

## Antiangiogenic Factors and Pre-eclampsia

By Sharon E. Maynard

Pre-eclampsia is a systemic syndrome occurring in the second half of pregnancy, with cardinal manifestations of hypertension and proteinuria. Pre-eclampsia is one of the most common glomerular diseases in the world; it affects approximately 3–5 percent of all pregnancies. Although careful obstetric management—including antihypertensive medications and seizure prophylaxis with intravenous magnesium—is important for the treatment of pre-eclampsia, delivery of the neonate and placenta remains the only definitive treatment. Thus, pre-eclampsia remains a leading cause of maternal mortality, preterm birth, and consequent neonatal morbidity and mortality. In developing countries, where access to safe, emergent delivery is less readily available, pre-eclampsia claims the lives of over 60,000 mothers every year (1).

### Maternal endothelial dysfunction

Our understanding of the pathogenesis of pre-eclampsia has evolved remarkably over the past decade and is summarized in a simplified way in Figure 1. Pre-eclampsia appears to originate in the placenta, where abnormal vascular development precedes the clinical syndrome by weeks to months. The target “organ” is the maternal vascular endothelium. The clinical manifestations of pre-eclampsia—hypertension, proteinuria (signaling glomerular endothelial damage), liver injury (including the HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets), cerebral edema, and seizures—reflect widespread endothelial dysfunction, with vasoconstriction and end-organ ischemia. Mounting evidence over the past several years has implicated antiangiogenic proteins, produced by the placenta and secreted into the maternal circulation, as the pathogenic link between placental dysfunction and maternal endothelial damage.

Pre-eclampsia is a final common pathway of maternal vascular dysfunction with diverse and multifactorial origins, many of which remain obscure. The development of pre-eclampsia in any individual woman results from a combination of placental dysfunction (leading to aberrant production of antiangiogenic proteins and other factors) and maternal susceptibility. Genetic predisposition probably contributes to risk at both those levels. Most cases of pre-eclampsia occur in otherwise healthy primiparous pregnant women, and in those cases excessive placental production of angiogenic factors is probably the key factor. However, in women with underlying endothelial disease (diabetes mellitus or chronic hypertension, for example), maternal susceptibility to placental angiogenic factors is probably responsible for an increased risk of pre-eclampsia.

### Soluble fms-like tyrosine kinase 1: a circulating antagonist to growth factors

Angiogenesis is defined as the formation of new blood vessels. Soluble fms-like tyrosine kinase 1 (sFlt1) is often referred to as an antiangiogenic protein because, when secreted into the circulation, it binds and inactivates the proangiogenic vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).

Although essential for angiogenesis, VEGF is also critical for the maintenance of the health of mature endothelial beds, especially the renal glomerular endothelium, a major target in pre-eclampsia. Placental expression of sFlt1 is increased in pre-eclampsia and is associated with a marked rise in the levels of maternal circulating sFlt1 (2).

Increased circulating sFlt1 binds and antagonizes VEGF and PlGF in the maternal circulation, leading to endothelial dysfunction and pre-eclampsia. Animal models support this theory: sFlt administered to pregnant rats results in a syndrome resembling human pre-eclampsia, including

hypertension, proteinuria, and glomerular endotheliosis (2). Circulating levels of sFlt1 and PlGF are altered several weeks before the onset of clinical disease and are correlated with the severity of disease (3–5). The levels of sFlt1 normalize within several days after delivery, coinciding with improvement in proteinuria and hypertension.

### Soluble endoglin: a circulating antagonist to transforming growth factor- $\beta$

Soluble endoglin (sEng), another antiangiogenic biomarker that is upregulated in pre-eclampsia in a pattern similar to that of sFlt1, is a truncated form of endoglin (CD105), a cell surface receptor for transforming growth factor- $\beta$  (TGF- $\beta$ ). sEng amplifies the vascular damage mediated by sFlt1 in pregnant rats, inducing a severe pre-eclampsia-like syndrome with features of the HELLP syndrome (6). As with sFlt1, circulating sEng levels are elevated weeks before the onset of pre-eclampsia (7), and increased sEng levels are observed in the rat model of pre-eclampsia induced by uterine ischemia (8). The similarity in the gestational patterns of circulating sFlt1 and sEng suggest that they may be regulated by a common upstream signaling pathway.

### Insights from pre-eclampsia risk factors

Higher sFlt1 levels have been noted in first versus second pregnancies (9), twin versus singleton pregnancies (10, 11), hydatidiform mole (12, 13), and pregnancies with fetuses having trisomy 13 (14). All these conditions are established risk factors for pre-eclampsia. Conversely, decreased levels of sFlt1 in pregnant smokers (15, 16) may explain the protective effect of smoking in pre-eclampsia.

