

## Dysregulation of anti-angiogenic agents (sFlt-1, PLGF, and sEng) in preeclampsia—a step forward but not the definitive answer

J.M. Foidart<sup>a,b</sup>, J.P. Schaaps<sup>a</sup>, F. Chantraine<sup>a</sup>, C. Munaut<sup>b</sup>, S. Lorquet<sup>a,b</sup>

<sup>a</sup> University of Liege, Department of Obstetrics and Gynaecology, Hospital de la Citadelle, Blvd du XII<sup>ème</sup> de Ligne, 4000 Liege, Belgium

<sup>b</sup> Laboratory of Biology and Tumor Development, Hospital de la Citadelle, Blvd du XII<sup>ème</sup> de Ligne, 4000 Liege, Belgium

### Abstract

Preeclampsia (PE) is a pregnancy-specific syndrome characterized by hypertension, proteinuria and edema, which resolves on placental delivery. It is thought to be the consequence of impaired placentation due to inadequate trophoblastic invasion of the maternal spiral arteries. In PE the maternal plasma concentration of free vascular endothelial growth factor (VEGF) and placental growth factor (PLGF) is decreased whereas the concentration of soluble fms-like tyrosine kinase-1 (sFlt-1) and of soluble endoglin (sEng) is increased. These soluble receptors may bind VEGF, PLGF and TGF $\beta$ 1 and TGF $\beta$ 3 in the maternal circulation, causing endothelial dysfunction in many maternal tissues. Hence there is a view that the pathogenesis is more or less clarified. According to the vascular theory, poor placentation leads to poor uteroplacental perfusion and hypoxia, which stimulates sFlt-1 and sEng production causing the maternal syndrome. This assumption has been recently challenged. The role of hypoxia as the main stimulus for release of sFlt-1 has been questioned and the role of inflammatory mechanisms has been emphasized. According to this inflammatory theory, poor placentation may predispose more to placental oxidative stress than hypoxia and endothelial dysfunction may be part of a broader disorder of systemic inflammation. Finally, the recent demonstration of activating auto-antibodies to the angiotensin 1 receptor that experimentally play a major pathogenic role in PE further suggests a pleiotropism of aetiologies for this condition. The purpose of this review is to critically evaluate the recent hypotheses and their possible insights on early diagnosis, prevention and treatment.

**Keywords:** PE; sFlt-1; sEng; Angiotensin 1 receptor auto-antibody; Oxidative stress; Inflammation

### 1. INTRODUCTION

Preeclampsia (PE), a major cause of feto-maternal morbidity and mortality, affects 3-5% of pregnancies. It is characterized by an onset of hypertension and proteinuria (>0.3g/24h) after 20 weeks of gestation. Severe forms may be complicated by visual disturbances, headache, epigastric pain, thrombocytopenia, and abnormal liver function (National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy, 2000). They result from mild to severe microangiopathy of target organs, including the brain, liver, kidney, and placenta (Stella and Sibai, 2006). PE may cause preterm delivery, small-for-gestational-age infancy, fetal/neonatal hypoxic neurologic injury or death. It is also associated with maternal renal failure, hemolysis, elevated liver enzymes, and thrombocytopenia (HELLP syndrome), convulsions, liver failure, stroke or death.

PE appears to progress in two stages: preclinical (asymptomatic) and clinical. In the first stage, poor development of the early placenta will be responsible for placental hypoxia, oxidative stress and maternal systemic inflammatory stress. In the second stage, an increasingly dysfunctional placenta causes the maternal signs of hypertension and proteinuria, as well as clotting and liver dysfunction.

The molecular mechanisms behind this disease are being unravelled. The purpose of this review is to highlight recent findings about the anti-angiogenic theory of PE but also to suggest that the vascular theory does not provide adequate explanation for all features of this condition and to stimulate new thinking and research that integrate other physiopathological aspects.

### 2. THE FIRST STAGE: ABNORMAL PLACENTATION – AN EARLY EVENT INDICATIVE OF IMMUNE DYSREGULATION

Recently, it was reported that 36 differentially expressed genes are detectable at 10 weeks gestation in the placentas of women who later develop PE (Founds et al., 2008). Thirty-one genes were down-regulated, many of which were related to inflammation/immuno-regulation and cell motility. Decidual gene dysregulation was

prominent, but no evidence was found for alterations in hypoxia, angiogenic and oxidative stress regulated genes. This dysregulation of gene expression in the early placentas of women ~6 months before PE manifests clinically reinforces the hypothesis of a placental origin of this disorder, and suggests that placentation in PE is compromised in the first trimester by maternal and fetal immune dysregulation, abnormal decidualization, or both, thereby impairing trophoblast invasion.

