Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction

Jeffrey S. Gilbert, Michael J. Ryan, Babette B. LaMarca, Mona Sedeek, Sydney R. Murphy, and Joey P. Granger

Department of Physiology and Biophysics and Center for Excellence in Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, Mississippi


Studies over the last decade have provided exciting new insights into potential mechanisms underlying the pathogenesis of preeclampsia. The initiating event in preeclampsia is generally regarded to be placental ischemia/hypoxia, which in turn results in the elaboration of a variety of factors from the placenta that generate profound effects on the cardiovascular system. This host of molecules includes factors such as soluble fms-like tyrosine kinase-1, the angiotensin II type 1 receptor autoantibody, and cytokines such as tumor necrosis factor-α, which generate widespread dysfunction of the maternal vascular endothelium. This dysfunction manifests as enhanced formation of factors such as endothelin, reactive oxygen species, and augmented vascular sensitivity to angiotensin II. Alternatively, the preeclampsia syndrome may also be evidenced as decreased formation of vasodilators such as nitric oxide and prostacyclin. Taken together, these alterations cause hypertension by impairing renal pressure natriuresis and increasing total peripheral resistance. Moreover, the quantitative importance of the various endothelial and humoral factors that mediate vasoconstriction and elevation of arterial pressure during preeclampsia remains to be elucidated. Thus identifying the connection between placental ischemia/hypoxia and maternal cardiovascular abnormalities in hopes of revealing potential therapeutic regimens remains an important area of investigation and will be the focus of this review.

Preeclampsia, a pregnancy-specific syndrome characterized by new onset hypertension and proteinuria, is a considerable obstetric problem and a significant source of maternal and neonatal morbidity and mortality (12, 95). Although preeclampsia and related hypertensive disorders of pregnancy continue to affect ~8% of all pregnancies, the incidence of preeclampsia has seen a 40% increase in recent years (81). Moreover, it has recently been recognized that women who endure preeclampsia are at a greater risk for cardiovascular disease than nonpreeclamptic women and the men who fathered those preeclamptic pregnancies (37). Despite thorough characterization of the preeclamptic syndrome and a suite of contributing circulating factors (12, 77, 80, 95), the mechanisms underlying the pathogenesis of this troubling condition remain nebulous. Interestingly, it has been proposed that not only are increased circulating factors responsible for much of the preeclamptic syndrome, but they may also predispose the maternal cardiovascular system to subsequent endothelial dysfunction as the mother ages (20).

The uncertainties regarding the mechanisms of preeclampsia are at least partially attributable to difficulties faced in the development of suitable animal models for mechanistic research of this disease (72). Consequently, it is held by many that more effective strategies for prevention and treatment of preeclampsia shall be forthcoming with the recent progress in developing animal models that allow careful mechanistic investigation of the underlying pathophysiological mechanisms involved in preeclampsia (32).

Placental Ischemia/Hypoxia and the Etiology of Preeclampsia

Although the pathophysiology of preeclampsia remains undefined, placental ischemia/hypoxia is widely regarded as a key factor (24, 28, 80). Inadequate trophoblast invasion leading to incomplete remodeling of the uterine spiral arteries is considered to be a primary cause of placental ischemia (24). Thus the poorly perfused and hypoxic placenta is thought to synthesize and release increased amounts of vasoactive factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), cytokines, and possibly the angiotensin II (ANG II) type 1 receptor autoantibodies (AT1-AA) (24, 66, 78, 79, 111). Figure 1 illustrates a model by which these and other candidate molecules are thought to induce widespread activation/dysfunction of the maternal endothelium in vessels of the kidney and other organs that ultimately results in hypertension.
The physiological mechanisms that mediate the alterations in cardiovascular and renal function that are requisite for a successful pregnancy have been studied in great detail. Nonetheless, experimental data investigating the mechanisms underlying preeclampsia have been limited because of the difficulty in performing mechanistic studies in pregnant women. Although several animal models have been developed to study preeclampsia, none to date completely represents the protean characteristics of the human syndrome. Furthermore, information on the mechanisms mediating the long-term increase in vascular resistance and arterial pressure associated with placental ischemia is lacking.

