

Review

Physiological basis of pregnancy induced hypertension

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Preeclampsia is a circulatory disorder, which is a pregnancy-specific syndrome characterized by new-onset hypertension and proteinuria, occurring usually after 20 weeks of gestation. Although the etiology remains unknown, placental hypoperfusion and diffuse endothelial cell injury are considered to be the central pathologic events. The main focus is to review recent studies that link endothelial dysfunction and hypertension in preeclampsia, providing knowledge on placental factors that have profound effects on blood flow and arterial pressure regulation. Our review showed that preeclampsia possibly does not have a single cause but certainly involves multiple pathophysiological interactions. In conclusion, this review provides evidence on the role of the various factors and their interplay in the pathophysiology of preeclampsia. There is however, the need for further research to examine the influence of uteroplacental RAS in the pathogenesis of preeclampsia.

Keywords: Preeclampsia, proangiogenic factors, antiangiogenic factors.

INTRODUCTION

Hypertensive disorders complicate approximately 5-7% of all pregnancies (Cunningham et al., 1993). These include: preeclampsia syndrome superimposed on chronic hypertension; preeclampsia syndrome occurring in a subsequent pregnancy and/or recurring with an underlying susceptibility state (Cunningham et al., 1993). Preeclampsia, a circulatory disorder, is a pregnancy-specific syndrome characterized by new-onset hypertension and proteinuria, occurring usually after 20 weeks' gestation. Although the etiology remains unknown, placental hypoperfusion and diffuse endothelial cell injury are considered to be the central pathologic events. Preeclampsia is classified into mild and severe types and, in its extreme, may lead to liver and renal failure, disseminated intravascular coagulopathy, and central nervous system abnormalities, including seizures. Because the only cure is delivery, preeclampsia is associated with high maternal and neonatal mortality and morbidity. In the United States, preeclampsia is believed to be responsible for 15% of premature deliveries and 17.6% of maternal deaths (Thadhani et al., 2005). Worldwide, preeclampsia and eclampsia are estimated

to be responsible for approximately 14% of maternal deaths per year.

The initiating event in preeclampsia has been postulated to be reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles. Placental ischemia is thought to lead to widespread activation/dysfunction of the maternal vascular endothelium that results in enhanced formation of endothelin and thromboxane, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide (NO) and prostacyclin. These endothelial abnormalities, in turn, cause hypertension by impairing renal-pressure natriuresis and increasing total peripheral resistance. Recent data show that an imbalance of pro- and anti-angiogenic factors produced by the placenta may play a major role in mediating endothelial dysfunction. The circulating proangiogenic factors secreted by the placenta include vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). The antiangiogenic factors include soluble fms-like tyrosine kinase I receptor (sFlt-1) otherwise known as soluble VEGF receptor type I and soluble endoglin (sEng). Other substances that have been proposed, but not proven, to contribute to this process include tumor necrosis factor, interleukins, various lipid molecules, and syncytial knots (Roberts et al., 2007).

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The main focus is to review recent studies that link endothelial dysfunction and hypertension in preeclampsia, providing knowledge on placental factors that have profound effects on blood flow and arterial pressure regulation.

Angiogenic Factors

Considerable clinical evidence has accumulated that preeclampsia is strongly linked to an imbalance between proangiogenic factors such as VEGF and PlGF and antiangiogenic factor such as soluble fms-like tyrosine kinase (sFlt-1) in the maternal circulation (Karumanchi et al., 2004). Both plasma and amniotic fluid concentrations of sFlt-1 are increased in preeclamptic patients, as well as placental sFlt-1 mRNA (Karumanchi et al., 2005). Recently, studies have reported that increased sFlt-1 may have a predictive value in diagnosing preeclampsia as concentrations seem to increase before manifestation of overt symptoms (Levine et al., 2004).

Maynard et al (2003) reported that exogenous administration of sFlt-1 into pregnant rats via adenovirus mediated gene transfer resulted in increased arterial pressure and proteinuria, and decreased plasma free VEGF and PlGF concentrations similar to that observed in the preeclamptic patients. Subsequently, similar observations using adenovirus transfection have been reported in the mouse (Lu et al., 2007).

Recently, Li et al (2007) showed that VEGF infusion attenuates the increased blood pressure and renal damage observed in pregnant rats over expressing sFlt-1. Thus, this study suggests that sFlt-1 and alterations in angiogenic factors may contribute to the clinical symptoms observed in preeclampsia; however, these observations did not shed any light on the mechanisms whereby sFlt-1 over expression occurs in preeclampsia. Similarly, Makris et al (2007) have reported uteroplacental ischemia increases sFlt-1 in the baboon as well.