It is not surprising that early gene dysregulation does not involve hypoxia or angiogenic related genes since during the first 12 weeks of pregnancy, fetal development occurs under low oxygen tension. Our group showed by *in vivo*, echographic, anatomic and physiological studies that in normal pregnancy, the endovascular extravillous trophoblasts penetrate the maternal decidual spiral arteries and obstruct their lumen up to the 11th week of gestation by forming invasive trophoblast plugs. Placental perfusion is then composed exclusively of plasma (Hustin and Schaaps, 1987; Foidart et al., 1992; Schaaps and Foidart, 1991) under low oxygen pressure. After 12 weeks, the uteroplacental arteries recanalize and deliver blood and oxygen to the intervillous space. Our studies have also yielded functional and anatomic evidence of an arteriovenous shunt located in the subplacental myometrium that may at least in part bypass the placental circulation in PE (Schaaps et al., 2005). These findings were subsequently confirmed by several other groups (for review see Redman and Sargent, 2005). During normal pregnancy, the spiral arteries are extensively remodeled by the invasive trophoblasts (De Wolf et al., 1980; Zhou et al., 1997). These high-resistance vessels rich in vascular smooth muscle cells are transformed to dilated, high-capacitance vascular channels. In contrast, in PE, trophoblast does not invade the myometrial segments of these arteries (Zhou et al., 1997; Robertson et al., 1967). Their remodeling is thus limited, with failure to convert high-resistance to high-capacitance vessels (Redman and Sargent, 2005). This causes a decreased circulation that will lead to placental ischemia with continued pregnancy. The initial events leading to these changes remain unknown. They likely involve both maternal vascular immunological genetic and fetal/placental factors (Redman and Sargent, 2005).

### **3. DEFECTIVE TROPHOBLAST DIFFERENTIATION**

Trophoblast differentiation during endovascular invasion involves alteration in expression of genes for a number of different classes of molecules, including cytokines, adhesion molecules, extracellular matrix molecules, metalloproteinases, and the class Ib major histocompatibility complex molecule, HLA-G. Trophoblasts obtained from women with PE do not show upregulated adhesion molecule expression or pseudo-vasculogenesis. Defective differentiation of trophoblast is one possible mechanism responsible for defective trophoblast invasion of the spiral arteries (Zhou et al., 1997).

### **4. THE SECOND STAGE: RELEASE OF FACTORS RESPONSIBLE FOR MATERNAL ENDOTHELIAL DYSFUNCTION**

Extensive evidence indicates that the placenta of women destined to develop PE releases into the maternal circulation factors that target endothelial cells to cause hypertension and the other clinical manifestations. Many markers of endothelial function are altered, including fibronectin, soluble tissue factor, platelet-derived growth factor, soluble E-selectin, and endothelin (Baumwell and Karumanchi, 2007). There is no question that the features of the disease that are clinically most prominent derive from dysfunctional endothelium.

### **5. THE VASCULAR THEORY**

#### **5.1. VEGF and sFlt-1**

VEGF, a potent angiogenic protein, is also a trophic cytokine essential for endothelial integrity. It promotes vasodilatation by inducing nitric oxide and prostacyclin synthesis by endothelial cells. Membrane-bound fms-like tyrosine kinase 1 (Flt 1) is a receptor for VEGF and placental growth factor (PlGF), a related pro-angiogenic protein. Soluble sFlt-1 is a circulating splice variant with antagonist activity of both VEGF and PlGF. It is produced in excessive amounts by the villous trophoblast in PE that neutralizes VEGF and PlGF [18,19]. Exposure of early pregnancy placental villi to low oxygen increases HIF1 $\alpha$  and sFlt-1 secretion (Munaut et al., 2008). Hypoxia is thus considered as one major trigger for release of sFlt-1

sFlt-1 concentrations are high 5-6 weeks prior to the onset of clinical disease and concentrations of free VEGF and PlGF are also found to be low prior to clinical PE. Decreased levels of urinary PlGF during midgestation predict subsequent development of clinical PE and quantification of sFlt-1 levels has correlated directly with severity of disease and inversely with time to onset of proteinuria and hypertension (Karumanchi and Lindheimer, 2008). There is thus no question that elevated levels of sFlt-1 play a major role in the

pathophysiology of PE.