Experimental induction of chronic uteroplacental ischemia appears to be a promising animal model to study potential mechanisms of preeclampsia since reductions in uteroplacental blood flow in a variety of animals lead to a hypertensive state that has many of the manifestations present in preeclamptic women (5–7, 9–11, 18, 22, 31, 33, 48, 49, 61, 94). It is important to note that the reduced uterine perfusion pressure (RUPP) model of placental ischemia-induced hypertension in pregnancy most closely relates to severe premature/preterm preeclampsia and not late-onset preeclampsia. The former is characterized by intrauterine growth restriction, hypertension, and proteinuria, whereas the latter is not regarded as mediated by placental ischemia and is usually not associated with intrauterine growth restriction. Thus a considerable strength of the RUPP model is that it allows mechanistic investigation of the preterm ischemic placenta and the factors it elaborates.

The relationship between reduced uteroplacental perfusion and hypertension during pregnancy has been demonstrated in a variety of animals, mostly those with hemochorial placenta. Previous studies have shown that chronic RUPP via partial ligation or placement of silver clips on the lower abdominal aorta or uterine arteries results in proteinuric hypertension in the baboon (18, 19, 61), rhesus monkeys (22, 124), rabbit (5, 59), and the dog (6, 35). Our laboratory has established a RUPP model in the pregnant rat (7, 9–11, 31, 33, 48, 49, 94). In this model, uteroplacental perfusion is reduced by ∼40% by the placement of silver clips on the aorta and ovarian arteries on day 14 of a 21-day gestation (94). On gestation day...
19, the RUPP animals display increased mean arterial pressure (MAP), decreased glomerular filtration rate, decreased renal pressure natriuresis, decreased renal plasma flow and proteinuria, and endothelial dysfunction (7, 9–11, 26, 31, 33, 48, 49). Recently, we demonstrated that these pregnant RUPP rats have increased total peripheral resistance, decreased cardiac index, and decreased uteroplacental blood flow (94), indicating that these animals have marked cardiovascular dysfunction similar to what is observed in preeclamptic women (11a, 17, 94, 109). We have also recently shown that RUPP hypertension in the rat is associated with an imbalance of angiogenic factors, in particular increased sFlt-1 and decreased VEGF and PIGF (30). Thus these models of preeclampsia have many of the features common in preeclamptic women and provide researchers with a valuable substrate from which to investigate the mechanisms of hypertension during pregnancy.

The role of a variety of endothelial, autacoid, and hormonal factors that mediate the cardiovascular and renal dysfunction produced by chronic reductions in uteroplacental perfusion pressure will be the primary focus of the remaining portion of this review. In the present review, we will also focus on the effects of reductions in uteroplacental perfusion pressure on vascular endothelial function since factors that emanate from the ischemic placenta are thought to be responsible for widespread chronic long-term alterations in arterial pressure.

Mediators of Endothelial Dysfunction in Response to Placental Ischemia

The maternal vascular endothelium appears to be an important target of factors that are triggered by placental ischemia/hypoxia in preeclampsia. The endothelium is a single-cell lining that covers the luminal side of blood vessels. This strategic location permits it to signal alterations in hemodynamics and humoral factors by synthesizing and releasing vasoactive substances. Thus a critical balance exists between endothelium-derived relaxing and contracting factors that maintain vascular homeostasis. When this delicate balance is disrupted, the vasculature is predisposed to vasoconstriction, increased total peripheral resistance, decreased cardiac index, and decreased uteroplacental blood flow (94), indicating that vascular endothelial cell dysfunction may serve as predictors of the syndrome in women that develop preeclampsia since many are often elevated weeks before observance of clinical manifestations.

Nitric oxide. Substantial evidence indicates that nitric oxide (NO) production is elevated in normal pregnancy and that these increases appear to play an important role in the renal vasodilation of pregnancy (97). In contrast, the role of NO in preeclampsia remains enigmatic (25, 76, 91). Taken together, these studies underscore the need for continued investigation into the (patho)physiological role of NO in preeclampsia.

Studies from several laboratories indicate that chronic NO synthase inhibition in pregnant rats produces hypertension associated with peripheral and renal vasoconstriction, proteinuria, intrauterine growth restriction, and increased fetal morbidity (23, 43). We have previously reported similar cardiovascular perturbations exist in the NO inhibition and RUPP models, the latter illustrated in Fig. 2 (94). In addition, we have also previously shown that placental ischemia results in the impairment of acetylcholine-mediated vasorelaxation and that nitrite and nitrate productions in aortic strips are both decreased in the RUPP rat compared with normal pregnant rats, shown in Fig. 3 (26). Chronic RUPP in pregnant rats also decreases renal protein expression of neuronal NO synthase but not urinary nitrite/nitrate excretion relative to control pregnant rats (9). Although no difference in urinary nitrate/nitrite excretion was found between RUPP and control pregnant rats, we have found that basal and stimulated release of NO from isolated vascular strips were significantly lower in RUPP rats (13). Although, whether there is a reduction in NO production in this spontaneous model of pregnancy-induced hypertension remains unclear.

