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REVIEW SERIES

# Pathophysiology of preeclampsia: an angiogenic imbalance and long-lasting systemic vascular dysfunction

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**Preeclampsia is a systemic vascular disorder characterized by new-onset hypertension and proteinuria after 20 weeks of gestation. This condition targets several organs, including the kidneys, liver and brain, and is the leading cause of maternal and perinatal morbidity and mortality. Furthermore, recent evidence has revealed preeclampsia as a significant risk factor for future cardiovascular diseases in these women. Over the past decade, increasing evidence has indicated that maternal angiogenic imbalances caused by placental antiangiogenic factors play a central role in the systemic vascular dysfunction underling preeclampsia. The severity of the maternal antiangiogenic state correlates closely with maternal and perinatal outcomes. Assessing angiogenic imbalance and several vascular function tests have also emerged as a way of detecting systemic vascular dysfunction during pregnancy. This review summarizes the current understanding of the pathophysiology of preeclampsia, its clinical applications and clinical evidence for future cardiovascular risks.**
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## INTRODUCTION

Preeclampsia, characterized by hypertension and proteinuria developing after 20 weeks of gestation, is a pregnancy-specific systemic vascular disorder. It is often accompanied by life-threatening events including seizures (eclampsia), renal failure, HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome, cerebral hemorrhage, pulmonary edema and placental abruption. Adverse perinatal complications of preeclampsia include preterm delivery, fetal growth restriction and perinatal death. This condition affects 3 to 5% of pregnancies and causes substantial maternal and neonatal morbidity and mortality.[1,2] Although the clinical symptoms of preeclampsia resolve completely by 12 weeks postpartum, recent evidence has demonstrated an association between a history of preeclampsia and future cardiovascular events.[3–5]

Generalized maternal endothelial dysfunction caused by 'placental factors' has long been proposed as integral to systemic vascular dysfunction in preeclampsia, as delivering the placenta usually resolves this condition.[6–9] Over the past decade, a maternal antiangiogenic state caused by placental antiangiogenic factors has emerged as one of the most important mechanisms underlying this generalized endothelial dysfunction.[10–13] Increased placental soluble fms-like tyrosine kinase 1 (sFlt1) has been shown to mediate this maternal antiangiogenic state by antagonizing vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).[10]

In clinical practice, hypertension severity does not necessarily correlate with maternal or perinatal adverse outcomes. A significant portion of pregnant women without hypertension develop severe complications such as eclampsia, pulmonary edema or HELLP syndrome.[14–16] Conversely, it is not unusual for women who meet the conventional diagnostic criteria for preeclampsia to have no adverse complications. Furthermore, termination of the pregnancy, which often requires premature delivery, remains the only way to ameliorate the symptoms of preeclampsia.[1,2] Therefore, discovering additional, highly sensitive indicators to identify pregnant women at risk for adverse outcomes has been a matter of great interest.[17,18]

Recently, the value of assessing the severity of the maternal antiangiogenic state has been evaluated as a method to identify pregnant women at risk for adverse outcomes. Several vascular function tests were also shown to be sensitive for detecting systemic vascular dysfunction during pregnancy. In addition, several therapeutic interventions designed to reverse maternal antiangiogenic states have been proposed. In this review, we summarize the current understanding of the pathophysiology of preeclampsia, its clinical applications and clinical evidence for future cardiovascular risks.

## ANGIOGENIC IMBALANCE IN PREECLAMPSIA

'The two-stage theory' (Figure 1) is widely accepted with regard to mechanisms of preeclampsia.[19] In early placentation, trophoblast cells invade the wall of the maternal uterine spiral arteries and transform

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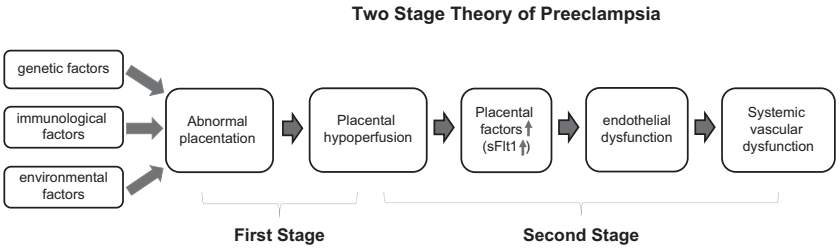


