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Soluble Fms-like Tyrosine Kinase 1 and Endothelial Dysfunction in the Pathogenesis of Preeclampsia

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ABSTRACT

Preeclampsia, a pregnancy-specific syndrome of hypertension and proteinuria, is characterized by defective placental vasculogenesis and widespread maternal endothelial dysfunction. Although the manifestations of preeclampsia are primarily maternal, the burden of morbidity and mortality is often on the neonate, since the only effective treatment—delivery of the fetus and placenta—often results in iatrogenic prematurity. In this review, we summarize recent advances in our understanding of the pathophysiology of preeclampsia, including normal and aberrant placental vascular development and evidence for endothelial dysfunction. We describe recent evidence that supports a novel mechanism in which a maladaptive shift in placental production of angiogenic factors such as soluble fms-like tyrosine kinase 1 (a circulating antiangiogenic protein) may play an important role in the pathogenesis of preeclampsia. **(*Pediatr Res* 57: 1R–7R, 2005)**

Abbreviations

AT1-AA, angiotensin receptor 1 auto-antibody
PlGF, placental growth factor
sFlt1, soluble fms-like tyrosine kinase 1
SGA, small for gestational age
VEGF, vascular endothelial growth factor

Preeclampsia affects 3–5% of all pregnancies (1) and is classically defined as the new onset of hypertension and proteinuria after wk 20 of gestation. Since E.W. Page first posited in 1939 that a placental defect might cause preeclampsia (2), our understanding of normal placental vasculogenesis and of the pathophysiology of preeclampsia has advanced significantly. Here we will review recent advances and summarize our current understanding of the pathogenesis of preeclampsia. We will describe evidence that preeclampsia may involve an imbalance among the pro- and antiangiogenic factors that regulate placental and systemic endothelial health.

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CLINICAL FEATURES AND EPIDEMIOLOGY OF PREECLAMPSIA

Preeclampsia is characterized by the new onset of hypertension and proteinuria during the last trimester of pregnancy. It is also usually associated with hyperuricemia and edema. Severe preeclampsia may also lead to SGA babies. The clinical onset of preeclampsia is often insidious and asymptomatic, but may include headache, visual disturbances, epigastric pain, weight gain, and edema of the hands and face. These early signs and symptoms are important to recognize clinically, since they may herald progression to a more severe and often life-threatening disease. Severe complications of preeclampsia can include acute renal failure; cerebral edema, cerebral hemorrhage, and seizures (eclampsia); pulmonary edema; thrombocytopenia, hemolytic anemia, coagulopathy; and liver injury, including HELLP, the syndrome of hemolysis, elevated liver enzymes, and low platelets. Although antihypertensive medications help to lower blood pressure and magnesium sulfate is effective in seizure prophylaxis (3), delivery remains the only definitive treatment. When preeclampsia threatens to lead to severe maternal complications, urgent delivery of the fetus and placenta are often undertaken to preserve maternal health.

In the developed world, where safe emergent cesarean delivery is available, the burden of morbidity and mortality due to

preeclampsia is on the neonate. Preeclampsia is associated with placental hypoperfusion, which can lead to intrauterine growth restriction and oligohydramnios. Abruptio placentae complicates about 4% of cases of severe preeclampsia (4). Neonatal morbidity is most often due to the sequelae of prematurity and low birth weight, including prolonged neonatal intensive care unit stays, respiratory distress, necrotizing enterocolitis, intraventricular hemorrhage, sepsis, and death (5,6). The HELLP syndrome has been associated with a 10–20% incidence of perinatal mortality, attributable largely to premature delivery (7,8).

The epidemiology of preeclampsia provides clues about the pathophysiology that scientists are still deciphering. Although most preeclampsia occurs in healthy nulliparous women, several risk factors are reminiscent of cardiovascular risk factors, including chronic hypertension [odds ratio (OR), 2.7] (9,10), renal disease (OR, 7.8) (11,12), diabetes mellitus (13), high body mass index and obesity (OR, 2.1–3.2) (9,14,15), and family history of cardiovascular disease (OR, 1.9) (16). The importance of cardiovascular risk factors has strengthened the hypothesis that preexisting maternal vascular dysfunction or susceptibility may have a pathologic role in at least some cases of preeclampsia. The association of preeclampsia with primiparity, increased interpregnancy interval, and possibly primipaternity (17) has generated hypotheses regarding dysregulation of placental immune tolerance, which remains an area for further study.

