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NEW DEVELOPMENTS IN THE PATHOGENESIS OF PREECLAMPSIA

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Abstract

Preeclampsia affecting 3-5% of all pregnancies is a major cause of maternal and perinatal morbidity and mortality worldwide. This disorder is characterized by a constellation of signs and symptoms, most notably new onset hypertension and proteinuria during the last trimester of pregnancy. In this review, the molecular mechanisms of preeclampsia with an emphasis on the role of circulating anti-angiogenic proteins in the pathogenesis of preeclampsia and its complications will be discussed.

Keywords

preeclampsia; angiogenesis; cardiovascular disease; proteinuria

Introduction

Preeclampsia, that affects 3-5% of all pregnancies is defined as new onset hypertension and proteinuria occurring after 20 weeks gestation [1]. Other features of the preeclampsia syndrome include seizures (eclampsia), thrombocytopenia, elevated transaminases, and microangiopathic hemolytic anemia (HELLP syndrome) [2]. Neonatal complications of preeclampsia include preterm delivery, fetal growth restriction, hypoxia-related neurologic injury, perinatal death, and long-term cardiovascular morbidity associated with low birthweight [1]. Delivery of the placenta is the only known treatment at this time, suggesting that this is a placental disease [3].

While edema is often noted in preeclampsia, it is not very specific for the disease. Moreover, there is evidence that even with patients who develop eclampsia before or after 32 weeks gestation, there are significant number of patients who do not develop edema [4]. Maternal and perinatal outcomes are better in patients with mild disease developing after 36 weeks'

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Disclosures

Dr. Karumanchi is a co-inventor of multiple patents related to angiogenic proteins for the diagnosis and therapy of preeclampsia. These patents have been licensed to multiple companies. Dr. Karumanchi reports having served as a consultant to Roche and Beckman Coulter and has financial interest in Aggamin LLC. Dr. Naljayan reports no conflicts.

gestation, but in patients with who develop the disease prior to 33 weeks have a higher maternal and perinatal morbidity and mortality[2, 1]. Mortality increases with maternal age for both preeclampsia and eclampsia, and black women were 3.1 times more likely to die from preeclampsia or eclampsia than white women [5].

Factors that increase the risk for preeclampsia development in a woman include prior history of preeclampsia, chronic hypertension, chronic kidney disease, pregestational diabetes, multiple gestations, obesity, and age >40 years old [6]. Other factors include a partner who fathered preeclamptic pregnancy with another woman, woman born as small for gestational age, and adverse outcomes in a previous pregnancy [7]. Women with a history of preeclampsia also develop cardiovascular disease later in their life. In this review, we will summarize the molecular mechanisms of preeclampsia and its related complications.

Pathogenesis of Preeclampsia (see Figure 1 for summary)

The placenta is the central to the pathogenesis of preeclampsia. Preeclampsia occurs only in the presence of the placenta, even when there is no fetus (as in hydatidiform mole) and usually remits when the placenta is delivered. Pathology specimens have shown placental infarcts, likely due to ischemia and occlusion of the spiral arteries. The physiological vascular remodeling of spiral arteries by trophoblasts does not occur in preeclampsia[8]. At the cellular level, cytotrophoblasts undergo pseudovasculogenesis by switching their adhesion molecules to mimic those of vascular cells [9]. In preeclampsia, this process does not occur appropriately, and therefore invasion into the spiral arteries is incomplete. Various pathways including deficient heme oxygenase expression, genetic factors, oxidative stress, immune factors such as angiotensin receptor autoantibodies or altered natural killer cell signaling and, more recently deficient catechol-*O*-methyl transferase or deficient corin enzymes have been all proposed to have key roles in inducing placental disease [10-15]. However it is not known whether any one of more of these pathways play a casual role in mediating the abnormal placentation noted in humans with preeclampsia. It is currently believed that abnormal placentation occurs early in pregnancy and that this leads to placental ischemia (Stage I). The ischemic placenta is thought to secrete soluble factors during the third trimester that in turn induces systemic endothelial dysfunction and the maternal syndrome of preeclampsia (Stage II)[16].