Oxidative stress. During oxidative stress, an imbalance of pro- and antioxidant factors results in endothelial dysfunction, either by direct actions on the vasculature or through reductions in the bioavailability of vasoactive mediators (113). Oxidative stress may mediate endothelial cell dysfunction and contribute to the pathophysiology of preeclampsia based on evidence of increased prooxidant activity along with decreased antioxidant protection. During preeclampsia, oxidative stress...
Experimental studies in animals have endeavored to determine the role of AA metabolites such as thromboxane in preeclampsia. Such evidence derives from studies indicating that short-term increases in systemic arterial pressure produced by acute RUPP in pregnant dogs can be prevented by thromboxane receptor antagonism (119). Furthermore, we have previously reported that urinary excretion of thromboxane B2 was increased in the RUPP rats compared with normal pregnant rats at day 19 of gestation (56). Additionally, inhibition of cytochrome P-450 enzymes with 1-aminobenzotriazole attenuated the hypertension and increased renal vascular resistance, 20-HETE formation, and cytochrome P-450 4A expression in women with preeclampsia (46, 68, 114). Thus, although there is evidence that AA metabolites play a part in preeclampsia, their role is not clearly defined.

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Renin-angiotensin system. The renin-angiotensin system (RAS) plays an important role in the long-term regulation of renal function and arterial pressure during a variety of physiological and pathophysiological conditions, and pregnancy and preeclampsia are no exception. During normal pregnancy, plasma renin concentration, renin activity, and ANG II levels are all elevated, yet vascular responsiveness to ANG II appears to be reduced (12, 92). In contrast, during preeclampsia, there appears to be a marked increase in the sensitivity to ANG II (92), although the mechanisms underlying these observations remain unclear.

Recent studies in preeclamptic women have revealed several exciting findings regarding the RAS. AbdAlla and colleagues (1, 2) have shown that the AT1 receptor forms heterodimers with the bradykinin B2 receptor and results in enhanced ANG II sensitivity. Furthermore, these authors (1, 2) have shown that AT1-B2 heterodimers are present in greater abundance in preeclamptic women, suggesting that this heterodimerization may play a part in the long-observed increased ANG II sensitivity in preeclampsia. Another intriguing observation regarding the involvement of the RAS in the pathophysiology of preeclampsia is the demonstration of increased circulating concentrations of an agonistic AT1-AA in preeclamptic women (111, 112). Interestingly, the AT1-AA appear to be responsible for a variety of effects in several different tissues ranging from increased intracellular Ca2+ mobilization to monocyte activation and stimulation of IL-6 production from mesangial cells (16, 99, 115, 120). Another effect that has recently been attributed to the AT1 receptor is stimulation of sFlt-1 expression from trophoblast cells but not endothelial cells via calcineurin signaling (123). Although these findings potentially implicate AT1 as a central mediator of several pathways in preeclampsia, both the specific mechanisms that lead to excess production and the mechanisms whereby AT1-AA increase blood pressure during pregnancy remain unclear. Consequently, this has become an area of intense interest.

Increased vascular responsiveness to ANG II during preeclampsia does not prove it is an important endogenous mediator of vasoconstriction or hypertension in experimental models of preeclampsia since it could merely reflect low endogenous ANG II formation. As such, the importance of increased ANG II to the control of renal function and blood pressure during preeclampsia remains to be determined. Early experiments in our laboratory indicated that chronic oral administration of converting enzyme inhibitor enalapril (250 mg/l for 6 days) decreased MAP to a similar extent in pregnant rats with RUPP and normal pregnant rats, suggesting that the RAS does not play a major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure in pregnant rats (7). Nevertheless, we have recently found that AT1 receptor antagonism attenuated the blood pressure response to placental ischemia and that RUPP rats have increased circulating levels of the AT1-AA (54). As described in Endothelin and illustrated in Fig. 4, we have also shown that serum from pregnant rats exposed to reductions in uterine perfusion enhances endothelin production by endothelial cells via AT1 receptor activation (82). Although the initial findings by our laboratory and others are exciting, there remains much to be investigated with respect to the manner in which the AT1-AA contribute to the pathophysiology of preeclampsia.