ROLE OF THE PLACENTA

Several early observations support the hypothesis for a placental trigger for preeclampsia. Preeclampsia only occurs in the presence of a placenta (though not necessarily a fetus, as in the case of hydatidiform mole). It almost always remits after delivery of the placenta. In cases of preeclampsia with extrauterine pregnancy, removal of the fetus alone is insufficient; symptoms persist until the placenta is delivered (18).

Long-standing and severe preeclampsia is associated with pathologic evidence of placental hypoperfusion and ischemia. Findings include acute atherosis, a lesion of diffuse vascular obstruction first described in 1945 (19): fibrin deposition, intimal thickening, necrosis, and endothelial damage. Infarcts, likely resulting directly from occlusion of maternal spiral arteries (20), are also common. Although these findings are not universal, they appear to be correlated with severity of clinical disease (21).

Abnormal uterine artery Doppler ultrasound, suggesting increased uteroplacental resistance to blood flow, is observed before the onset of clinical signs of preeclampsia (22), although this finding is nonspecific, limiting its use as a clinical screening test (23). In a recent study, abnormalities in uterine artery Doppler correlated with poor clinical outcome among women with pregnancy-induced hypertension and preeclampsia (24). Hypertension and proteinuria can be induced by constriction of uterine blood flow in pregnant primates (25,26) and rodents (27,28). These observations suggest placental ischemia may be an early, and perhaps precipitating, event. However, evidence for a causative role for placental ischemia remains circumstantial, and several observations call the hypothesis into question. For example, the animal models based on uterine hypoperfusion universally fail to induce several of the multiorgan features of preeclampsia, including seizures and the HELLP syndrome. In most cases of human preeclampsia, there is no evidence of growth restriction or fetal intolerance of labor, which would be expected from significant placental hypoperfusion. It may be that the pathologic evidence of placental ischemic damage that accompanies late-stage preeclampsia may be a secondary event: no studies have examined placental changes before the onset of clinical signs of preeclampsia. Nevertheless, recent studies provide evidence for inadequate spiral artery remodeling, the understanding of which requires a closer review of normal placentation.

PLACENTAL VASCULAR REMODELING

Early in placentation, 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 (29,30). This vascular transformation allows the increase in uterine blood flow needed to sustain the fetus through pregnancy.

In preeclampsia, this transformation is incomplete (31,32). Cytotrophoblast invasion of the arteries is limited to the superficial decidua, and the myometrial segments remain narrow and undilated (33,34). Fisher and colleagues (35,36) have shown that in normal placental development, 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 referred to as pseudovasculogenesis. In preeclampsia, cytotrophoblasts fail to undergo this switching of cell-surface integrins and adhesion molecules (37) and fail to adequately invade the myometrial spiral arteries.

The factors that regulate this process are just beginning to be elucidated. Hypoxia-inducible factor-1 (HIF-1) is up-regulated in preeclampsia and HIF-1 target genes such as transforming growth factor beta 3 may block cytotrophoblast invasion (38,39). Invasive cytotrophoblasts express several angiogenic factors and receptors, including VEGF-A, PlGF, and VEGFR-1 (Flt1); expression of these proteins by immunolocalization is altered in preeclampsia (40). Interestingly, uteroplacental ischemia produced in monkeys by aortic constriction late in gestation appears to enhance trophoblast invasion, thus producing a pathologic change quite different from that observed in preeclampsia (41). This again suggests the inadequacy of animal models based on aortic or uterine vessel constriction.

MATERNAL ENDOTHELIAL DYSFUNCTION

Placental pathology notwithstanding, preeclampsia is a multisystem disorder, and its manifestations reflect widespread endothelial dysfunction, often resulting in vasoconstriction and end-organ ischemia (42,43). Several serum markers of endothelial activation are altered in women with preeclampsia, including von Willebrand antigen (44), cellular fibronectin (45), soluble tissue factor, soluble E-selectin, platelet-derived

growth factor, and endothelin (46). There is evidence for oxidative stress (47), increased lipid peroxidation (48), and platelet activation (49). Leptin levels are increased as early as 20 wk (50). Decreased PGI2 (an endothelial cell–derived prostaglandin) production well before the onset of clinical symptoms is consistent with the hypothesis that dysfunctional endothelial cells are central to the pathogenesis of the syndrome (51). Maternal vascular reactivity to the vasopressors such as angiotensin II and norepinephrine is increased in preeclampsia (52). Endothelium-dependent vasorelaxation is impaired, both in the myometrial vessels *in vitro* (53) and in forearm blood flow *in vivo* (54).