An additional antiangiogenic factor, soluble endoglin (sEng), has also been revealed as a factor in the pathogenesis of preeclampsia (Levine et al., 2006). Endoglin is a component of the transforming growth factor (TGF)- β receptor complex and is a hypoxia inducible protein associated with cellular proliferation and NO signaling. sEng, on the other hand, has been shown to be antiangiogenic as it is thought to impair TGF- β 1 binding to cell surface receptors. Venkatesha et al (2006) have shown that sEng inhibits in vitro endothelial cell tube formation to a similar extent as sFlt-1. Further, the authors reported in vivo data in the pregnant rat indicating that adenovirus mediated increase of sFlt-1 and sEng in concert exacerbated the effects of either factor alone and resulted in fetal growth restriction, severe hypertension and nephritic range proteinuria.

Nitric Oxide

The cells lining the inner surface of blood vessels are endothelial cells. These cells produced a very potent vascular relaxant referred to as Endothelium Derived Relaxing Factor (EDRF). Ebeigbe et al (1999) confirmed that EDRF relaxes vascular smooth muscles and so lowers blood pressure. It follows that in situations where there is endothelial cell dysfunction, the ability of the blood vessels to relax will be impaired because EDRF production will be diminished or completely abolished. The EDRF was suggested to be nitric oxide based on the similarity of the properties of EDRF and that of nitric oxide.

Nitric Oxide (NO) production is significantly elevated in normal pregnancy. Experimental studies also suggest that NO production plays an important role in the cardiovascular adaptations of pregnancy (Granger et al., 2001). Noris et al (2004) suggested that L-arginine depletion, caused by arginase II over expression, may orient NO synthase toward oxidant species in placenta in preeclampsia. In addition, McCord and colleagues (2006) reported that a relative deficiency of arginine in peripheral blood mononuclear cells may favor superoxide and peroxynitrite production and contribute to oxidative stress in preeclampsia. In a study by Conrad et al (1999), under conditions that were carefully monitored to reflect endogenous production and not dietary intake, there was no evidence for a decrease in NO production by measure of plasma or urinary excretion of nitrite and nitrate. In contrast, previous studies have indicated that serum levels of nitrite and nitrate are increased relative to severity of the disorder in women that develop preeclampsia (Shaamash et al., 2000). Elevated asymmetrical dimethylarginine (ADMA) concentration before clinical onset of preeclampsia also suggests a role of this NO synthase inhibitor in the pathophysiologic condition of preeclampsia (Speer et al., 2008).

The activity of the NO system has also been assessed in animal models of placental ischemia and cytokine excess. Placental ischemia in pregnant rats has no effect on urinary nitrite/nitrate excretion relative to control pregnant rats (Alexander et al., 2004). However, basal and stimulated releases of NO from isolated vascular strips were significantly lower in the pregnant rats with placental ischemia (Crews et al., 2000). Moreover, study by Orshal and Khalil (2004) found reduced endothelial NO-mediated vascular relaxation in hypertensive pregnant rats chronically infused with the inflammatory cytokine, interleukin (IL-6).

Oxidative Stress

In disease states of oxidative stress, an imbalance of prooxidant and antioxidant forces results in endothelial

dysfunction, either by direct actions on the vasculature or through vasoactive mediators (Noris et al., 2004). During preeclampsia, oxidative stress may result from interactions between the maternal component which may include preexisting conditions such as obesity, diabetes, and hyperlipidemia, and the placental component which may involve secretion of lipid peroxides (Noris et al., 2004). Oxidative stress may mediate endothelial cell dysfunction and contribute to the pathophysiology of preeclampsia as there is evidence of increased prooxidant activity formation along with decreased antioxidant protection in preeclampsia.

Dihyronicotinamide adenine dinucleotide phosphate (NADPH) oxidases are an important source of superoxide in neutrophils, vascular endothelial cells, and cytotrophoblast. Increased expression of (NADPH) oxidase subunits have been reported in both trophoblast and placental vascular smooth muscle cells in placental tissue of women with preeclampsia (Raijmakers et al., 2004). Moreover, higher placental (NADPH) oxidase activity has been reported by (Raijmakers et al., 2004) in women with early-onset preeclampsia as compared with those with late-onset of disease which is consistent with the concept that early-onset preeclampsia is more dependent on placental dysfunction than the later-onset disease. Thus, there is considerable evidence to suggest that activation of (NADPH) oxidase plays an important role in the placental oxidative stress associated with preeclampsia.

