

Pathophysiology of Hypertension in Preeclampsia


 Clinical Practice

Hypertensive disorders in pregnancy, including preeclampsia, are the second largest contributor to maternal mortality worldwide. Despite the seriousness of the disease the pathophysiology of preeclampsia remains poorly understood. This article explores the latest research into the multifactorial nature of preeclampsia and how these various pathways intertwine.

KEYWORDS: Preeclampsia, abnormal placentation, fetal morbidity, hypertensive disorders

Introduction

Preeclampsia is a hypertensive disorder of pregnancy, classically it is defined as the onset or worsening of hypertension in pregnancy and proteinuria of at least 300 mg in 24 hours. It is among the most common disorders in pregnancy, affecting 8% of all pregnant women worldwide [1]. Associated with severe maternal and fetal morbidity and mortality, preeclampsia can result in eclampsia and HELLP syndrome in the mother, and preterm birth, intrauterine growth restriction, and perinatal death in the fetus [1]. Though in developed countries maternal morbidity and mortality due to preeclampsia has decreased, patients who experience are at an increased risk of cardiovascular disease later in life [1,2].

While it is widely accepted that the pathophysiology of preeclampsia begins with abnormal placentation, it remains a poorly understood multisystem disease. The means by which abnormal placentation results in systemic dysfunction is an area of ongoing research. In normal pregnancy cytotrophoblasts invade the uterine spiral arteries and cause arterial remodeling, destroying the tunica media and replacing the maternal endothelium. The previously high-resistance, low-capacitance uterine arteriolar system is converted to a low-resistance, high-capacitance system, allowing for increased fetal blood flow and delivery of oxygen and nutrients [3].

In preeclampsia, due to abnormal cytotrophoblast invasion and deficient spiral

artery remodeling this low resistance vasculature does not form, which results in decreased blood flow to the placenta. This placental ischemia appears to play an overarching role in the development of preeclampsia. Placental ischemia as an inciting event for systemic dysfunction is supported by the reduced uterine perfusion pressure (RUPP) rat model. This animal model has restricted uterine arterial supply. Thus, in pregnancy this results in uteroplacental ischemia and a clinical picture of hypertension, proteinuria, and glomerular endotheliosis [4]. Preeclampsia can therefore be thought of as a multistep disease process. In the first stage, abnormal placentation and deficient spiral artery remodeling leads to placental ischemia. Placental ischemia in turn leads to the clinical manifestations of preeclampsia, including the development of hypertension and proteinuria [5,6]. However, the precise cause for both deficient spiral artery remodeling and its effects on the development of hypertension remain unclear.

Angiogenic Imbalance

To date research has revealed a collection of biomarkers implicated in the pathophysiology of preeclampsia, including angiogenic, inflammatory, oxidative, and genetic factors. Placental ischemia is thought to cause hypoxia-induced release of placental factors, leading to widespread vascular and endothelial dysfunction [7]. Endothelial dysfunction, which is associated with the development of hypertension, occurs due to an imbalance in angiogenic factors [6-8]. Thus angiogenic factors have drawn increasing

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attention for their role in the pathogenesis of preeclampsia.

Preeclampsia is characterized by an excess of anti-angiogenic factors with a simultaneous deficiency in pro-angiogenic factors. These anti-angiogenic factors include soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng). sFlt-1 is a splice variant of fms-like tyrosine kinase 1 (Flt-1), a transmembrane receptor for vascular endothelial growth factor (VEGF). sFlt-1 circulates in the maternal bloodstream and antagonizes both VEGF and placental growth factor (PlGF) by binding them and preventing their interaction with their cellular receptors. Both VEGF and PlGF are pro-angiogenic factors; VEGF, as its name implies, is a mediator of angiogenesis and the maintenance of endothelial health. PlGF is not fully understood, but it is thought to operate synergistically with VEGF to promote angiogenesis [6,9]. Thus sFlt-1 appears to enact its anti-angiogenic effects through the antagonism of VEGF and PlGF.

sFlt-1 is known to be elevated in preeclamptic women by up to five times the levels found in a normal pregnancy [10]. Furthermore, injection of an adenovirus expressing sFlt-1 into rat models resulted in preeclampsia-like symptoms, including significant hypertension, proteinuria, glomerular endotheliosis, and fetal growth restriction [10,11]. This effect of sFlt-1 is dose-dependent fashion, with a strong correlation of sFlt level and severity of disease [9,10]. Interestingly, a recent study by Thadhani *et al.* demonstrated a significant reduction in protein/creatinine ratio following removal of sFlt-1 via whole blood apheresis in preterm preeclamptic women [12]. This both reinforces sFlt-1's role in the pathogenesis of preeclampsia and suggests a novel therapy that may be explored further.