In the kidney, endothelial damage results in proteinuria and produces the characteristic pathologic lesion, glomerular endotheliosis (55,56). Glomerular endotheliosis is characterized by generalized swelling and vacuolization of the endothelial cells with obliteration of the endothelial fenestrae and loss of the capillary space. Mesangial cells may occasionally show nonspecific changes that are likely related to the proteinuria. There are deposits of fibrinogen and fibrin within and under the endothelial cells (57). The injury is specific to endothelial cells: the foot processes of the podocytes are almost completely normal early in disease, an unusual finding in proteinuric renal disease. Although once considered pathognomonic for preeclampsia, recent studies have shown that mild glomerular endotheliosis may also occur in a significant percentage of normal pregnancies at term and that it is more severe in preeclamptics (58). This suggests the endothelial dysfunction of preeclampsia may in fact be an exaggeration of a process present near term in all pregnancy.

Long-term outcomes among women with a history of preeclampsia suggest the endothelial changes are not limited to pregnancy. Cardiovascular morbidity and mortality are increased among such women, including stroke (59), ischemic heart disease (60,61), and chronic hypertension (62). Impaired endothelium-dependent vasodilation, a marker for endothelial dysfunction, persists for years postpartum (54,63) It is also interesting to note that women with preeclampsia appear to have a decreased risk of malignancy in several studies (59,64,65), consistent with an antiangiogenic milieu that may extend beyond the pregnancy itself. Whether these long-term observations are due to endothelial damage done as a result of preeclampsia, or simply reflect the consequences of the vascular risk factors that are more common in these women remains speculative.

LINKING THE PLACENTA AND THE MATERNAL RESPONSE

These two lines of evidence—the central role of the placenta and the subsequent endothelial dysfunction responsible for the end-organ damage—have converged to produce a pathophysiologic paradigm that has been the framework for investigation over the past few decades. The placenta, possibly as a result of ischemia, secretes a factor or factors into the maternal circulation that directly or indirectly damages maternal endothelial cells. This paradigm begs two essential questions about the pathophysiology of preeclampsia: first, why does placental vasculogenesis fail, resulting in incomplete remodeling of decidual arteries? And second, what is the placental factor that produces the clinical manifestations of disease?

In vitro data provide compelling supportive evidence for a factor in preeclamptic serum that produces endothelial dysfunction. Plasma from women with preeclampsia increases production of nitric oxide (66), cellular fibronectin (67), prostacyclin (68), and other markers of activation/dysfunction *in vitro*. Incubation of uterine vessels with plasma from women with preeclampsia results in impaired endothelium-dependent vasorelaxation (69). Many other observations also support this hypothesis and are recently reviewed elsewhere (70).

The identity of the "preeclampsia factor" has remained elusive, however. Several candidate factors have been studied. Page and colleagues (71) found that levels of neurokinin-B (NK-B), a neurotransmitter apparently produced by the placenta, were elevated in women with preeclampsia, and that rats infused with high doses of NK-B developed transient hypertension. However, their findings have not borne out in subsequent studies (72,73). There is also recent data that increased syncytiotrophoblast shedding in preeclampsia as a consequence of placental apoptosis may contribute to endothelial dysfunction in cell culture studies. However, there is no *in vivo* evidence so far that circulating placental debris induce preeclampsia-like syndrome (74). AbdAlla *et al.* (75) have found increased heterodimerization between the angiotensin AT-1 receptor and the bradykinin B-2 receptors; this resulted in increased responsiveness to angiotensin-2. The T235 polymorphism of the angiotensinogen gene also appears to increase risk (76). However, no single gene mutation/polymorphism has been consistently associated with preeclampsia in all populations. Patients with preeclampsia have also been reported to have circulating AT1-AA (77). These autoantibodies are thought to antagonize the AT1 receptor and have been hypothesized to participate in the angiotensin II–induced vascular lesions in preeclamptic patients (78,79). However, direct causal evidence implicating AT1-AA in preeclampsia has not yet been established. Moreover, the temporal relationship of these auto-antibodies with the clinical syndrome of preeclampsia has not been studied.

sFLT1: AN ANTI-ANGIOGENIC FACTOR AND ITS ROLE IN PREECLAMPSIA

The search for the elusive preeclampsia factor led our group to use gene expression profiling of placental tissue using microarray technology. Using this approach, the antiangiogenic protein sFlt1 (soluble fms-like tyrosine kinase or sVEGFR1) was found to be up-regulated in the placenta of women with preeclampsia (80). In addition, circulating levels of sFlt-1 were found to be elevated in conjunction with decreased VEGF and PlGF in the bloodstream at the time of disease presentation, a finding that has been reported by multiple groups (80–84). The *in vitro* effects of sFlt1 included vasoconstriction and endothelial dysfunction, mimicking the effects of plasma from women with preeclampsia (80). Adenoviral gene transfer of sFlt1 to pregnant rats produced a syndrome resembling preeclampsia, including hypertension, pro-

teinuria, and glomerular endotheliosis (80). Furthermore, a soluble form of VEGF receptor-2 antagonist (sFlk-1), which does not antagonize PlGF when given exogenously, did not induce a preeclamptic phenotype in pregnant rats. This suggests that antagonism of both VEGF and PlGF is necessary to induce the maternal syndrome. This work has generated considerable enthusiasm for sFlt1 as an important mediator in preeclampsia. Much of the remainder of this article will explore the nature of this protein and how it might improve our understanding of preeclampsia.