Several important antioxidants are significantly decreased in women with preeclampsia. Vitamin C, vitamin A, vitamin E, beta carotene, glutathione levels, and iron-binding capacity are lower in the maternal circulation of women with preeclampsia than women with a normal pregnancy. Gandley et al (2005) suggested that the higher circulating levels of S-nitrosoalbumin in women with preeclampsia reflect a deficiency in ascorbate-mediated release of NO from S-nitrosoalbumin. These deficiencies in antioxidants may have important vascular effects in preeclampsia. Ascorbate deprivation increases mesenteric artery myogenic responsiveness during pregnancy and that this increase may result from a decrease in NO-mediated modulation of the myogenic contractile response.

In view of the abnormally low plasma vitamin C concentrations in preeclampsia, investigators suggested that a combination of vitamins C and E may be a promising prophylactic strategy for prevention of preeclampsia (Raijmakers et al., 2004). However, a recent multi-center clinical trial showed that antioxidant supplementation with vitamins C and E during pregnancy did not reduce the risk of preeclampsia in nulliparous women, the risk of intrauterine growth restriction, or the risk of death (Rumbold et al., 2006). Thus the use of high dose vitamin C and vitamin E does not appear to be

justified during preeclampsia.

Endothelin

Another endothelial-derived and contracting factor that may play a role in preeclampsia is the vasoconstrictor, endothelin-1 (ET-1). Although some studies have reported no significant changes in circulating levels of ET-1 during moderate forms of preeclampsia, a possible role for ET-1 as a paracrine or autocrine agent in preeclampsia remains worthy of consideration (Granger et al., 2002). Because ET-1 is released toward the vascular smooth muscle in a paracrine fashion, changes in plasma levels of ET may not reflect its local production. Indeed, this is one of the reasons why it has been difficult to ascertain whether preeclampsia is associated with altered ET production. Local synthesis of ET has been assessed in preeclamptic women, and investigators have found preproendothelin mRNA to be elevated in a variety of tissues (Roberts et al., 2007).

Alexander et al (2001) examined the role of ET-1 in mediating hypertension in a placental ischemic rat model of preeclampsia. They found that renal expression of preproendothelin was significantly elevated in both the medulla and the cortex of pregnant rats with chronic reductions in uterine perfusion pressure compared with control pregnant rats. Moreover, they reported that chronic administration of the selective endothelin type A receptor antagonist, (ET_A) ABT627 markedly attenuated the increase in mean arterial pressure in pregnant rats with reductions in uterine perfusion pressure. In contrast, ET_A receptor blockade had no significant effect on blood pressure in the normal pregnant animal. These findings suggest that ET-1 plays a major role in mediating the hypertension produced by chronic reductions in uterine perfusion in pregnant rats.

Sera from pregnant rats exposed to chronic reductions in uterine perfusion pressure increases ET-1 production by cultured endothelial cells. The exact mechanism linking enhanced renal production of ET-1 to placental ischemia in pregnant rats or in preeclamptic women is unknown. One potential mechanism for enhanced ET-1 production is via transcriptional regulation of the ET-1 gene by TNF- α . TNF- α is elevated in preeclamptic women and has been implicated in the disease processes (Conrad et al., 1997). LaMarca et al (2005) reported that chronic infusion of TNF- α in pregnant rats significantly increases blood pressure. They further explained that the increase in arterial pressure produced by a 2- to 3-fold elevation in plasma levels of TNF- α in pregnant rats is associated with significant increases in local production of ET-1 in the kidney, placenta, and vasculature. Collectively, these findings suggest that endothelin, via ET_A receptor activation, plays an important

role in mediating TNF- α -induced hypertension in pregnant rats.

