold for delivery. Currently, this is done using clinical and biochemical profiles with routine laboratory tests, but this approach shows poor predictive accuracy [43,44]. Addition of angiogenic biomarkers has been shown to significantly improve the predictive value.

Chaiworapongsa *et al.* [45] in 2011 evaluated the role of angiogenic proteins among patients presenting with the diagnosis ‘rule out preeclampsia’ to the obstetrical triage area at less than 37 weeks of gestation ($n = 87$). A plasma concentration of PlGF/sFlt1 0.05 or less multiples of median (MoM) or PlGF/soluble endoglin (sEng) 0.07 or less MoM had the highest likelihood ratio of an early delivery [8.3, 95% confidence interval (CI) 2.8–25 and 8.6, 95% CI 2.9–25, respectively]. Among patients who presented less than 34 weeks gestation ($n = 59$), a plasma concentration of PlGF/sFlt1 below 0.033 MoM identified patients who delivered within 2 weeks with a sensitivity of 93% and a specificity of 78%. This cut-off was associated with a shorter interval to delivery due to preeclampsia (hazard ratio 6, 95% CI 2.5–14.6).

Rana *et al.* [26[•]] prospectively evaluated 616 women who presented to an obstetric triage unit for evaluation of suspected preeclampsia. Adverse outcomes were defined as presence of hypertension (BP $\geq 140/90$) and one of the following: elevated liver enzymes, low platelet count, disseminated intravascular coagulopathy, cerebral hemorrhage, seizure, or acute renal failure. The adverse fetal/ neonatal outcomes included iatrogenic delivery indicated for hypertensive complications of pregnancy as reported by the primary obstetrician, small-for-gestational-age birth weight, abnormal umbilical artery Doppler, fetal death, and neonatal death. Adverse outcomes occurred in 43.5% of all patients within 2 weeks of admission. The median sFlt1/PlGF ratio at presentation was 47.0 in women with adverse outcome versus 10.8 in those with no adverse outcome. When divided by tertile of sFlt1/PlGF ratio, 71.7% of women in the highest tertile had an adverse outcome as compared to 21% in the lowest tertile. Receiver operating curve analysis showed that sFlt1/PlGF cut-off of 85 would allow the maximum number of participants to be correctly classified with regard to adverse outcomes (87%). In women presenting at less than 34 weeks' gestation, a cut-off point of 85 gave a sensitivity of 72.9% and a specificity of 94.0%. This was higher than those presenting after 34 weeks, reinforcing the idea of worse angiogenic profile in this group of patients. The predictive model of sFlt1/PlGF ratio along with SBP and proteinuria was better than SBP, proteinuria, and uric acid levels and predicted delivery within 2 weeks of enrollment (Fig. 1a and 1b). Also, the sFlt1/PlGF ratio was markedly elevated in patients with preeclampsia as compared to those with gestational hypertension or chronic hypertension.

A similar study was performed by Moore *et al.* [46^{••}]. Serum samples were collected at the time of presentation to a triage unit for suspected preeclampsia. Of the 276 patients enrolled, 128 were later classified to have preeclampsia and 78 women had a composite endpoint that included maternal or neonatal complications. An important point was that even those who did not meet diagnostic criterion for preeclampsia had a similar incidence of adverse outcomes and had comparable changes in angiogenic profile, suggesting that there are shortcomings in the current definition of preeclampsia. Again, the sFlt1, PlGF, and sEng levels were different in women with adverse outcomes. The odds ratio for complications with every 100 unit increase of sFlt1/PlGF (2.37) was higher than the odds ratio with a similar increase in individual levels of sFlt1 or sEng or decrease in PlGF levels. Again, these differences were more marked for those who presented before 37 weeks' gestation.

In looking at the role of measurement of angiogenic factors late in pregnancy for identification of outcomes, a recent study by Chaiworapongsa *et al.* [47^{••}] showed significant predictive value of angiogenic markers for late preeclampsia, and stillbirth. This was a prospective study done in a big cohort of 1269 singleton pregnant women. The ratio of PlGF/sEng and PlGF/sFlt1 from blood samples drawn between 30–34 weeks' gestation was significantly predictive for late preeclampsia and severe late preeclampsia. Also, PlGF/sFlt1 below 0.12 MoM at 30–34 weeks had a sensitivity of 89%, specificity of 94%, and a likelihood ratio of 14 for identification of subsequent stillbirth.

USE OF ANGIOGENIC BIOMARKERS IN DIFFERENTIAL DIAGNOSIS

Chronic kidney disease (CKD) and preeclampsia can both present in pregnancy as worsening proteinuria and hypertension. Rolfo *et al.* [48[•]] tested whether maternal serum levels of PlGF and sFlt1 could be used to discriminate between these two groups. Serum levels of sFlt1 were significantly elevated in 34 patients with preeclampsia as compared to 23 CKD patients and 38 healthy pregnant women. Similarly, PlGF levels were lower in preeclampsia as compared to CKD and controls. The sFlt1/PlGF ratio was significantly increased in preeclampsia (median 436) compared with controls (median 9.4) and CKD (median 4.0). No differences were found between controls and patients with CKD.