Cytokines. Several groups have suggested that the etiology of preeclampsia may involve a hypoxia-induced upregulation of placental inflammatory cytokines (24, 78, 116). Although IL-6 and TNF-α are reportedly elevated in preeclamptic women, the importance of these cytokines in mediating the cardiovascular and renal dysfunction in response to placental ischemia during pregnancy remains unclear. We have previously shown that serum levels of TNF-α and IL-6 are elevated in RUPP rats and that chronic infusion of TNF-α (Fig. 5) or IL-6 into pregnant rats at concentrations similar to what is observed in preeclamptic women increases arterial pressure and decreases renal plasma flow and glomerular filtration rate (8, 29, 49). Furthermore, we have found that a low-dose infusion of TNF-α results in decreased renal neuronal NO synthase expression (8) while also increasing ET-1 mRNA in the kidney, placenta, and vasculature (49). Likewise, we have also reported that ET-1 is complicit in the mediation of this form of pregnancy-induced hypertension since the increased MAP in response to TNF-α is completely abolished in pregnant rats treated with an ETA receptor antagonist (49). Collectively, these findings suggest that TNF-α-induced hypertension in pregnant rats is mediated in part by endothelin, via ETA receptor activation. These studies also suggest that selective ETA receptor antagonists for the treatment of hypertension in women with preeclampsia should receive further attention.

Another mechanism by which cytokines may contribute to hypertension during pregnancy is through the modulation of sympathetic nerve activity. Previous studies have shown that women with preeclampsia have increased sympathetic tone (34, 86). Although few studies have examined the effect of specific inflammatory cytokines on blood pressure and the regulation of sympathetic activity, one recent experiment has demonstrated that an acute forebrain infusion of TNF-α in rats increased arterial pressure, heart rate, and renal sympathetic nerve activity, effects mediated by prostaglandins in the paraventricular nucleus (122). Similarly, another study showed that intracisternal or intravenous infusion of IL-1β increases blood pressure in a prostaglandin-dependent manner in rats (121).
Whether chronic elevations in inflammatory cytokines contribute to the increased sympathetic activity during preeclampsia remains to be determined.

Angiogenic factors. Although VEGF is primarily recognized for its potent angiogenic and mitogenic effects on endothelial cells, it has also been recognized as an important contributor to cell homeostasis, in particular with respect to the balance of oxidative stress (3, 4). VEGF exerts its actions mainly by two receptors, VEGF receptor-1 and -2, also known as Flt-1 and the kinase domain region (Flk/KDR), respectively. A soluble and endogenously secreted form of Flt-1 is produced mainly in the placenta by alternative splicing and contains the extracellular ligand-binding domain but not the transmembrane and cytoplasmic portions (21, 44, 45). sFlt-1 disrupts VEGF signaling either by binding VEGF and PIGF or by forming heterodimers with the KDR receptor (45). Although sFlt-1 is not a vasoconstrictor, it does significantly inhibit the dilatory actions of both VEGF and PIGF in vitro, and chronic elevations in circulating concentrations result in increased blood pressure (60, 66). An additional antiangiogenic factor, soluble endoglin (sEng), has also been revealed as a factor in the pathogenesis of preeclampsia (64, 108). Endoglin is a component of the TGF-β receptor complex and is a hypoxia-inducible protein associated with cellular proliferation and NO signaling (38, 52). sEng, on the other hand, has been shown to be antiangiogenic since it is thought to impair TGF-β1 binding to cell surface receptors (38, 108).

Considerable clinical evidence has accumulated that preeclampsia is strongly linked to an imbalance between proangiogenic (VEGF and PIGF) and antiangiogenic (sFlt-1) factors in the maternal circulation (47, 50, 51, 66, 74, 93, 103, 104, 117). Both plasma and amniotic fluid concentrations of sFlt-1 are increased in preeclamptic patients, as well as placental sFlt-1 mRNA (41, 47, 60, 65, 66, 107, 110). Recently, studies have reported that increased sFlt-1 may have a predictive value in diagnosing preeclampsia since concentrations seem to increase before manifestation of overt symptoms (e.g., hypertension and proteinuria) (47, 51). Similarly, recent clinical evidence also suggests that sEng may also presage the onset of preeclampsia (50).

