Placental ischemia during preeclampsia is thought to lead to widespread activation/dysfunction of the maternal vascular endothelium. This results in enhanced formation of endothelin and thromboxane and decreased formation of nitric oxide and prostacyclin. These endothelial abnormalities, in turn, cause hypertension by impairing renal pressure natriuresis and increasing total peripheral resistance.

Preeclampsia is estimated to affect 7–10% of all pregnancies in the U.S. (6). Despite being one of the leading causes of maternal death and a major contributor to maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia are unclear. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the disease. An initiating event in preeclampsia has been postulated to be reduced placental perfusion that leads to widespread dysfunction of the maternal vascular endothelium by mechanisms that remain to be defined (6, 15, 16). The mechanisms leading to reduced placental perfusion in preeclampsia may be multiple, but most studies in humans suggest abnormal cytotrophoblast invasion of spiral arterioles as an important factor (6, 15, 16).

Several lines of experimental evidence support the hypothesis of the placenta as a central culprit in preeclampsia. For example, studies in various animal models, including sheep, dog, rabbit, and rat, have shown that reductions in uteroplacental blood flow can lead to a hypertensive state that closely resembles preeclampsia in women (8). Additional support for this concept derives from studies in humans with preeclampsia that indicate increased circulating levels of fibronectin and von Willebrand factor, both markers of endothelial cell injury (15, 16). Decreases in the production of endothelial-derived relaxing factors, such as nitric oxide (NO) and prostacyclin, increased production of endothelin and thromboxane, and enhanced vascular reactivity to angiotensin II (ANG II) in women with preeclampsia also suggest abnormal endothelial function (15, 16).

During normal pregnancy, significant changes in cardiovascular and renal function occur to meet the metabolic needs of the mother and the fetus. For example, maternal cardiac output and blood volume increase by ~40–50% while total peripheral resistance and arterial blood pressure decrease (6). In addition, there are marked changes in renal function such as elevations in renal plasma flow and glomerular filtration rate. Renin concentration, renin activity, and ANG II levels are elevated; however, the vascular responsiveness to ANG II appears to be reduced (6). The mechanisms that are involved in mediating these significant cardiovascular and renal changes during pregnancy have been studied extensively, and judging from animal studies it appears that endothelial factors such as NO play an important role (4, 7, 17).

The marked hemodynamic and renal changes that normally occur during pregnancy do not manifest themselves in women who develop preeclampsia. Instead, preeclampsia is associated with significant elevations in total peripheral resistance, enhanced responsiveness to ANG II, and marked reductions in renal blood flow and glomerular filtration rate and proteinuria compared with normal pregnancy (1). Although the physiological mechanisms that mediate the alterations in cardiovascular and renal function have been extensively studied during normal pregnancy in animal models, information regarding the mediators of the reduction in renal and cardiovascular function during preeclampsia has been limited because of the difficulty in performing mechanistic studies in pregnant women. Although several animal models have been developed to study preeclampsia, information on the mechanisms involved in mediating the long-term reduction in kidney function and increase in arterial pressure is lacking. Experimental induction of chronic uteroplacental ischemia appears to be the most promising animal model to study potential mechanisms of preeclampsia since reductions in uteroplacental blood flow in a variety of animal models lead to a hypertensive state that closely resembles preeclampsia in women (1, 8).

Chronic reductions in uteroplacental perfusion pressure in gravid rats after 14 days of gestation, as reported by Eder and MacDonald (11), lead to significant increases in arterial pressure and proteinuria. We have recently begun to work with this model to examine potential pathophysiological mechanisms that mediate the hypertension during chronic reductions in uteroplacental perfusion pressure (3). We reduced uterine perfusion pressure in the gravid rat at day 14 of gestation by ~40% by placing a silver clip around the aorta below the renal arteries. Because this procedure has been shown to cause an adaptive increase in uterine blood flow via the ovarian artery, we also placed a silver clip on both the right and left uterine arcades at the ovarian end just before the first segmental artery. We found that reducing uteroplacental perfusion with this approach results in significant and consistent elevations in arterial pressure of 20–30 mmHg compared with control pregnant rats at day 19 of gestation (Fig. 1). Our data also indicate that this hypertension is associated with proteinuria, reductions...
in renal plasma flow and glomerular filtration rate, and a hypertensive shift in the pressure natriuresis relationship. Moreover, our data indicate that endothelial function (Fig. 2) is significantly altered in response to chronic reductions in uteroplacental perfusion pressure in the pregnant rat (10). Finally, we have found intrauterine growth restriction in response to chronic reductions in uteroplacental perfusion pressure in the pregnant rat since the average pup size in this group is smaller than in normal pregnant rats (3). Thus a chronic reduction in uteroplacental perfusion pressure in the pregnant rat has many of the features of preeclampsia in women. The role of various endothelial, autacoid, and hormonal factors in mediating the reduction in renal hemodynamic and excretory function and elevation in arterial pressure produced by chronic reductions in uteroplacental perfusion pressure will be the main focus of the remaining portion of this brief review.