A similar dilemma may occur when managing pregnancy with underlying lupus nephritis. The clinical features of hypertension, proteinuria, and elevated creatinine can be present in both disorders. To complicate matters further, lupus nephritis is also a risk factor for development of preeclampsia, whereas the underlying nephritis may flare anytime during pregnancy. However, the management differs considerably, with immunosuppression required for lupus nephritis and delivery for preeclampsia. In a retrospective case-control study of 52 patients with systemic lupus erythematosus (SLE), Qazi *et al.* [49] showed that serum concentration of sFlt1 was significantly higher in SLE pregnancies with preeclampsia ($n = 18$) than in those with SLE but without preeclampsia (1768 versus 1177 pg/ml). This was further investigated by Verdonk *et al.* [50], who found different angiogenic profiles in three complicated pregnancies. A cut-off value of sFlt1/PIGF of 85 was used to differentiate among preeclampsia, activation of underlying lupus nephritis, and combined occurrence of these two conditions. These data suggest that perhaps angiogenic bio-markers may be used instead of renal biopsy to diagnose preeclampsia in patients with underlying kidney disease.

Another major challenge in obstetric care is diagnosing and managing superimposed preeclampsia in patients with chronic hypertension. Chronic hypertension is a risk factor for development of preeclampsia, and early diagnosis may help in differentiating the two as management differs considerably with delivery indicated for preeclampsia and conservative management for chronic hypertension. Perni *et al.* [51] prospectively followed a cohort of 109 pregnant women with chronic hypertension. They measured sFlt1, sEng, and PIGF levels at 12, 20, 28, and 36 weeks' gestation and postpartum. sFlt1 and sFlt1/PIGF ratio were elevated at 20 and 28 weeks in women who developed early-onset superimposed preeclampsia (<34 weeks, $n = 9$) as compared to normal control and late-onset superimposed preeclampsia (>34 weeks, $n = 28$). Late-onset superimposed preeclampsia had higher sFlt1 and sFlt1/PIGF levels noted at 36 weeks as compared to normal control, but not at 20 or 28 weeks. These alterations were similar to normotensive women who later developed preeclampsia [21,22], suggesting similar pathophysiology.

Preeclampsia can also present in atypical fashion. Also, several disorders in pregnancy can have similar features, which may mimic preeclampsia or one of its complications. Angiogenic profile again seems to differentiate between these two groups. Young *et al.* [52] in a pilot study showed that these biomarkers could help in distinguishing pregnant women with non-HELLP thrombo-cytopenia from those with severe preeclampsia and HELLP. Serum levels of sFlt1, sEng, and PIGF were measured in patients with HELLP syndrome ($n = 11$), preeclampsia ($n = 11$), and non-HELLP thrombocytopenia ($n = 9$), which included gestational thrombocytopenia and immune thrombocytopenic purpura (ITP). Patients with non-HELLP thrombocytopenia had remarkably lower levels of sEng and sFlt1, and elevated levels of PIGF, as compared to patients with HELLP and preeclampsia. These levels were comparable to normotensive controls.

USE OF ANGIOGENIC BIOMARKERS IN THE MANAGEMENT OF PREECLAMPSIA

Current evidence suggests that preeclamptic patients with relatively lower sFlt1/PIGF ratio could be managed expectantly and pregnancy prolonged safely. In a study, Rana *et al.* [53] compared the clinical characteristics and outcomes of preeclamptic women presenting with a normal plasma angio-genic profile (nonangiogenic preeclampsia, sFlt1/PIGF <85) with those who were characterized by an abnormal angiogenic profile (angiogenic preeclampsia, sFlt1/PIGF ≥ 85). They found that the patients with nonangiogenic preeclampsia ($n = 46$) were more obese, more likely to have pre-existing diabetes, and presented at a later gestational age as compared with women with angiogenic preeclampsia ($n = 51$). Women

with nonangiogenic pre-eclampsia had no serious adverse outcomes except for preterm delivery between 34 and 37 weeks. They also had increased resource utilization (hospital admission days). These data suggest that in contrast to the angiogenic form, the nonangiogenic form of preeclampsia is characterized by little to no risk of preeclampsia-related adverse outcomes, other than iatrogenic prematurity. This further suggests that incorporation of angiogenic biomarkers in the evaluation of preeclampsia might allow accurate and early identification of severe disease and possibly prevention of preterm delivery.

Although not a chronic disease, the potential adverse outcomes related to preeclampsia necessitate a very close monitoring of suspected preeclampsia, especially in inpatient settings. This requires repetitive clinical assessment and a battery of laboratory and radiological tests for maternal and fetal well being. Schnettler *et al.* [54] looked at the use of angiogenic factors in risk stratification of 176 patients presenting with suspected preeclampsia in triage and the cost outcome over the next 2 weeks. The patients were categorized using a novel approach based on sFlt1/PlGF ratio and were compared to standard approach (categorization based on BP, proteinuria, and laboratory tests). The improved specificity of the novel approach decreased the proportion of women falsely labeled as test-positive from 42.3% (34.4–50.2%) to 4.0% (0.85–7.15%), and increased the proportion correctly labeled as test-negative from 23.5% (16.7–30.3%) to 61.7% (53.9–69.5%). This potentially reduces average per-patient costs by \$1215. Hadker *et al.* [55] saw similar outcomes in a recent German study.