**Figure 1** The two-stage theory of preeclampsia. A defective cytotrophoblast invasion into maternal uterine spiral arteries (abnormal placentation) has been proposed as an initial step (stage 1). The resulting hypoperfused placenta releases antiangiogenic factors (soluble fms-like tyrosine kinase 1 (sFlt1)) into the maternal circulation that induce maternal generalized endothelial dysfunction and systemic vascular dysfunction (stage 2). A full color version of this figure is available at the *Hypertension Research* journal online.

these arteries into large diameter vessels with low resistance to blood flow.[20,21] In preeclampsia, this transformation is impaired (abnormal placentation)[22–25] and the resulting hypoperfused placenta releases 'placental factors' into the maternal circulation that cause generalized endothelial dysfunction, leading to systemic vascular dysfunction. The primary cause of abnormal placentation remains unclear, but genetic, immunological and environmental factors are all likely to be involved.[26]

The identification of these 'placental factors' has been a primary research interest for decades. In 2003, three research groups (Maynard *et al.*,[10] Koga *et al.*[27] and Tsatsaris *et al.*[28]) reported abnormal increases in serum sFlt1 (also referred to soluble vascular endothelial growth factor receptor 1 (sVEGFR1)) in women with preeclampsia. Maynard *et al.*[10] also reported that adenoviral gene transfer of sFlt1 to pregnant rats induced preeclamptic phenotypes, such as hypertension and proteinuria. Subsequently, Levine *et al.*[11] showed that sFlt1 begins to increase before the onset of clinical preeclampsia symptoms, and that the level of sFlt1 correlates well with preeclampsia severity. These reports generated great enthusiasm for sFlt1 as the most promising 'placental factor', and angiogenic imbalance emerged as one of the most important pathogenic mechanisms of preeclampsia.

sFlt1 is an alternatively spliced version of VEGFR1 (Flt1) that retains the extracellular ligand-binding domain of VEGFR1 but lacks the transmembrane and cytoplasmic domains.[29] VEGF interacts with VEGFR1 (Flt1) and VEGFR2 (KDR/FlK1), and PlGF specifically interacts with VEGFR1 (Flt1).[30] sFlt1 is mainly released from the placenta into the maternal circulation,[31] where it antagonizes VEGF and PlGF by binding to them and preventing their interaction with their endothelial receptors.[29] As VEGF and PlGF are potent endothelial cell mitogens that regulate blood vessel development and homeostasis,[32–35] binding of VEGF and PlGF to sFlt1 results in an angiogenic imbalance that leads to generalized endothelial dysfunction and systemic vascular dysfunction (Figure 2). We exploited the model of preeclampsia in mice by specifically overexpressing sFlt1 in placenta.[36] Consequently, the placenta produced excessive sFlt1 as gestation progressed, and the mice developed hypertension and proteinuria that resolved soon after delivery. The clinical observation that a VEGF inhibitor used as an anticancer treatment causes preeclampsia-like symptoms such as hypertension and proteinuria also supports the hypothesis that inducing an antiangiogenic state by inhibiting VEGF signaling contributes to the pathogenesis of preeclampsia.[37,38]

The mechanisms regulating sFlt1 production by trophoblastic cells are largely unknown. Placental hypoxia stimulates sFlt1 production in primary cytotrophoblast culture.[39] Recently, the upregulation of endometrial VEGF was identified as an upstream regulator of sFlt1 production by trophoblastic cells.[40] In addition, pleiotropic sFlt1 functions have recently attracted attention.[41] Our group reported cytotoxic effects of sFlt1 against ovarian and colorectal cancer cell lines, and demonstrated therapeutic effects of sFlt1 in a mouse model of ovarian cancer.[42]

A placenta-derived soluble TGF-β coreceptor, endoglin (sEng), also induces a preeclampsia-like syndrome in concert with sFlt1 in pregnant rats.[12] Serum sEng levels were significantly higher in women with preeclampsia, with this increase beginning before the onset of clinical symptoms.[13,43,44] Thus, sFlt1 and sEng are thought to synergistically induce an antiangiogenic state.