### Screening and prediction

Effective preventive and therapeutic strategies for pre-eclampsia have remained elusive. Nevertheless, early detection, monitoring, and supportive care are considered beneficial in improving outcomes for both mother and neonate. Reliable prediction of pre-eclampsia would allow closer prenatal monitoring, early diagnosis, and timely intervention—with steroids to enhance fetal lung maturity, magnesium for seizure prophylaxis, antihypertensive medications, bed rest, and expeditious delivery when indicated.

Results from dozens of studies have confirmed that maternal serum levels of PlGF, sFlt1, and/or sEng are significantly altered before the onset of pre-eclampsia. Whether these changes are marked enough to constitute an effective screening or early diagnostic test remains to be seen. Changes in PlGF are seen by the first or early second trimester, and reproducible alterations in sFlt1 and sEng are noted in the middle to late second trimester onward.

The discrimination of sFlt1 for pre-eclampsia has been reported as high as 96 percent (17), although sensitivity and specificity appear to be much lower for late-onset pre-eclampsia, especially when sFlt1 is sampled early in pregnancy. Maternal sFlt1 levels are particularly elevated in severe pre-eclampsia, early-onset pre-eclampsia, and pre-eclampsia with intrauterine growth restriction (3, 18). Urinary PlGF is lower in women with pre-eclampsia before the onset of symptoms (19), especially in early-onset and severe disease (20).

The timing, source (i.e., serum versus urinary), and combination of biomarkers and other tests that will prove most predictive of pre-eclampsia and its complications are now being explored. For example, the combination of ultrasonographic changes and angiogenic biomarkers in the second trimester may be more predictive of pre-eclampsia than angiogenic markers alone (21). Combining biomarkers into a single angiogenic index appears to be more predictive than any single marker, and some of these combinations meet

the likelihood ratios and other criteria required for a prediction test to be clinically useful (7, 22–26).

### Diagnosis and risk stratification

Angiogenic proteins may prove useful in establishing the diagnosis of pre-eclampsia in challenging, ambiguous, or atypical cases. For example, angiogenic biomarkers may distinguish pre-eclampsia from other causes of hypertension in pregnancy in patients with pre-existing renal disease (27) and from other causes of gestational thrombocytopenia such as idiopathic thrombocytopenic purpura (28); they may also identify pre-eclampsia in cases of gestational hypertension or proteinuria before 20 weeks gestation (29). The observation that derangements in circulating angiogenic biomarkers appear to correlate with the severity of pre-eclampsia and complications such as placental abruption and intrauterine growth restriction has suggested that they might be useful for risk stratification. In 2009, angiogenic factor testing was approved as a diagnostic test for pre-eclampsia in the European Union (PlGF and sFlt1 immunoassay, Roche Diagnostics), and a similar assay is being prepared for approval in the United States. Larger studies are in progress that probe the utility of angiogenic biomarkers in the clinical arena.