On the basis of the above-mentioned studies, larger prospective studies should be conducted to confirm whether use of angiogenic factors in clinical decision-making can decrease the incidence of pre-term delivery and reduce resource utilization without increasing the risk of adverse maternal and neonatal outcomes.

OTHER EMERGING MARKERS

Studies of sEng levels in women with and without preeclampsia have not been studied as extensively, but similar to levels of sFlt1, levels of sEng are high among women with preeclampsia. Women with preeclampsia have elevated sEng levels in the third trimester, with levels rising 4–5 weeks prior to clinical diagnosis [22]. Addition of sEng measurement to sFlt1 and PlGF or measuring it as a single analyte has been shown to characterize preeclampsia and its adverse outcomes, reiterating the combined role of these factors [34,56]. In preeclampsia-associated placental abruption, sFlt1, PlGF, and sEng levels have all been shown to be altered [57,58]. There are also emerging data that podocyturia – the shedding of live podocytes – can be used as a predictive test for preeclampsia. Podocyturia is present at delivery in women with preeclampsia [59]. In a recent study, podocyturia in the second trimester was found to have excellent sensitivity and specificity for diagnosis of preeclampsia [60]. However, podocyturia is not specific for preeclampsia as other kidney diseases are associated with podocyturia, and further larger studies are needed to elucidate the role of podocyturia in the diagnosis and management of preeclampsia.

TREATMENT MODALITIES

The emerging literature linking the magnitude of antiangiogenic proteins to adverse outcomes has been accompanied by small but promising publications investigating the therapeutic potential of agents that can reduce sFlt1 levels or raise VEGF. Animal studies have shown that recombinant VEGF or PlGF itself may serve as an effective strategy to ameliorate sFlt1-induced vascular damage [61,62]. Whether these recombinant proteins will be well tolerated during human pregnancies remains unknown. Additionally, there are

interesting studies, mainly involving animal models, suggesting that statins and the hormone relaxin are potential candidates for up-regulating proangiogenic factors [63,64]. Trials are currently underway evaluating safety and use of these in humans [65,66].

Of particular interest is a human pilot study published by Thadhani *et al.* [67], who were able to successfully prolong gestation far beyond traditional management in three women with pre-term preeclampsia (28–30 weeks) using dextran sulfate cellulose apheresis treatment. During a course of 2–4 sessions they were able to decrease sFlt1 levels, reduce proteinuria, and stabilize BP. The pregnancies lasted for 2–3 weeks with evidence of fetal growth, truly remarkable for such complicated gestations.

CONCLUSION

During the past decade, the molecular mechanisms of preeclampsia have been elucidated. It also appears the preeclampsia is associated with the development of hypertension and chronic renal disease in later years [4]. A large body of work suggests that anti-angiogenic factors such as sFlt1 play a central role in the pathogenesis of preeclampsia and are closely associated with preeclampsia-related adverse outcomes. This work has led to the availability of angiogenic biomarkers (sFlt1 and PlGF) on automated platforms for clinical use as an aid in establishing the diagnosis and prognosis of preeclampsia. During the next decade, we are hopeful that the discovery of mechanisms of preeclampsia will lead to availability of molecular therapies that can be used to ameliorate preeclampsia safely.

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- of special interest
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KEY POINTS

- The current definition of preeclampsia seems to miss a significant proportion of patients who have similar adverse outcomes and comparable changes in angiogenic profile.
- Recent studies of antiangiogenic factors, specifically sFlt1, have brought remarkable objective insight into pathogenesis and diagnosis of preeclampsia.
- A sFlt1/PlGF ratio of more than 85 helps in diagnosis of preeclampsia, differentiating it from other diseases with similar presentation and predicting adverse outcomes especially in patients presenting before 34 weeks' gestation.
- A recent study has shown prolongation of pregnancy after decreasing sFlt1 levels with apheresis. However, the therapeutic potential of interventions to modulate these antiangiogenic factors needs to be studied further.

FIGURE 1.

Predictive accuracy and correlation with duration of pregnancy of the sFlt1/PlGF ratio. (a) Shows receiver operating characteristic curves for prediction of adverse outcomes using the sFlt1/PlGF ratio, alanine aminotransferase (ALT), uric acid, SBP (highest SBP measured in triage), and creatinine, in patients presenting less than 34 weeks' gestation. All laboratory values were measured in blood collected at the time of presentation. The area under the curve (AUC) is given for each potential predictor in the legend. All AUCs were significantly different from that of the sFlt1/PlGF ratio alone ($P < 0.01$). (b) Shows the Kaplan-Meier survival function for time to delivery in participants presenting less than 34 weeks' gestation. Patients were censored at delivery or at 34 weeks' gestation [26[¶]]. PlGF, placental growth factor; sFlt1, soluble fms-like tyrosine kinase-1.