Prostaglandins

Several lines of evidence suggest that changes in the prostaglandin system may play a role in mediating the renal dysfunction and increase in arterial pressure during preeclampsia. Significant alterations in prostacyclin and thromboxane production occur in women with preeclampsia (August and Lindheimer, 1995). Plasma and urine levels of thromboxane are elevated in women with preeclampsia, whereas synthesis of prostaglandins, such as prostacyclin, is reduced (Taylor, 1999). Additional evidence for a potential role of thromboxane in preeclampsia derives from a study demonstrating that short-term increases in systemic arterial pressure produced by acute reductions in uterine perfusion in pregnant dogs can be prevented by thromboxane receptor antagonist. Although some studies suggest a potential role for thromboxane in preeclampsia, the quantitative importance of this substance in mediating the long-term reduction in renal hemodynamics and elevation in arterial pressure produced by chronic reductions in uterine perfusion pressure in pregnant rats is still uncertain. In preliminary experiments (Llinas et al., 2002) found that urinary excretion of thromboxane B₂ was higher in the hypertensive pregnant rats with chronic reductions in uterine perfusion pressure than in normal pregnant rats at day 19 of gestation. In contrast, inhibition of cytochrome P450 enzymes with 1-aminobenzotriazole (ABT) attenuated the hypertension and increased renal vascular resistance, 20-hydroeicosatetraenoic (20-HETE) formation, and cytochrome P450 monooxygenases (CYP4A) expression in the renal cortex normally observed in the placental ischemic pregnant rat. (Llinas et al., 2004).

Renin-Angiotensin System

During normal pregnancy, plasma renin concentration, renin activity, and angiotensin II (ANG II) levels are all elevated, yet vascular responsiveness to ANG II appears to be reduced (Shah et al; 2005). Though there seems to be increase in sensitivity to AGN II during preeclampsia. Although the mechanisms underlying these observations remain unclear, there is growing evidence to suggest that deregulation of the tissue-based and circulating renin-angiotensin system (RAS) may be involved in the pathophysiology of preeclampsia.

Studies in preeclamptic women demonstrate increased circulating concentrations of an agonistic autoantibody to the angiotensin type 1 receptor (AT1-AA) (Wallukat et. al., 1999). In addition to being elevated during preeclampsia,

the AT1-AA has also been reported to be increased in postpartum women. Hubel et al (2007) demonstrated that the AT1-AA does not regress completely after delivery and that the increase in AT1-AA correlated with insulin resistance and sFt-1. The importance of AT1-AA after preeclampsia, especially in the context of increased cardiovascular risk remains to be determined. Dechend and colleagues (2005) used the cardiomyocyte contraction assay to detect the presence of AT1 agonistic antibody in pregnant transgenic rats over expressing components of the human RAS.

LaMarca et al (2006) provided evidence demonstrating that placental ischemia in pregnant rats is associated with increased circulating levels of the AT1-AA. In addition, chronic elevation of TNF alpha in pregnant rats was also associated with increased production of the AT1-AA. Moreover, they found that the hypertension in response to placental ischemia in pregnant rats and in response to chronic infusion of TNF alpha in pregnant rats was markedly attenuated by antagonism of the AT1 receptor. Collectively, these novel findings indicate that placental ischemia and TNF- α are important stimuli of AT1-AA production during pregnancy and that activation of the AT1 receptor appears to play an important role in the hypertension produced by placental ischemia and TNF- α in pregnant rats. Although these findings indicate that reduced placental perfusion may be an important stimulus for AT1-AA production, the fact that AT1-AA are present in patients with pathological uterine artery Doppler independent of preeclampsia suggests that AT1-AA may not be the primary cause of preeclampsia (Walther et al., 2005).

Cytokines

Several groups have also suggested a potential role for inflammatory cytokines in the etiology of preeclampsia (Conrad and Benyo, 1997). Aldosterone could play an important role in the genesis of this increased susceptibility of inflammatory process in preeclampsia, other factors such as obesity, diabetes, and placental ischemia could also be involved (LaMarca et al., 2005). Several lines of evidence support the hypothesis that the ischemic placenta contributes to endothelial cell activation/dysfunction of the maternal circulation by enhancing the synthesis of cytokines such as TNF- α (Hagedom et al., 2007).

TNF α is an inflammatory cytokine that has been shown to induce structural and functional alterations in endothelial cells. This inflammatory cytokine also enhances the formation of a number of endothelial cell substances such as endothelin and reduces acetylcholine-induced vasodilatation. TNF- α directly induces oxidative damage as TNF- α destabilizes electron flow in mitochondria, resulting in release of oxidizing free

radicals and formation of lipid peroxides. Lipid peroxides and oxygen radicals can damage endothelial cells as they are highly reactive compounds. Also supporting a potential role of TNF- α in preeclampsia are findings that plasma levels of TNF- α are significantly elevated, by $\approx$ 2-fold, in women with preeclampsia (Hagedorn et al., 2007).