### Novel treatment strategies

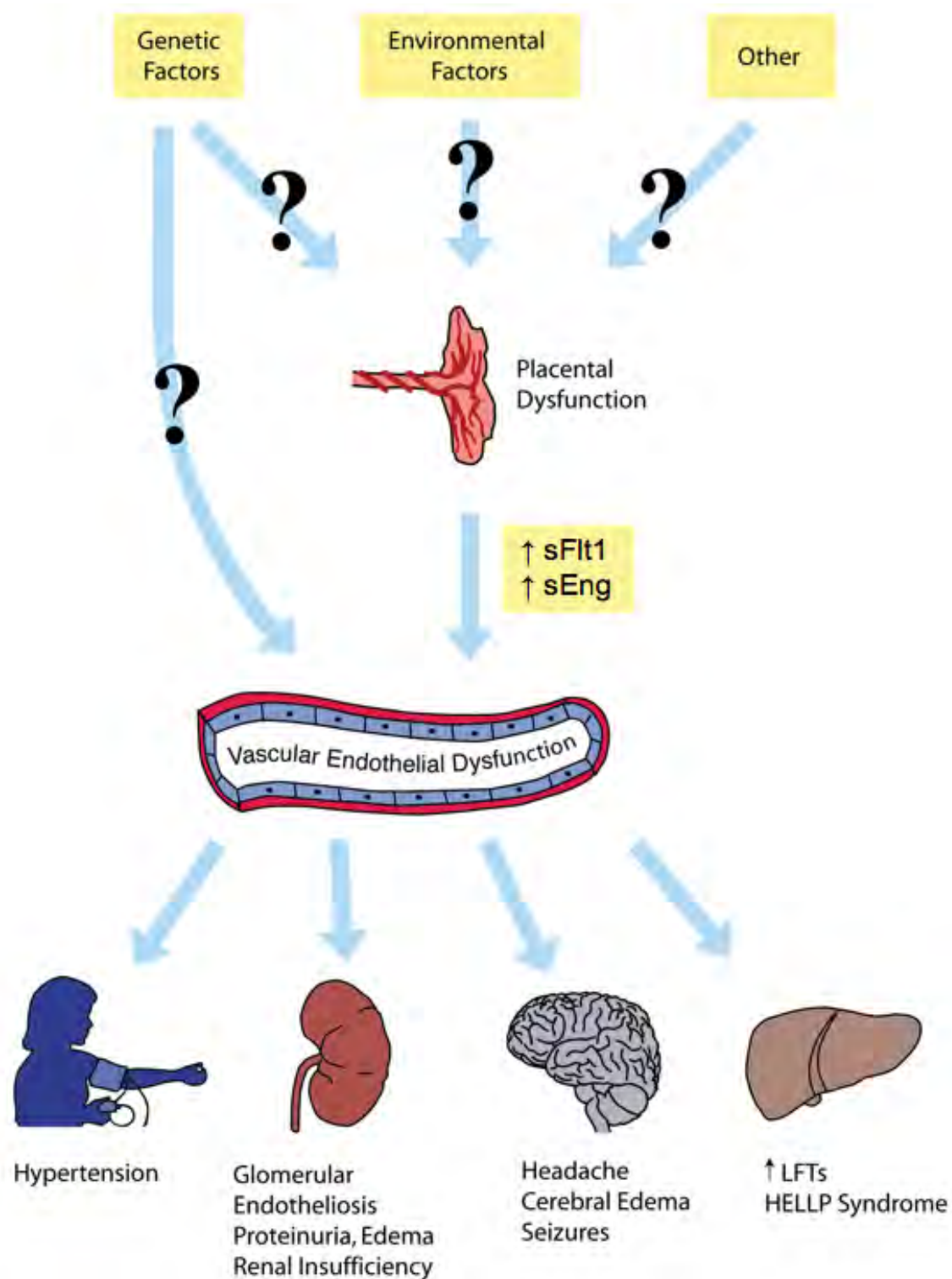
The identification of sFlt1 and sEng as key links between placental pathology and maternal endothelial damage suggests that these biomarkers may also be effective therapeutic targets. Potential therapies would be directed at restoring normal angiogenic balance in the maternal circulation—that is, the biologic activity of proangiogenic factors such as VEGF, PlGF, and TGF- $\beta$  relative to antiangiogenic factors such as sFlt1 and sEng. For example, both VEGF (30) and PlGF (31) diminish hypertension and ameliorate proteinuria in rodent models of sFlt1-induced pre-eclampsia, without apparent harm to the fetus. Direct administration of VEGF and/or PlGF in humans would be burdensome because it would require continuous intravenous infusion, so agents that enhance endogenous VEGF, PlGF, or TGF- $\beta$  production are also being explored. For example, pravastatin induces endogenous PlGF production and ameliorates hypertension and proteinuria in a mouse model of sFlt1-induced pre-eclampsia (32). An effective treatment for pre-eclampsia could have an enormous impact. In cases of extremely early-onset pre-eclampsia (22–28 weeks), for example, a treatment that allowed delivery to be safely postponed for just days to weeks could markedly improve neonatal outcomes. Unfortunately, clinical research involving novel treatments in pregnant women has ethical, medicolegal, and logistic challenges in addition to the usual scientific challenges. These issues have slowed progress from bench to bedside for this promising breakthrough in our understanding of the disease. ●

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Figure 1



Source: Karumanchi SA, Maynard SE, Stillman IE, et al: Preeclampsia: A renal perspective. *Kidney Int* 67:2101-2113, 2005.

**Hypothetical framework for the pathogenesis of pre-eclampsia. Placental dysfunction triggered by poorly understood mechanisms—including genetic, immunologic, and environmental—plays an early and primary role in the development of pre-eclampsia. Placental dysfunction leads to aberrant production of antiangiogenic factors (soluble fms-like tyrosine kinase 1 and soluble endoglin), contributing to systemic endothelial cell dysfunction. Endothelial dysfunction, in turn, results in the systemic manifestations of pre-eclampsia.**

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