In addition, injection of sFlt-1 into pregnant rats results in glomerular endotheliosis proteinuria, hypertension (Maynard et al., 2003). VEGF is also necessary for the maintenance of glomerulus ultrastructure and for the fenestration of glomerular endothelial cells (Ballermann, 2005). Anti-VEGF antibody in mice results in glomerular endothelial damage and proteinuria. In mice heterozygous for podocyte-specific VEGF expression, a 50% reduction of VEGF expression induces proteinuria and glomerular endotheliosis (Eremina et al., 2003). In humans, VEGF antagonists, such as bevacizumab in renal cell carcinoma, result in hypertension and proteinuria (Yang et al., 2003; Kuenen et al., 2002). Thus, VEGF antagonism by sFlt-1 may cause many of the clinical manifestations of PE, including proteinuria, glomerular endotheliosis, and hypertension.

## **5.2. Soluble endoglin (sEng)**

In pregnant women, sEng is upregulated in PE 2-3 months prior to clinical manifestations, particularly in severe and preterm PE (Levine et al., 2006). sEng is a coreceptor for TGF $\beta$ 1 and TGF $\beta$ 3 which is highly expressed by vascular endothelial cells and syncytiotrophoblasts. Mutations in endoglin results in loss of capillaries and multiple arteriovenous malformations (hereditary hemorrhagic telangiectasia) (Maynard et al., 2008). In addition, it contributes to regulation of vascular tone through its interactions with endothelial nitric oxide synthase. Pregnant rats with overexpression of both sEng and sFlt-1 develop nephrotic-range proteinuria, severe hypertension, a HELLP syndrome, and intrauterine growth restriction of the pups (Venkatesha et al., 2006). Histological analysis reveals severe glomerular endotheliosis in the kidney, infarction in the placenta, areas of necrosis in the liver, and schistocytes in the peripheral blood.

## **6. HYPOXIC OR INFLAMMATORY STIMULATION OF sFlt-1 AND sEng RELEASE?**

Although hypoxia is one important stimulus for release of sFlt-1 from the PE placenta (Nevo et al., 2006), inflammatory mechanisms may also contribute or even predominate. Since TNF $\alpha$  provokes sFlt-1 release from cultured placental explants in a dose-response manner (Ahmad and Ahmed, 2004), and since HIF-1 $\alpha$  can be stimulated and stabilized by inflammatory stimuli under normoxic conditions (Blouin et al., 2004; Görlach and Bonello, 2008; Taylor, 2008; van Uden et al., 2008; Rius et al, 2008), Redman and Sargent recently hypothesized that the primary placental problem that generates the PE syndrome is likely to be oxidative stress rather than hypoxia (Redman and Sargent, 2009). Oxidative stress is an inflammatory stimulus mediated by reactive oxygen species. They speculate that this provokes the release of sFlt-1 and possibly sEng via NF $\kappa$ B to a similar or greater extent than hypoxia.

## **7. THE INFLAMMATORY THEORY: PLACENTAL STRESS – AN OXIDATIVE AND INFLAMMATORY STRESS**

It is known that the PE placenta is affected by oxidative stress (reviewed in (Hung and Burton, 2006)) and nitrosative stress (Myatt et al., 1996). Women predisposed to PE, particularly those with a metabolic syndrome, antiphospholipid antibody syndrome and those who are obese, chronically hypertensive or diabetic, begin pregnancy with a certain degree of endothelial dysfunction. It is assumed that this endothelial dysfunction precedes shallow placentation. The proposed sequence of events comprises endothelial dysfunction, defective trophoblast invasion, and consequential impaired placental perfusion, immune maladaptation and inflammation (Kontic-Vucinic et al., 2008). The possible link between these events could be oxidative stress by excessive production of reactive oxygen species coupled with inadequate or overwhelmed antioxidant defence mechanisms. These defence mechanisms, involving antioxidant vitamins and enzyme systems, may restrain the extent of damage caused by oxidative stress.

Markers of oxidative stress in pregnant women are increased and those with established PE are considerably more stimulated. According to this theory, antioxidant therapy could prevent PE and other pregnancy-related disorders. Several studies have tested this hypothesis. Despite the logic behind using antioxidant vitamins, the data thus far are at best conflicting (Rumbold et al., 2008).