## VASCULAR PATHOPHYSIOLOGY OF PREECLAMPSIA

Hypertension and proteinuria are hallmarks for the conventional diagnosis of preeclampsia. Normally during pregnancy, maternal circulation undergoes remarkable physiological adaptations, including increased intravascular volume and markedly decreased vascular resistance.[45–48] These adaptations result in an arterial blood pressure slightly below the nonpregnant level[49,50] and an enhanced glomerular filtration rate.[51] In preeclampsia, increased placental sFlt1 is thought to increase peripheral vascular resistance (and thus arterial pressure) by counteracting VEGF- and PlGF-induced microvascular relaxation.[10] VEGF signaling is also important for the maintenance of fenestrated endothelium; inhibiting VEGF signaling narrows the glomerular endothelial fenestrae and causes endothelial swelling, termed glomerular capillary endotheliosis, that decreases glomerular filtration rate and increases urinary protein excretion.[52,53] Inhibition of VEGF signaling also induces podocyte dysfunction that may contribute to glomerular capillary endotheliosis and renal thrombotic microangiopathy.[54,55]

As described above, preeclampsia can be characterized as a systemic vascular disorder with generalized endothelial dysfunction caused by a maternal antiangiogenic state. Recently, several noninvasive vascular function tests have received considerable attention in nonpregnant subjects as they were found to relate more closely with endothelial function and future cardiovascular disease risk (CVD) than conventional brachial blood pressure measurements.[56] Among these tests, flow-mediated dilation (FMD, a measure of conduit artery endothelial function), pulse wave analysis (a composite measure of conduit and resistance artery stiffness) and pulse wave velocity (PWV, a measure of conduit artery stiffness) have been increasingly incorporated into clinical practice in nonpregnant subjects.[56] As these vascular function tests reflect endothelial function to varying degrees,[57] they are expected to reflect the severity of systemic vascular dysfunction in women with preeclampsia to a varying degree.

FMD is a well-established technique for assessing endothelial dysfunction in a large vessel, the brachial artery, as well as predicting future cardiovascular risk.[58,59] Pregnancy is normally associated with

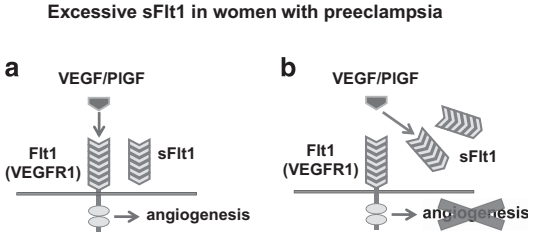


**Figure 2** Excessive soluble fms-like tyrosine kinase 1 (sFlt1) in women with preeclampsia. Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) bind to VEGF receptor 1 (VEGFR1: also known as Flt1) and induce angiogenesis that is essential for normal pregnancy (**a**). In preeclampsia, the hypoperfused placenta produces excess soluble form of VEGFR1 (sFlt1) that antagonizes VEGF and PlGF in maternal serum and impairs angiogenesis (**b**). A full color version of this figure is available at the *Hypertension Research* journal online.

increased FMD, reflecting enhanced endothelial function.[60] A recent systematic review and meta-analysis reported significantly lower FMD in women with preeclampsia both before and after the onset of preeclampsia as well as for 3 years postpartum; these results indicate that endothelial dysfunction precedes the onset of preeclampsia and persists after pregnancy.[61] These results also suggest the potential of FMD to predict preeclampsia, and represent a possible mechanism for future cardiovascular risk in these women.[61]