In an elegantly designed study reported several years ago, Maynard et al. (66) 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 PIGF concentrations similar to that observed in the preeclamptic patients. The authors (66) also showed that sFlt-1 impaired VEGF- and PIGF-induced vasorelaxation. Subsequently, similar observations using adenovirus transfection have been reported in the mouse (60). Recently, we have developed a model of increased circulating sFlt-1 in pregnant rats using recombinant sFlt-1 delivered via osmotic minipump placed intraperitoneally and found that the dams are hypertensive, have smaller placentae and fetuses, are proteinuric, and show evidence of impaired vascular function on day 18 of gestation (J. P. Granger, unpublished observations). Although these studies have established the importance of sFlt-1 as an important preeclamptic factor, further studies are needed to elucidate mechanisms governing the expression and actions of this protein.
Recently, Li and coworkers (53) showed that VEGF infusion attenuates the increased blood pressure and renal damage observed in pregnant rats overexpressing sFlt-1. Thus, from this study, it can be gleaned that sFlt-1 plays a role in the hypertension and renal dysfunction in preeclampsia; however, these observations did not shed any light on the matter of pathological sFlt-1 overexpression. To this end, we have recently demonstrated that uteroplacental ischemia increased plasma and placental sFlt-1, and this is associated with decreased VEGF and PlGF in the late gestation pregnant rat (30) (Fig. 6). Similarly, Makris and colleagues (61) have reported that uteroplacental ischemia increases sFlt-1 in the baboon as well.

Recent work investigating sEng has furthered progress with respect to the role of antiangiogenic factors in preeclampsia (108). Venkatesha et al. (108) have shown that sEng inhibits in vitro endothelial cell tube formation to a similar extent as sFlt-1. Furthermore, the authors reported in vivo data in the pregnant rat, indicating that an 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 (108). Thus there is compelling experimental evidence that compliments the clinical observations that sEng is an important factor in the pathogenesis of preeclampsia.

**Metabolic factors.** There are other comorbid conditions that have been proposed as potential contributors to endothelial dysfunction in preeclampsia. Recent studies have indicated a relationship between elements of the metabolic syndrome such as elevated serum triglycerides and free fatty acids (40, 57), insulin resistance (14, 36, 62, 90, 118), and glucose intolerance (39, 98) and the occurrence of preeclampsia. In fact, several authors have suggested that insulin resistance may presage the manifestation of preeclampsia (98, 118), whereas Thadhani et al. (105) have proposed that insulin resistance during pregnancy may collude with other conditions such as impaired angiogenesis to generate a preeclamptic phenotype.

Fatty acids may contribute to endothelial dysfunction by serving as substrates to generate lipid peroxides that are significantly increased in plasma from women with preeclampsia (69). Therefore, the generation of free radicals, lipid peroxides, and reactive oxygen species may be an important mechanism contributing to endothelial dysfunction in preeclampsia (101). 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 (57, 58). This significantly increased plasma triglycerides in women with preeclampsia correlates with an increased plasma of concentrations low-density lipoproteins (84). The nature of this correlative data has provided difficulty in determining a causal effect for abnormal lipid metabolism in the pathogenesis of preeclampsia.

Because there was no definitive data indicating whether or not metabolic derangements were sequelae or potential contributors to placental ischemia, we recently tested this question in our RUPP model. Data obtained from the RUPP model suggest that metabolic derangements similar to the metabolic syndrome X are not a direct consequence of RUPP (31). Rather, it appears that factors associated with metabolic abnormalities may contribute to cardiovascular dysfunction in preeclampsia rather than resulting from poor placental perfusion (31). Further studies are underway to determine what influence obesity may exert during experimental placental ischemia.

**Summary**

Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia remain enigmatic. The initiating event in preeclampsia has been postulated to be reduced uteroplacental perfusion as a result of abnormal cytотrophoblast 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, thromboxane, and superoxide, increased vascular sensitivity to ANG II, and decreased formation of vasodilators such as NO and prostacyclin. These endothelial abnormalities, in turn, cause hypertension by impairing renal-pressure natriuresis and increasing total peripheral resistance (summarized in Fig. 1). The quantitative importance of the various endothelial and humoral factors in mediating vasoconstriction and increased arterial pressure during preeclampsia remains unclear.

Although recent studies support a role for angiogenic factors, the AT1-AA, cytokines, and other factors as potential mediators of endothelial dysfunction, finding the link between placental ischemia and maternal endothelial and vascular abnormalities remains an important area of investigation. Microarray analysis of genes within the ischemic/hypoxic placenta of women with preeclampsia and in animal models of preeclampsia should provide new insights into novel factors that may provide additional links between placental ischemia/hypoxia and hypertension. More effective strategies for the prevention of preeclampsia should be forthcoming once the underlying pathophysiological mechanisms that are involved in preeclampsia are completely understood.

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