Although inflammatory cytokines such as IL-6 and TNF- α have been reported by some laboratories to be elevated in preeclamptic women, it has been uncertain whether moderate and long-term increases in cytokines during pregnancy could result in elevations of blood pressure.

Metabolic and Dietary Factors

There are other comorbid conditions such as obesity, diabetes, hyperlipidemia, and hyperhomocysteinemia that have been proposed as potential contributors to endothelial dysfunction in preeclampsia (Bartha et al., 2002). Recent studies have indicated a relationship between elements of the metabolic syndrome such as elevated serum triglycerides and free fatty acids, insulin resistance, and glucose intolerance and the occurrence of preeclampsia (Powers et al., 2004).

In fact, several authors have suggested insulin resistance may presage the manifestation of preeclampsia (Seely and Solomon, 2003). However, insulin resistance during pregnancy may interact with other conditions such as impaired angiogenesis to generate a preeclamptic phenotype. Although plasma levels of lipids are increased during normal pregnancy, plasma concentrations of both triglyceride-rich lipoproteins and nonesterified fatty acids are significantly increased in women that develop preeclampsia relative to normal pregnant women. This significantly increased plasma triglycerides in women with preeclampsia correlates with increased plasma concentrations of low-density lipoproteins (Sattar et al., 1997). The nature of this correlative data has provided difficulty in determining a causal effect for abnormal lipid metabolism in the pathogenesis of preeclampsia. Though there are no definitive data indicating whether or not metabolic derangements were sequel or potential contributors to placental ischemia; (Gilbert et al., 2007) show that data obtained from such model suggest that metabolic derangements similar to the metabolic syndrome X are not a direct consequence of reduced uterine perfusion. Rather, it appears that factors associated with metabolic abnormalities may contribute to cardiovascular dysfunction in preeclampsia rather than resulting from poor placental perfusion.

Several clinical studies have also shown that women with higher plasma homocysteine (hyperhomocysteinemia) levels early in pregnancy have a higher incidence of preeclampsia and intrauterine growth

restriction (IUGR) (Rajkovic et al., 1999). Powers et al (2004) suggested that the vasculature during pregnancy may manifest increased sensitivity to homocysteine. They found that endothelial-dependent vasodilation in pregnant mice is more sensitive to the effect of increased homocysteine than arteries from nonpregnant mice and that this effect of homocysteine appears to result from a loss in NO-mediated relaxation attributable to oxidative inactivation of the NO synthase cofactor, tetrahydrobiopterin.

Homocysteine concentrations are affected by nutritional deficiencies, particularly decreased folic acid and B12, leading to increased homocysteine. Patrick et al (2004) reported that homocysteine and folic acid are inversely related in black women with preeclampsia. The importance of folate intake is also highlighted by a study by Torrens et al (2006) where they reported that folate supplementation during pregnancy improve offspring cardiovascular dysfunction induced by protein restriction in laboratory animals.

Influence of weather pattern

Studies have shown a variable association of preeclampsia and eclampsia with the changing weather patterns of different season. These association studies often compared the incidence of preeclampsia and eclampsia against the patterns seen in three or four characteristic seasons in the study area. Studies from different parts of the world frequently give opposing results. Two studies which demonstrate no relationship of meteorological factors on the incidence of eclampsia (Alderman et al., 1998; Maggann et al., 1995). Most data, however, tends to suggest or with increased humidity or rainfall (Neela and Rama, 1993; Neutra, 1974; Agobe et al., 1981).

Okojie et al (2008), identified a seasonal variation in preeclampsia that appears to be more strongly related to the timing of conception than to the timing of delivery and the highest prevalence of preeclampsia was associated with conception in the wet season. Though the specific contribution of season to the pathophysiology of preeclampsia remains unknown, seasonal effects could include dietary changes, changes in circadian rhythms, differences in ambient temperature or humidity changes and possibly changes in plasma volume. Exploring this association will help us to gain further insight into the pathophysiology of this condition.

CONCLUSION

In conclusion, preeclampsia possibly does not have a single cause but certainly involves multiple pathophysiological interactions. This review provides evidence on the

the role of the various factors and there interplay in the pathophysiology of preeclampsia. There is however the need to further research to examine the influence of uteroplacental RAS in the pathogenesis of preeclampsia.

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