Pulse wave analysis measures the vascular compliance of the entire arterial tree[62–64] and reflects relatively early changes in arterial aging.[65] The pulse wave analysis indices of augmentation index (AIx) and central systolic pressure (CSP) are more closely correlated than conventional brachial blood pressure measurements with future cardiovascular events.[66–69] AIx and CSP decline markedly in normal pregnancy, reaching a nadir in mid-pregnancy and then increasing toward term.[70–72] In women with preeclampsia, AIx and CSP are significantly elevated, suggesting increased systemic arterial compliance.[73,74] Abnormal AIx or CSP values have been observed from the first trimester of pregnancy in women who ultimately develop preeclampsia.[75,76] In addition, abnormal AIx or CSP might be involved in the pathogenesis of intrauterine growth restriction, a major phenotype in pregnancies with preeclampsia.[77,78] Magnesium sulfate decreases AIx in women with preeclampsia, suggesting a possible mechanism for seizure prophylaxis.[79] Increased AIx even 6 to 24 months postpartum in women with a history of early-onset preeclampsia and intrauterine growth restriction may represent a possible mechanism for future cardiovascular risks in these women.[80]

PWV reflects histopathological changes in the structure and stiffness of conduit arteries that are relatively late changes in the process of arterial aging in large vessels.[65,81] PWV has also been reported to predict future cardiovascular events.[82,83] Brachial-to-ankle PWV decreases significantly in the second trimester of normal pregnancy.[84] Several studies have suggested increased PWV in women with preeclampsia.[71,84] The increased PWV values have also been observed from the first trimester of pregnancy in women who later develop preeclampsia.[85]

Although further research is needed, these vascular function tests combined with assessing antiangiogenic imbalance could better provide a comprehensive picture of the vascular pathophysiology of preeclampsia.

## CLINICAL IMPLICATIONS OF ANGIOGENIC IMBALANCE

As previously mentioned, angiogenic imbalance is an important pathogenic mechanism of preeclampsia. In addition, this imbalance precedes the definitive diagnosis of preeclampsia.[11,13,86,87] Thus, assessing and, if possible, correcting this angiogenic imbalance may play important roles in various clinical settings, such as predicting, diagnosing, managing and treating preeclampsia.

Several studies have attempted to demonstrate the potential of assessing angiogenic imbalance as a predictor of preeclampsia.[43,87–89] In the first trimester of pregnancy, the measurement sensitivity for these factors is insufficient to predict the development of preeclampsia.[89–92] However, late in pregnancy, the level of angiogenic imbalance adequately predicts the development of preeclampsia.[93,94] In clinical settings, predicting adverse maternal and fetal outcomes is clearly more important than predicting the development of preeclampsia. In patients with 'suspected' preeclampsia, the severity of angiogenic imbalance correlated more closely than brachial blood pressure with maternal and neonatal complications, suggesting that assessing the severity of angiogenic imbalance may overcome the shortcomings of the conventional diagnostic criteria for preeclampsia.[88,94] For example, in women with suspected preeclampsia presenting at $<34$ weeks, 86.0% of women with an sFlt1/PlGF ratio of $\geqslant 85$ had iatrogenic delivery within 2 weeks compared with 15.8% of women with an sFlt1/PlGF ratio of $<85$,[88] suggesting that women with preeclampsia and relatively low sFlt1/PlGF ratios could be managed expectantly.[95] In addition to distinguishing pregnant women with and without preeclampsia,[96,97] assessing angiogenic imbalance can successfully differentiate preeclampsia from other diseases mimicking preeclampsia, such as chronic and gestational hypertension,[98] acute and chronic glomerulonephritis,[99] lupus nephritis[100,101] and non-HELLP syndrome-related thrombocytopenia.[102] Assessing angiogenic imbalance for risk stratification as well as differential diagnoses for preeclampsia is expected to decrease the incidence of unnecessary iatrogenic preterm deliveries in women at low risk for adverse outcomes and to reduce resource utilization without increasing the risk of adverse maternal and neonatal outcomes.