Multiple studies have also demonstrated the importance of VEGF and PlGF in the pathogenesis of preeclampsia. For example, Maynard *et al.* demonstrated significantly decreased levels of VEGF and PlGF in the serum of preeclamptic patients compared to normotensive pregnancies [10]. Interestingly, clinical trials for bevacizumab, an anti-VEGF monoclonal antibody used in chemotherapy, patients often suffered from side effects of hypertension and proteinuria supporting the idea that VEGF deficiency is a component of preeclampsia [13,14]. PlGF, with its known angiogenic function also is a factor in the

development of preeclampsia. Maynard *et al.* showed that both VEGF and PlGF blockade are likely needed for the development of a preeclamptic picture [10]. In his model VEGF deficiency alone did not lead to a preeclamptic sequale. Injections of recombinant human PlGF in multiple animal models for preeclampsia has demonstrated a reversal in the hypertensive component of the disease, suggesting a potential therapeutic role for PlGF [15,16].

Soluble endoglin (sEng) is another anti-angiogenic factor involved in preeclampsia. sEng is a truncated form of a cellular receptor endoglin that binds transforming growth factor (TGF)- β 1. sEng appears to have multiple similarities with sFlt-1. It is also a circulating factor within the maternal bloodstream, antagonizing pro-angiogenic TGF- β 1. Venkatesha *et al.* demonstrated a dose-dependent elevation in sEng correlated with preeclampsia disease severity, with an up to ten-fold increase in the sera of women with HELLP syndrome [17]. Furthermore, rats injected with adenovirus expressing sEng developed hypertension and proteinuria. Interestingly, rats co-injected with both sEng and sFlt-1 developed symptoms of increased severity, including nephrotic-range proteinuria, severe hypertension, and HELLP syndrome, suggesting that the two anti-angiogenic factors work in concert in the pathogenesis of preeclampsia. Thus in preeclampsia, multiple abnormalities in angiogenesis involving sFlt1, sEng, VEGF, and PlGF are required to occur congruently for endothelial dysfunction and clinical symptoms to develop.

Oxidative Stress

One proposed link between the angiogenic imbalance of preeclampsia and the resulting endothelial dysfunction is the role of endothelial nitric oxide synthase (eNOS) and its product nitric oxide (NO). VEGF contains vasodilatory properties typically enacted through eNOS, and it has been suggested that sFlt1 antagonism of VEGF may therefore contribute to vasoconstriction [9,10,17]. Li *et al.* showed that sFlt-1 overexpression and eNOS deficiency may work synergistically to produce more severe renal dysfunction than would be seen individually [18]. Similar to sFlt1, a link between sEng and NO has also been demonstrated. Venkatesha *et al.* found that TGF- β 1, a target of sEng, may play a role in the activation of eNOS, leading to vasorelaxation. The addition of sEng appeared

to counteract this process of eNOS activation and vasorelaxation [17].

Other enzymes such as heme oxygenase (HO) have also been found to play a role in preeclampsia. Heme oxygenase is an enzyme present in two forms: HO-1 and HO-2. Among its various functions, HO is responsible for the conversion of heme to carbon monoxide (CO), iron, and biliverdin. The role of HO is not fully understood, but it is thought to be important for normal fetal development and the invasiveness of trophoblasts, especially given the presence of HO-2 on all villous and extravillous trophoblasts [19]. For example, blockade of HO-2 using antibodies inhibits trophoblast invasion *in vitro* [20]. HO-2 was also shown to have diminished expression in the placentas of preeclamptic patients [21]. Studies of HO-1 have shown conflicting results, which some demonstrating increases in HO-1 in preeclamptic women and others showing no change [22,23]. There are also conflicting results on HO-1's ability to decrease sFlt-1's effects on hypertension [23,24].

CO, a metabolite produced by HO, is known to have vasodilatory properties on placental vasculature, reducing placental perfusion pressure and allowing for increased blood flow [25]. Inhibition of HO using inhibitor zinc protoporphyrin-9 resulted in increased placental perfusion pressure, supporting the hypothesis of CO playing a role in placental perfusion [26].

Another important factor in preeclampsia is hypoxia-inducible factor 1-alpha (HIF-1 α), a transcription factor that regulates cell responses to hypoxic environments, such as the ischemic placenta. Iriyama *et al.* used preeclampsia rat models injected with AT1-AA and found elevated levels of HIF-1 α compared to normotensive rats [27]. Furthermore, they found that downregulation of HIF-1 α in these preeclampsia rat models resulted in a significant reduction in hypertension and proteinuria compared to control rats, thus directly implicating elevated HIF-1 α in the pathogenesis of preeclampsia. Interestingly, Flt-1 is a transcriptional target of HIF-1 α . Iriyama *et al.* additionally showed that preeclampsia rat models with downregulated HIF-1 α also had decreased levels of sFlt-1, suggesting HIF-1 α may have upstream activity from sFlt-1 in the development of preeclampsia [27].

Endothelin-1 (ET-1) and angiotensin-II type 1 receptor autoantibody (AT1-AA) have

gained the interest of researchers over the past several years. ET-1 is a potent endothelial-derived vasoconstrictor which is elevated in preeclampsia. There remains a postulated link between ET-1 and sFlt-1 in patients who become preeclamptic [4,28,29]. Two studies have noted that protective effect of an ET-1 receptor antagonist in the development of hypertension in both RUPP rats and pregnant rats infused with sFlt-1 [30,31]. This suggests that ET-1 may mediate the pathway from excess sFlt-1 to hypertension.