sFlt1 is an antiangiogenic molecule that antagonizes VEGF and PlGF. VEGF is important in both angiogenesis (the growth of new blood vessels) and in the maintenance of endothelial cell health in the basal state. Although the function of PlGF is still ill defined, it appears to act synergistically with VEGF and may be necessary for wound healing and angiogenesis in ischemic tissues (85,86).

VEGF has a family of receptors, the most important of which are Flt1 (VEGFR1) and Flk1 (VEGFR2) (87). sFlt1 is a truncated form of the Flt1 receptor (Fig. 1). It includes the extracellular ligand-binding domain, but not the transmembrane and intracellular domains; it is secreted (hence "soluble") and antagonizes VEGF and PlGF in the circulation by binding and preventing their interaction with their endothelial receptors (88). The regulation of Flt1 splicing to produce the full Flt1 receptor *versus* the truncated sFlt1 remains unexplored. It was recently shown that hypoxic trophoblasts grown *in vitro* produces excess quantities of sFlt-1 (89), however, whether this phenomenon occurs *in vivo* remains unknown. Although sFlt1 is made in small amounts by other tissues (endothelial cells and monocytes), the placenta seems to be the major source of circulating sFlt1 during pregnancy, as evidenced by the dramatic fall in circulating concentrations of sFlt1 after the delivery of the placenta (80).

sFlt1 levels are increased, and free (unbound) PlGF and free VEGF levels are suppressed, in the serum of women during clinical preeclampsia (80). The changes in these markers precede the onset of clinical disease by at least 5 wk (90); in fact, decreased free PlGF levels are observed even before 20 wk gestation in women who go on to develop preeclampsia (84,90,91). The diminished PlGF levels early in pregnancy are not accompanied by reciprocal increases in systemic sFlt1.

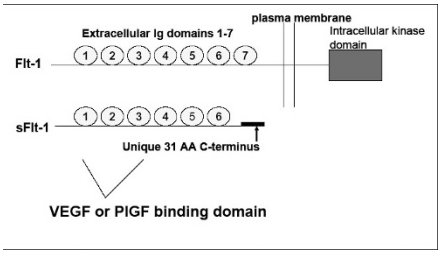

Figure 1. Protein structure of Flt-1 and sFlt-1 are illustrated. Flt-1 has 7 immunoglobulin domains (IgG), which are thought to mediate ligand binding to VEGF and PlGF. sFlt-1 protein has a unique 31 AA C-terminus region derived from alternative splicing and lacks the transmembrane and cytoplasmic domains. *Figure reproduced with permission from Karumanchi SA et al. 2004 Pathogenesis of preeclampsia. In: Rose BD (ed) UpToDate. UpToDate, Wellesley, MA. ©2004 UpToDate Inc.*

This may reflect either less placental production of PlGF or increased binding to local circulating and membrane-bound receptors, but the precise mechanisms for this remain unexplored.

There is much supportive evidence suggesting VEGF and PlGF antagonism by sFlt1 may produce the endothelial dysfunction in preeclampsia. VEGF is highly expressed by glomerular podocytes, and VEGF receptors are present on glomerular endothelial cells (92,93). In experimental glomerulonephritis, VEGF is necessary for glomerular capillary repair (94,95). In antiangiogenesis cancer trials, VEGF antagonists produce proteinuria and hypertension in human subjects (96,97). Recent data suggests that VEGF may be particularly important in maintaining the health of fenestrated endothelium (98), which is found in the renal glomerulus, brain, and liver—organs disproportionately affected in preeclampsia. It is tempting to speculate that cigarette smoking may exert its protective influence on preeclampsia risk (99) by its pro-angiogenic effects (100). A 50% reduction of renal VEGF production in genetically modified mice resulted in glomerular endotheliosis and proteinuria, providing genetic evidence that impaired VEGF signaling may lead to preeclampsia-like phenotype (101). Finally, trisomy 13 has long been associated with preeclampsia (102), suggesting that a protein on this chromosome may be important. The Flt1/sFlt1 gene is located on chromosome 13q12. Hence, one could hypothesize that 50% higher concentrations of circulating sFlt1 in trisomy 13 patients may account for the increased risk of preeclampsia; however, definitive proof for this hypothesis is lacking. On the other hand, other reported genetic associations with preeclampsia have no apparent link to sFlt1. For example, both an Australian/New Zealand cohort (103) and an Icelandic cohort (104) have suggested a maternal susceptibility locus on chromosome 2, bearing no known relationship to sFlt1. Although it is possible that such loci are associated with transcription factors or splicing factors affecting sFlt1 production, it seems more likely that there are other yet unidentified genetic factors that contribute to this multifactorial disease.

