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Pathophysiology of hypertension in preeclampsia

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1. Introduction

Preeclampsia is a hypertensive disorder of pregnancy, classically defined as new-onset hypertension and proteinuria of at least 300 mg in 24 h. It is among the most common disorders of pregnancy, occurring in up to 8% of all pregnant women worldwide (Roberts et al., 2003). Preeclampsia is associated with significant maternal and fetal morbidity and mortality, including eclampsia and HELLP syndrome in the mother, and preterm birth, intrauterine growth restriction, and perinatal death in the fetus (Roberts et al., 2003). Though in developed countries, maternal morbidity and mortality due to preeclampsia has decreased, preeclampsia is associated with increased risk of cardiovascular disease later in maternal life (Roberts et al., 2003; Harskamp and Zeeman, 2007).

Preeclampsia is a complex, multisystem disease with a still unclear etiology. It is commonly accepted that the pathophysiology of preeclampsia begins with abnormal placentation, given the resolution of the disorder following delivery of the placenta. However, the means by which abnormal placentation results in systemic dysfunction is still not well understood. 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 (Fisher, 2015).

In preeclampsia, this low resistance vasculature does not form due to abnormal cytotrophoblast invasion and deficient spiral artery remodeling, leading to decreased blood flow to the placenta. This placental ischemia is a critical step 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, in which uterine blood supply is restricted to simulate uteroplacental ischemia, leading to a clinical picture of hypertension, proteinuria, and glomerular endotheliosis (Granger et al., 2006). Preeclampsia can thus be thought of as a two-stage disease. In the first stage, abnormal placentation and

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[1] The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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deficient spiral artery remodeling leads to placental ischemia. In the second stage, placental ischemia leads to the clinical manifestations of preeclampsia, including the development of hypertension and proteinuria (George and Granger, 2011; Maynard et al., 2005). However, the precise cause for both deficient spiral artery remodeling and its effects on the development of hypertension remain unclear.

2. Angiogenic imbalance

A wide variety of biomarkers have been implicated in the pathophysiology of preeclampsia, including angiogenic, inflammatory, oxidative, and genetic factors. One area of great interest is vascular and endothelial dysfunction. Placental ischemia is thought to cause hypoxia-induced release of placental factors, leading to widespread vascular and endothelial dysfunction (Palei et al., 2013). Endothelial dysfunction occurs due to an imbalance in angiogenic factors and appears to play an important role in the development of hypertension (Maynard et al., 2005; Palei et al., 2013; Maynard and Karumanchi, 2011). Thus angiogenic factors have come under intense focus due to their seemingly important 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 plays an important role in both angiogenesis and the maintenance of endothelial health, and though the role of PlGF is not fully understood, it is thought to act in concert with VEGF to promote angiogenesis (Maynard et al., 2005; Chaiworapongsa et al., 2004). Thus sFlt-1 appears to enact its anti-angiogenic effects through the antagonism of VEGF and PlGF.

sFlt-1 is thought to be a key player in preeclampsia and has been shown to be elevated in preeclamptic women by up to five times the levels found in healthy pregnant women (Maynard et al., 2003). Furthermore, injection of an adenovirus expressing sFlt-1 into pregnant rats resulted in preeclampsia-like symptoms, including significant hypertension, proteinuria, glomerular endotheliosis, and fetal growth restriction (Maynard et al., 2003; Lu et al., 2007). sFlt-1 also appears to work in a dose-dependent fashion, with the degree of sFlt elevation positively correlated with the severity of disease (Chaiworapongsa et al., 2004; Maynard et al., 2003). 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 (Thadhani et al., 2016). 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 (Maynard et al., 2003). Interestingly, clinical trials for bevacizumab, an anti-VEGF monoclonal antibody used in chemotherapy, demonstrated preeclampsia-like side effects of hypertension and proteinuria supporting the idea that VEGF deficiency is a component of preeclampsia pathogenesis (Kabhinavar et al., 2003; Yang et al., 2003). PlGF also has important implications in preeclampsia. Maynard et al. showed that VEGF antagonism alone in rat models was not sufficient for the development of hypertension and proteinuria, and both VEGF and PlGF blockade are likely needed for the development of a preeclamptic picture (Maynard et al., 2003). Additionally, administration of recombinant human PlGF in both rat and primate preeclampsia models reverses the hypertensive component of the disease, suggesting a potential therapeutic role for PlGF (Makris et al., 2016; Spradley et al., 2016).

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)-β1. sEng appears to have multiple similarities with sFlt-1. It is also a circulating factor within the maternal bloodstream, antagonizing pro-angiogenic TGF-β1. 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 (Venkatesha et al., 2006). 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 occur simultaneously, leading to the endothelial dysfunction and clinical manifestations of this disease.

3. 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 (Chaiworapongsa et al., 2004; Maynard et al., 2003; Venkatesha et al., 2006). 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 (Li et al., 2012). Similar to sFlt1, a link between sEng and NO has also been demonstrated. Venkatesha et al. found that TGF-β1, 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 (Venkatesha et al., 2006).

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 (George and Granger, 2013). For example, blockade of HO-2 using antibodies inhibits trophoblast invasion in vitro (McCaig and Lyall, 2009). HO-2 was also shown to have diminished expression in the placentas of preeclamptic patients (Zenclussen et al., 2003). Studies of HO-1 have shown conflicting results, which some demonstrating increases in HO-1 in preeclamptic women and others showing no change (Eide et al., 2008; Tong et al., 2015). There are also conflicting results on HO-1′s ability to decrease sFlt1's effects on hypertension (Tong et al., 2015; George et al., 2011).

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 (Bainbridge et al., 2002). 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 (Lyall et al., 2000).

Another important factor in preeclampsia is hypoxia-inducible factor 1-alpha (HIF-1α), 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-1α compared to normotensive rats (Iriyama et al., 2015).