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

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Invited 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 (32). 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.

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Placental ischemia and cardiovascular dysfunction during pregnancy

Reduced Uterine Perfusion Pressure as a Model to Study the Pathophysiology of Hypertension During Pregnancy

Fig. 1. Pathways by which reduced uterine perfusion pressure (RUPP) and placental ischemia may lead to endothelial and cardiovascular dysfunction during pregnancy. Placental ischemia results in increased synthesis of soluble fms-like tyrosine kinase-1 (sFlt-1), TNF-α and IL-6, angiotensin II type 1 receptor autoantibodies (AT1-AA), and thromboxane (TX). Elevations in these factors are proposed to result in endothelial dysfunction by decreases in bioavailable nitric oxide (NO) and increased reactive oxygen species (ROS) and endothelin-1 (ET-1), which in turn results in altered renal function, increased total peripheral resistance (TPR), and ultimately hypertension. PIGF, placental growth factor.

Perhaps the most prominent molecule postulated to play a key role in the pathogenesis of preeclampsia is sFlt-1. Several lines of evidence (15, 41, 42, 47, 50, 51, 74, 93, 103, 104, 117) support the hypothesis that the ischemic placenta contributes to endothelial cell dysfunction in the maternal vasculature by inducing an alteration in the balance of circulating levels of angiogenic/angiogenic factors such as vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and sFlt-1. Although recent data suggest that circulating sFlt-1 concentrations may presage the clinical onset of preeclamptic symptoms (47, 51, 75, 106), several studies indicate that placental hypoxia and poor placental perfusion may initiate this imbalance of angiogenic factors (61, 71). Nevertheless, it remains unclear whether impaired placental perfusion initiates preeclamptic symptoms such as hypertension, endothelial dysfunction, and increased sFlt-1 or whether inadequate placental development occurs initially and is followed by a pathological rise in sFlt-1 expression and secretion (41).

Hypertension associated with preeclampsia develops during late pregnancy and remits after delivery or termination of the pregnancy, suggesting that the placenta is a central culprit in the disease. The foremost hypothesis regarding the initiating event in preeclampsia is postulated to be reduced placental perfusion that, in turn, leads to widespread dysfunction of the maternal vascular endothelium. Although numerous other factors including genetic, immunological, behavioral, and environmental influences have been implicated in the pathogenesis of preeclampsia (95, 96), the main focus of this review is to describe the links between placental ischemia/hypoxia and the cardiovascular dysfunction that is widely recognized as a part of the preeclampsia syndrome.

Reduced Uterine Perfusion Pressure as a Model to Study the Pathophysiology of Hypertension During Pregnancy

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 protein 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 PlGF (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, decreased 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 nitrite/nitrate 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

![Graph](http://ajpheart.physiology.org/Downloadedfrom)
may result from interactions between the maternal component that may include preexisting conditions such as obesity, diabetes, and hyperlipidemia and/or the placental component that may involve secretion of lipid peroxides (79).

Several important antioxidants are significantly decreased in women with preeclampsia. Vitamin C, vitamin A, vitamin E, β-carotene, glutathione levels, and iron-binding capacity are lower in the maternal circulation of women with preeclampsia than in women with a normal pregnancy. Interestingly, supplementation does not appear to ameliorate the incidence of preeclampsia in multicenter clinical trials (73, 83). Reduced superoxide dismutase (SOD) levels and decreased SOD activity have been reported in neutrophils and placentas of women with preeclampsia (113). The decrease in SOD levels and activity in women with preeclampsia is important as diminished oxidative stress in placental villi (27). Thus endothelin may have additional effects on the maternal cardiovascular system not only by direct actions on the vasculature but also indirectly via oxidative stress.

Previously, we have investigated the role of endothelin in mediating RUPP hypertension in conscious, chronically instrumented pregnant rats (11). Furthermore, we have shown that RUPP elicits increased renal cortical and medullary expression of preproendothelin and that chronic administration of the selective endothelin type A (ET₄) receptor antagonist (ABT-627, 5 mg·kg⁻¹·day⁻¹ for 10 days) markedly attenuates the increased mean arterial pressure in these rats (11). In contrast, ET₄ receptor blockade had no significant effect on blood pressure in the normal pregnant animal, suggesting that ET-1 plays an important role in mediating the hypertension produced by chronic RUPP pregnant rats (11). Furthermore, recent work in our laboratory has shown that sera from pregnant rats exposed to chronic RUPP increase ET-1 production by cultured endothelial cell and that this increase is mediated via the AT₁ receptor (82). Although the exact mechanism linking enhanced production of ET-1 to placental ischemia in pregnant rats or in preeclamptic women remains unknown, possibilities include the production of an agonistic AT₁-AA and/or increased TNF-α as we shall describe later.

Arachidonic acid metabolites. Several lines of evidence suggest that changes in the metabolites of arachidonic acid may play a role in mediating the renal dysfunction and increase in arterial pressure during preeclampsia (114). Significant alterations in the balance of prostacyclin and thromboxane production occur 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.

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). 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 the renal cortex normally observed in the RUPP rat (55). Nevertheless, experimental data are limited in this area, and the quantitative importance of prostaglandins in mediating long-term reduction in renal hemodynamics and increased arterial hypertension (89), suggesting that there may be other pathways generating reactive oxygen species in this model. Although oxidative stress is implicated in the pathogenesis of preeclampsia, it remains unclear whether it is a primary or secondary mediator of increased blood pressure and deranged renal function.

Endothelin. Another endothelial-derived factor that may play a role in preeclampsia is the vasoconstrictor endothelin-1 (ET-1) (63, 67, 102). Since endothelial damage is a known stimulus for ET-1 synthesis, increases in the production of endothelin may participate in the pathophysiology of preeclampsia (12). Furthermore, ET-1 is also reported to increase oxidative stress in placental villi (27). Thus endothelin may play a role in preeclampsia, it remains unclear whether it is a primary or secondary mediator of increased blood pressure and deranged renal function.

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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 monotocyte 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 vasocostriction 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 a potent mediator 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 endothein, 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 PlGF 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 PlGF 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 PlGF) 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 PI GF concentrations similar to that observed in the preeclamptic patients. The authors (66) also showed that sFlt-1 impaired VEGF- and PlGF-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 pre-eclampsia 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 cytortrophoblast 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 placaenta 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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