Despite promising basic research investigating the therapeutic potential of reducing sFlt1 levels or raising PlGF levels,[36,103–106] there is little clinical evidence that modulating angiogenic factors improves maternal or perinatal outcomes in women with preeclmapsia. However, in the only report in women with preeclampsia, extracorporeal removal of sFlt1 by dextran sulfate cellulose apheresis resulted in prolongation of pregnancy.[107] Statins (HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, a class of lipid-lowering medications) promote PlGF expression in animal models,[36] and a pilot human trial to support the safety and efficacy of a statin (pravastatin) for the prevention of preeclampsia in high-risk pregnant women was recently reported.[108]

## FUTURE CARDIOVASCULAR RISK OF PREECLAMPSIA

Traditionally, preeclampsia was thought to completely resolve after delivery in otherwise healthy young women, but recent studies demonstrate that women with a history of preeclampsia have an increased risk of developing CVD later in life.[3–5] In a large cohort study of 1 30 000 births, Smith *et al.*[109] reported that women with preeclampsia had twice the risk of hospital admission and death because of ischemic heart disease over 15–19 years of follow-up compared with women without preeclampsia. According to a meta-analysis on the postpartum risk of CVD, the relative 10–15-year risk in women with a history of preeclampsia is 3.7 (95% confidence interval: 2.70 – 5.05) for hypertension, 2.16 (1.86 – 2.52) for ischemic heart disease, 1.81 (1.45 – 2.27) for cerebral infarction and 1.79 (1.37 – 2.33) for venous thrombosis.[110]

The precise mechanisms linking preeclampsia with future CVD may be complex, as both have common preexisting risk factors and endothelial dysfunction is considered a basic pathological feature underlying both diseases. As mentioned above, the systemic vascular dysfunction that occurs during preeclampsia persists after delivery[61,80] and may increase the risk of subsequent CVD. sFlt1 levels are increased in individuals with acute myocardial infarction and may predict the progression to heart failure in these patients.[111] Depressed cardiac function in women with preeclampsia correlated with circulating sFlt1 levels, and exogenous sFlt1 induced cardiac dysfunction in a mouse model of peripartum cardiomyopathy.[112] In women with a history of preeclampsia, increased sFlt1 and high-sensitivity C-reactive protein persisted from delivery to 5–8 years postpartum.[113] Increased sFlt1 levels and sFlt1/PlGF ratio were also reported 1 year postpartum, and these parameters significantly correlated with the intima and media thickness of the common carotid artery as well as their ratio that indicates arterial aging.[114]

The occurrence of CVD later in life in women with a history of preeclampsia has also been reported in Japan,[115–117] where the incidence of CVD is lower than in Western countries. In an analysis of Japanese women aged $\geqslant 40$ years using the 'Boshi kenkou techou (Mother and baby health handbook)', which includes information on blood pressure, proteinuria and maternal weight gain throughout the pregnancy, women with a history of preeclampsia had increased risk of antihypertensive medication use (odds ratio: 4.28 (2.14 − 8.57)) and dyslipidemic medication use (odds ratio: 3.20 (1.42 − 7.22)) compared with women without preeclampsia.[118]

Although there is an association between preeclampsia and CVD later in life, it is unclear whether early identification of women at high risk of CVD and subsequent intervention reduces the increased cardiovascular risk. Lifestyle interventions, including smoking cessation and weight reduction, has been reported to decrease cardiovascular risk after preeclampsia by 4 − 13%.[119] In 2011, the American Heart Association guidelines advised yearly blood pressure, lipid profile and blood glucose concentration checks for women with a previous history of preeclampsia.[120] In Japan, a lifestyle intervention is now recommended after delivery for women with preeclampsia,[121] and the Japanese Society of Hypertension guidelines recommend referring to the 'Boshi kenkou techou' for health management in hypertensive women.[122]

## CONCLUSION

Considerable advancement in the understanding of the pathophysiology of preeclampsia has occurred in the past decade. A maternal antiangiogenic state induced by placental antiangiogenic factors has emerged as one of the most important mechanisms for systemic vascular dysfunction, a central feature of preeclampsia.

Pathophysiology-oriented diagnostic criteria might improve the prediction of adverse maternal and neonatal outcomes, and pathophysiology-oriented management strategies might improve maternal and neonatal outcomes by decreasing the incidence of preterm delivery without increasing adverse maternal outcomes. Further research has the potential to reveal novel therapeutic and preventive strategies.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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