The maternal syndrome and clinical features of preeclampsia are unified by the presence of systemic endothelial dysfunction and microangiopathy, in which the target organ may be the brain (seizures or eclampsia), liver (HELLP syndrome), or kidney (glomerular endotheliosis and proteinuria)[17]. Recent studies by our group and others have led to an extremely plausible hypothesis that the clinical manifestations of preeclampsia result, in part, from an imbalance between circulating pro-angiogenic and anti-angiogenic factors in the maternal circulation [18-25]. The two placental derived circulating anti-angiogenic factors that have received greatest attention are soluble vascular endothelial growth factor 1 (sVEGFR1) (also referred to as soluble fms-like tyrosine kinase 1 or sFlt1) and soluble endoglin (sEng) whose levels are elevated in women with preeclampsia, while the pro-angiogenic proteins, whose circulating concentrations (free levels) are reduced in women with the disease are vascular endothelial and placental growth factors (VEGF, PlGF) [6]. sFlt1 is an endogenous soluble

anti-angiogenic protein that acts by binding pro-angiogenic proteins – VEGF and PlGF. Soluble endoglin is another anti-angiogenic protein that is thought to act by disrupting transforming growth factor beta signaling in the vasculature [6]. Overexpression of sFlt1 and sEng in pregnant rats appear to induce severe preeclampsia-like syndrome including severe hypertension, nephrotic range proteinuria, glomerular endotheliosis thrombocytopenia, and fetal growth restriction[25]. The renal manifestations of preeclampsia can be explained almost entirely by excess sFlt1 with accompanying loss of VEGF actions in the glomeruli, as genetic deficiencies of VEGF in mice also lead to glomerular endotheliosis, the classic histological lesion of preeclampsia[26]. Loss of endothelial fenestrae due to lack of glomerular VEGF signaling leads to significant reduction in glomerular filtration rate and renal failure in preeclampsia [27]. Overexpression of sFlt1 and sEng in rodents also has been shown to induce focal vasospasm, hypertension, increased vascular permeability, and cerebral edema that resembles the reversible posterior leucoencephalopathy of human eclampsia [28]. Interesting several anti-angiogenic compounds (anti-VEGF antibodies) used as part of cancer chemotherapy to treat tumor related angiogenesis is also been associated with preeclampsia/eclampsia like changes such as hypertension, proteinuria and reversible posterior leucoencephalopathy [29-32]. While there a number of signaling pathways downstream of anti-angiogenic factors, increased endothelin-1 (ET1) signaling may be a critical pathway that mediates sFlt1 induced endothelial dysfunction [33].

Placental syncytiotrophoblasts and in particular syncytial knots were identified as a major source of sFlt1 and soluble endoglin production [34, 35]. Syncytial knots are induced by placental hypoxia and are noted predominantly in preeclamptic placentas. Syncytial knots have been shown to release aggregates into the maternal circulation suggesting an additional source of increased sFlt1 in the maternal blood besides secretion by the placenta [35]. It has been suggested that shed syncytial aggregates get trapped in the capillary beds of lung tissue, where they further undergo disaggregation or apoptosis/necrosis to release the smaller microparticles into the systemic circulation. The relative contribution of these processes to the formation of trophoblast microparticles within the maternal circulation remains to be determined. .

Epidemiologic studies have revealed that blood levels of angiogenic proteins (sFlt1, PlGF and sEng) are altered in women with preeclampsia both during and prior to clinical signs and symptoms of the disease, consistent with a pathogenic role for these angiogenic factors in preeclampsia [21, 22, 24, 36-38]. In addition, several studies have demonstrated that the alterations in circulating angiogenic factors may explain a number of risk factors for preeclampsia such as multiple gestation, trisomy 13, nulliparity and molar pregnancies [39-43]. More recent data suggests that alterations in sFlt1, PlGF, and sEng in women with preeclampsia correlate with maternal vascular dysfunction as measured by flow mediate vasodilation and uterine artery pulsatility index[24]. In addition, alterations in these angiogenic factors have been found in complications of preeclampsia. In preeclampsia-associated placental abruption, sFlt1, PlGF, and sEng levels have all been shown to be altered [44, 45]. In eclampsia, sFlt1, PlGF, and sEng are also altered to a similar degree as in patients with severe preeclampsia, reiterating synergistic role of these factors in both of these conditions [46]. In a prospective study of pregnant women, patients who develop preeclampsia had higher levels of sFlt1, higher sEng, and lower PlGF but these findings

were not seen in patients with gestational hypertension. Those patients that developed gestational hypertension, but not preeclampsia, were found to have higher brachial flow-mediated dilatation, suggesting a more hyperdynamic circulation as compared to patients with preeclampsia [24]. These findings suggest that the pathophysiologies of these two diseases are fundamentally different, but that there may be some overlap with risk factors for patients who are likely to develop these diseases. Finally, other predisposing factors such as obesity and chronic hypertension may sensitize the maternal vascular endothelium to the anti-angiogenic effects of sFlt1 and sEng and thus lower threshold to develop preeclampsia. Clinical studies support this hypothesis as obese women tend to have lower circulating sFlt1 and sEng [21, 22].