Multiple interconnected pathways may thus involve oxidative stress, inflammatory cytokine release by the placenta, and a generalized intravascular inflammatory response. This culminates in increased endothelial cell permeability, lipid peroxidation, platelet activation, activation of the coagulation cascade, oxidative stress, and a shift in the balance of vasoactive mediators favouring vasoconstriction (Hubel et al., 1996; Kolben et al., 1995; Davidge, 1998). Syncytiotrophoblast secretes many bioactive factors which are significantly increased in PE. Many of these factors are proinflammatory including corticotrophin releasing hormone (CRH), activin-A, leptin,

and trophoblast-derived microparticles (for a review see Redman and Sargent, 2009).

The anti-endothelial or other proteins released by syncytiotrophoblast (sFlt-1, sEng) are more likely to be the primary causes of the endothelial dysfunction. Of particular interest is the increased release into the maternal circulation of placental microparticles shed from trophoblast cells (Redman and Sargent, 2008). Microparticles comprise syncytiotrophoblast membrane microparticles, cytokeratin fragments, soluble RNA and DNA of fetal origin, and even intact cytotrophoblast cells. This material is proinflammatory and is increased in amount in PE, so its disposal probably imposes a maternal inflammatory burden. Microparticles interact with both immune and endothelial cells and may contribute to the systemic inflammation of preeclamptic pregnancies (Redman and Sargent, 2009).

## **8. THE RENIN ANGIOTENSIN SYSTEM (RAS)**

The RAS activation has been implicated in the pathogenesis of PE, at least in part because it is functionally present in the human placenta and the levels of its angiotensin 1 receptors (AT1-R) are increased in the trophoblasts of preeclamptic women (Xia et al., 2007; AbdAlla et al., 2001; Shah, 2007). In addition, the generation of locally produced placental angiotensin II is responsible for the activation of AT1-Rs on trophoblasts (Li et al., 1998; Qin, 2008). It has been reported that sera from women with PE, but not from normotensive women, contain auto-antibodies that stimulate the AT<sub>1</sub>-R (Wallukat et al, 1999). Such AT1-R antibodies that directly induce higher blood pressure and proteinuria, may be secondary to placental ischemia, vascular damage, and enhanced inflammatory response. They may therefore represent a consequence rather than a cause of the disease.

Angiotensin II and AT1-R antibody contribute to an increased secretion of inflammatory cytokines (e.g. TNF $\alpha$ ), which induce reactive oxygen species production and an enhanced inflammatory response through activation of NADPH oxidase (Wallukat et al., 1999).

Finally this auto-antibody and angiotensin II enhance the release by trophoblast of sFlt-1 (Xia et al., 2007). If this data are confirmed, it would indicate that sFlt-1 secretion by the trophoblast could be mediated not only by hypoxia but also by other signalling cascades. Overall, these findings support the view that Angiotensin II is a key regulator of sFlt-1 synthesis and secretion during normal pregnancy and that the excessive accumulation of sFlt-1 observed in women with PE is because of additional activation of AT1 receptors mediated by AT1-R antibody.

Hypoxia caused by reduced placental perfusion may lead to an inflammatory response that contributes to the generation of AT1 -R antibody. This antibody may further contribute to decreased trophoblast invasion, increased hypoxia, and an enhanced placental and systemic inflammatory response. In this way, the enhanced production of sFlt-1 and sEng by the trophoblast would not be the end of the story, but these anti-angiogenic modulators would rather be part of a complex multifaceted response to poor placentation.

## **9. CONCLUSIONS**

PE is a complex disorder with a range of clinical presentations. This heterogeneity suggests the possibility of varied pathogenic mechanisms. The initial etiologic factors are not well understood, nor are the interactions between the ischemic placenta, sFlt-1, sEng, and other inflammatory cytokines such as TNF $\alpha$ , lipid peroxides and angiotensin II, angiotensin 1 receptors, all of which are implicated in PE.

Even with our growing knowledge of the pathogenesis of PE, treatment options remain limited. A promising approach is the early detection from week 11 to 13 of the severe and precocious forms of the disease. This would allow closer surveillance and may lead to prophylactic approaches that will require targeted therapies. The ability to prolong pregnancy safely with these therapies, even for a short period of time, potentially could make a significant improvement in morbidity.

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