The excess sFlt1 theory certainly does not offer a complete picture of preeclampsia. There are several elements that remain unexplained. No coagulation, liver function, or brain abnormalities (eclampsia) were reported in sFlt-1-treated animals. Elements of maternal predisposition such as insulin resistance and hypertension seem to be independent of the placenta (105). Preeclampsia is associated not only with primiparity, but also with increased interpregnancy interval (106) and shorter cohabitation of partners before pregnancy (107). Some have suggested that this implies some role for reduced maternal-fetal immune tolerance or decreased exposure to paternal sperm antigens. It is interesting to note, however, that primiparous pregnant women appear to have higher baseline levels of sFlt1 compared with multiparous pregnant women, which may account for the increase in risk (91). Several maternal cardiovascular risk factors are also risk factors for preeclampsia, most notably diabetes mellitus, hypertension, and renal disease. It is possible that placental factors such as PlGF and sFlt1 interact with elements of maternal susceptibility in complex ways to produce a disease that varies dramatically in its timing and

severity (108). Finally, the relationship of sFlt-1 with previously hypothesized mechanisms of systemic damage in preeclampsia such as increased angiotensin II sensitivity, increased circulating AT1-AA, hyperuricemia, and increased sympathetic activation is unknown at the present time.

ROLE OF ANGIOGENIC FACTORS IN PLACENTAL VASCULAR DEVELOPMENT

VEGF ligands and receptors are highly expressed by placental tissue in the first trimester (40). Thus, it is intuitive to hypothesize that placental vascular development might be regulated by a local balance between pro- and antiangiogenic factors, and that excess sFlt1 in early gestation could contribute to inadequate placental vasculogenesis. Circulating sFlt1 levels are relatively low early in pregnancy and begin to distinctly rise in the third trimester. Although the reason for this increase is unclear, we posit that it may reflect an antiangiogenic shift in the placental milieu toward the end of pregnancy, corresponding to completion of the vasculogenic phase of placental growth. In preeclampsia, this rise in sFlt1 production is early and exaggerated. Furthermore, circulating concentrations of free PlGF levels is altered well before 20 wk of gestation in preeclamptic patients. We therefore have hypothesized that this early alteration in the angiogenic balance may therefore contribute to inadequate vascular cytotrophoblast invasion in the early stages of pregnancy, and its overflow into the circulation may produce maternal endothelial dysfunction in the third trimester. In this case, placental ischemia may not be causative, but rather one of the several mechanisms affected by this deranged angiogenic balance. Although *in vitro* studies using primary cytotrophoblast cultures and villous explants have demonstrated a role for sFlt1 in interfering with trophoblast invasion (40,109,110), definitive *in vivo* evidence for this hypothesis is lacking.

CONCLUSIONS

In summary, we believe that preeclampsia is a state of endothelial dysfunction secondary to excessive amounts of circulating antiangiogenic factors of placental origin, such as sFlt1 (110). If other investigators confirm the importance of sFlt1 in preeclampsia, the clinical implications could be significant. Currently, there is no useful and practical screening test for preeclampsia. The syndrome can be silent in its early stages, and it sometimes presents as severe and even explosive disease. If serum sFlt1 or PlGF levels were found to be sensitive and specific predictors of preeclampsia in prospective clinical trials, the efficacy of various nonspecific interventions could be investigated, including bedrest and antihypertensive and antiplatelet therapy. Of course, a screening/diagnostic test will become truly useful only when an effective treatment becomes available. Investigations are currently underway of various pharmacologic agents to counteract the effects of sFlt1 as a treatment for preeclampsia. If such agents are effective in alleviating the end-organ manifestations to safely postpone delivery for even a few weeks, a significant impact on neonatal morbidity and mortality could be made.

Clearly, a multifactorial approach is required as we continue to deepen our understanding of the preeclampsia syndrome. As our understanding continues to advance based on molecular and genetic techniques, we are hopeful that new interventions may improve our management of this important syndrome in the near future.

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