Clinical Implications for Diagnosis and Treatment of Preeclampsia

A number of recent studies have suggested that circulating angiogenic factors in plasma or urine can be used to differentiate preeclampsia from other diseases that mimic preeclampsia such as chronic hypertension, gestational hypertension, lupus nephritis and gestational thrombocytopenia [47-56]. To demonstrate clinical utility, we prospectively studied the role of angiogenic biomarkers in the prediction of preeclampsia related adverse outcomes among women evaluated at our institution for suspected preeclampsia. We found that the plasma sFlt1/PlGF ratio on presentation predicts adverse maternal and perinatal outcomes (occurring within two weeks) in the preterm setting. This simple, quantitative, rapid test outperformed the standard battery of clinical diagnostic measures including blood pressure, proteinuria, uric acid, and other laboratory assays [57]. Importantly, sFlt1 and/or PlGF levels at presentation were strongly associated with the remaining duration of pregnancy [53, 57-60]. We also recently evaluated the role of sEng measurements and found that it has comparable performance to sFlt1/PlGF ratio[61]. Interestingly, a number of patients with preeclampsia, particularly those presenting late in pregnancy present with no angiogenic factor abnormalities[62]. Whether these patients are misclassified as preeclampsia or if they truly represent a benign variant of preeclampsia remain unknown. In summary, current evidence supports the hypothesis that circulating angiogenic factors are useful in risk stratification of women with preeclampsia to predict development of complications.

Animal studies have suggested that sFlt1 ligands such as VEGF or PlGF itself can safely ameliorate preeclampsia [63-65]. In addition, compounds that upregulate pro-angiogenic factors such as statins have been used to ameliorate preeclampsia in animal models [66]. A clinical proof-of-concept trial to test the effects of pravastatin (that does not cross the placenta) in preeclampsia is ongoing [67]. Extracorporeal apheresis to lower circulating sFlt1 has also been attempted as a treatment modality in women with preeclampsia. In exciting studies, Thadhani et al using dextran sulfate apheresis have been able to extend three preeclamptic pregnancies by 2-4 weeks, all of which resulted in healthy deliveries with no neonatal or maternal morbidity [68]. During the course of the treatment, the extracorporeal adsorption device only lowered soluble sFlt1 levels by 30% on average, validating the idea that just partially lowering circulating sFlt1 levels is sufficient to successfully prolong preeclamptic pregnancies. Experimental studies suggest that the hormone relaxin may also be used to ameliorate preeclampsia by improving vascular compliance and upregulating

VEGF locally[69]. A phase I study to test the safety of human relaxin in women with preeclampsia has recently been completed[70].

Long-term Complications of Preeclampsia

As endothelial dysfunction is a hallmark of preeclampsia, it is not surprising that the long-term sequelae in women with a history of preeclampsia are centered around cardiovascular complications such as hypertension, ischemic heart disease and stroke. Women with a history of a preeclampsia are several times more likely to die from cardiovascular disease (CVD) [71, 72]. This risk is greatest among women who have a history of preterm preeclampsia or preeclampsia that was complicated with a growth-restricted fetus[73, 74]. It is not know whether preeclampsia directly *causes* CVD or merely unmask subclinical CVD risk. Recent study of CVD risk factors present before and after pregnancy suggests that nearly half of the elevated risk for future hypertension after preeclampsia can be explained by pre-pregnancy risk factors[75]. Therefore, pregnancy may be viewed as a stress test that can reveal subclinical CVD phenotypes long before overt disease. Small studies have shown that levels of sFlt-1 remained higher in women with a history of preeclampsia in the post-partum period [76, 77] Whether a persistent anti-angiogenic milieu in the post-partum period may contribute to lasting endothelial dysfunction and an elevated risk of CVD in women remains unknown. Recent studies also suggest that preeclampsia is a major risk factor for peripartum cardiomyopathy and that imbalances in angiogenic factors may be critical for both disorders [78]. Babies born to preeclampsia are also at risk for pulmonary hypertension in the long term [79].

Epidemiologic studies have also shown an increased risk for end-stage renal disease (ESRD) in women with a history of preeclampsia [80, 81]. Although the relative risk for ESRD in women with preeclampsia is robust with hazard ratios ranging from 4-12, the absolute risk is still quite low. A recent meta-analysis suggested there is at least four times increased risk of microalbuminuria in women following preeclampsia, possibly due to persistent kidney damage after preeclampsia [82]. Other studies have also suggested that familial factors may not be responsible for the development of chronic kidney disease following preeclampsia [83]. A small pilot study suggested that angiotensin II sensitivity was noted in the post-partum period in women with a history of preeclampsia [76]. However, it is not known whether the increased angiotensin II sensitivity contributes to the development of hypertension and/or chronic renal disease.