The renin-angiotensin system (RAS) also likely plays a role in preeclampsia. Pregnancy has been shown to be a state of increased resistance to angiotensin II (Ang II), thus allowing the maternal vasculature to remain low-resistance. However, preeclamptic women demonstrate an increased sensitivity to the actions of Ang II. The precise cause of this sensitivity is not fully understood, though one proposed mechanism is the formation of heterodimers between angiotensin II type I receptors (AT1) and bradykinin B₂, with AbdAlla *et al.* showing a significant increase in AT1-B2 heterodimers in preeclamptic patients [32]. These heterodimers appear to have an increased sensitivity for Ang II. Another mechanism is AT1-AA, an agonistic autoantibody to angiotensin-II receptors. Not present in normal pregnancies it has been detected in the serum of women suffering from preeclampsia [33]. This relationship has a dose dependent relationship with levels of AT1-AA positively correlating with the severity of disease [34]. Furthermore, injection of AT1-AA into pregnant rats resulted in the induction of preeclampsia symptoms, including hypertension, proteinuria, glomerular endotheliosis, and intrauterine growth restriction [35]. A link between AT1-AA and angiogenic imbalance and suggesting that the presence of AT1-AA may precede the rise in sFlt-1 as AT1-AA injections elevated sFlt-1 [36]. The interactions of these various signals can be seen in [Table 1](#) below.

While placental hypoxemia remains a key component in the development of preeclampsia unclear additional factors are involved. If ischemia alone was the cause the delivery of the placenta would resolve the disease process [37,38]. While this is true for the majority of patients some studies have demonstrated patients suffering from continued symptomatology for weeks. Berks *et al.* reported 39% of women in their study demonstrating hypertension at

Table 1: Factors involved in preeclampsia.

Factor	Type	Role	Change in Normotensive Pregnancy	Change in Preeclampsia Compared to Normal Pregnancy	Experimental Effects (animal model)
VEGF	Dimeric glycoprotein	Promotes endothelial cell proliferation, migration, survival	Decreased [31]	Decreased in late pregnancy	Anti-VEGF chemotherapy induces HTN, proteinuria (human) [16,17]
PlGF	Dimeric glycoprotein	Potentiates VEGF angiogenesis	Increased in first two trimesters [31]	Decreased	Infusion reduces HTN (rat, primate) [19,20]
sFlt-1	Circulating soluble tyrosine kinase receptor	Inhibits angiogenesis Antagonism of VEGF and PlGF	Increased in 3 rd trimester [31]	Elevated	Excess sFlt-1 induces HTN, proteinuria (rat) [10,11] Removal via whole blood apheresis decreases UP/Cr ratio (human) [9]
ET-1	Peptide	Vasoconstriction	Decreased [32]	Elevated	Antagonism decreases HTN (rat) [10,23]
AT1-AA	Autoantibody	Agonist of angiotensin II receptor Inhibits trophoblast invasiveness (in vitro) [30]	Absent	Elevated	Infusion from preeclamptic women into rats induces HTN, proteinuria, elevated sFlt-1 [27]
PGI ₂	Lipid	Antiinflammatory Vasodilation Antithrombotic	Elevated	Decreased	sFlt-1 decreases PGI ₂ levels [27]
TxA ₂	Lipid	Prothrombotic Vasoconstrictor	Elevated	Elevated	Elevation is used to create murine models for growth restriction [41]

Abbreviations: Vascular Endothelial Growth Factor (VEGF); Placental Growth Factor (PlGF); Soluble Fms-like Tyrosine Kinase 1 (sFlt-1); Angiotensin II Receptor Type 1 Autoantibody (AT1-AA); Prostacyclin (PGI₂); Thromboxane A2 (TxA₂); Hypertension (HTN); Urine Protein/Creatinine (UP/Cr)

3 months postpartum [39]. The cause of this prolonged hypertension and proteinuria is not known and requires further investigation.

In preeclampsia there is an imbalance of thromboxane and prostacyclin. Prostacyclin (PGI₂), which functions as a vasodilator is diminished in patients with preeclampsia. With this decrease there is noted to be a concurrent elevation in thromboxane which stays stable through normal pregnancies. Thromboxane A2 (TxA₂) is associated with platelet cell function and activation. Wang *et al.* speculated that this imbalance results in endothelial cell damage, further exacerbating the pathways that contribute to preeclampsia [40].

Conclusion

In summary preeclampsia remains a complex disease process with multiple components intertwined in its development including

angiogenic and endothelial dysfunction. While research has revealed multiple molecular markers involved in the pathophysiology of preeclampsia links between them and the clinical symptoms of the disease remain poorly understood and require additional research. With further understanding of the pathophysiology of preeclampsia, further possibilities can emerge for novel treatments of this disease.

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