Conclusion

In summary, current evidence suggests that placental derived anti-angiogenic factors such as sFlt-1 and sEng play a role in the development of the maternal syndrome of preeclampsia. The identification and characterization of circulating anti-angiogenic factors in preeclampsia syndrome has allowed a better understanding of not only the pathogenesis, but has raised hope that this research area will lead to early identification and specific therapies in the immediate future. More work is needed to further define the regulation of placenta vascular development and expression of these angiogenic factors in normal and in preeclamptic pregnancies. Following pregnancy, women with preeclampsia have a higher risk for

developing hypertension, renal disease and CVD in future years. Although the precise mechanisms for these long term vascular complications among women with preeclampsia are not known, these patients should be assessed yearly for the development of hypertension and/or proteinuria and managed appropriately to reduce the risk for CVD and ESRD.

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Clinical Summary

- Increased levels of circulating anti-angiogenic proteins contribute to the pathogenesis of the maternal syndrome
- Targeting anti-angiogenic proteins may safely ameliorate preeclampsia and prolong pregnancy, however randomized trials are still needed
- Preeclampsia is associated with hypertension and cardiovascular disease in later life

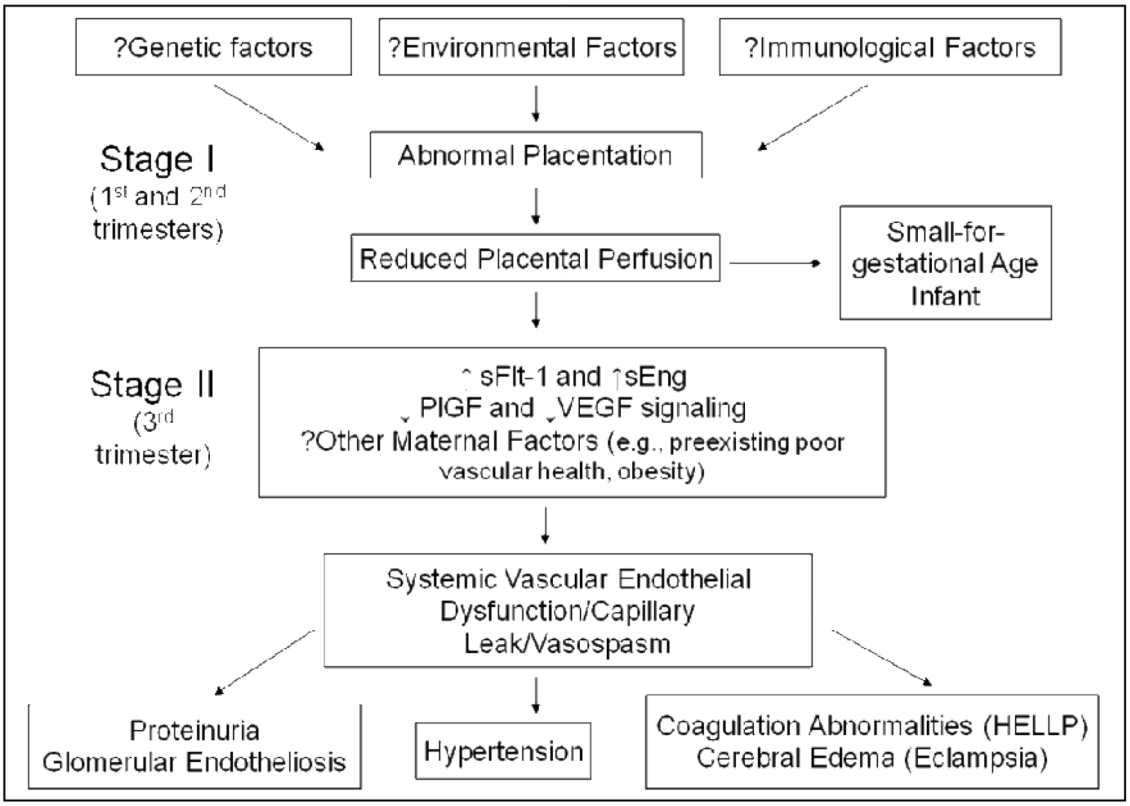

Figure 1.
Summary of the Pathogenesis of Preeclampsia