Vascular mediators of preeclampsia

NO. One potential mechanism for the elevation in arterial pressure in response to a chronic reduction in uteroplacental perfusion pressure in the pregnant rat is a reduction in renal NO synthesis (7). Studies from our laboratory (1) and others (7, 17) have indicated that NO plays an important role in the regulation of renal function and arterial pressure under various physiological and pathophysiological conditions (1). Of possible relevance to preeclampsia is the finding that reducing NO synthesis causes a hypertensive shift in the pressure natriuresis relationship.

Substantial evidence indicates that NO production is elevated in normal pregnancy (17). Plasma and urinary levels of cGMP, the second messenger of NO, increase during pregnancy in rats (7, 17). Marked increases in 24-h urinary nitrate/nitrite excretion have also been reported during normal pregnancy in the rat (7, 17). Increases in NO production appear to play an important role in the renal vasodilatation of pregnancy (7, 17). Recent studies by Conrad and others clearly demonstrated that the renal vasodilatation in the pregnant rat is due to an increased NO production (17). Because NO appears be an important physiological vasodilator in normal pregnancy, NO deficiency during preeclampsia might be involved in the disease process. Studies from several laboratories have found that chronic NO synthase inhibition in pregnant rats produces a hypertension associated with peripheral and renal vasoconstriction, proteinuria, intrauterine growth retardation, and increased fetal morbidity, a pattern that closely resembles the symptoms of human pregnancy-induced hypertension (7). However, whether there is a reduction in NO production during pregnancy-induced hypertension is unclear. Much of the uncertainty originates from the difficulty in directly assessing the activity of the NO system in a clinical setting (7). Assessment of whole body NO production via measurement of 24-h nitrate/nitrite excretion has yielded variable results due to difficulties in controlling for factors such as nitrate intake. In fact, in one study in which nitrate intake was controlled, nitrate/nitrite excretion was not elevated (17). We have recently reported that normal pregnancy in the rat is associated with significant increases in whole body NO production and renal protein expression of neuronal and inducible NO synthase (4). We also recently determined whether whole body and renal NO production is reduced in a rat model of preeclampsia produced by chronically reducing uterine perfusion pressure (3). Chronic reductions in uterine perfusion pressure resulted in increases in arterial pressure of 20–25 mmHg as well as decreases in renal plasma flow and glomerular filtration rate but no difference in urinary nitrate/nitrite excretion relative to control pregnant rats. In contrast, reductions in uterine perfusion pressure in virgin rats resulted in no significant effects on arterial pressure. The results of this study indicated that the increase in arterial pressure observed in response to chronic decreases in uterine perfusion pressure in pregnant rats is associated with no change in whole body NO production and a decrease in renal protein expression of neuronal NO synthase. Whether the reduction in renal protein expression of neuronal NO synthase occurs as a result of the hypertension or whether the reduction in renal protein expression of neuronal NO synthase plays a role in mediating the reduction in renal hemodynamics and elevation in arterial pressure remains to be determined.

Endothelin. Another endothelial-derived factor that may play

![FIGURE 1](http://physiologyonline.physiology.org/) Mean arterial pressure and urinary protein excretion responses to chronic reductions in uterine perfusion pressure (RUPP) in pregnant rats. All data are expressed as means ± SE.

![FIGURE 2](http://physiologyonline.physiology.org/) Vascular responses to acetylcholine (ACh) are reduced in pregnant rats with chronic RUPP. All data are expressed as means ± SE.
a role in preeclampsia is the vasoconstrictor endothelin. Since endothelial damage is a known stimulus for endothelin synthesis, increases in the production of endothelin may participate in preeclampsia. Plasma concentration of endothelin has been measured in a number of studies involving normal pregnant women and women with pregnancy-induced hypertension (6). Most investigators have found higher plasma concentrations of endothelin of approximately two- to threefold in women with preeclampsia. Typically, plasma levels of endothelin are highest during the latter stage of the disease, suggesting that endothelin may not be involved in the initiation of preeclampsia but rather in the progression of disease into a malignant phase. Although the elevation in plasma levels of endothelin are only two- or threefold above normal during preeclampsia, we found that this level of plasma endothelin can have significant long-term effects on systemic hemodynamics and arterial pressure regulation (18). Thus long-term elevations in plasma levels of endothelin comparable with those measured in patients with preeclampsia could play a role in mediating the reductions in renal function and elevations in arterial pressure observed in women with preeclampsia.

Although some studies have reported no significant changes in circulating levels of endothelin during pregnancy-induced hypertension, a role for endothelin as a paracrine or autocrine agent in preeclampsia remains worthy of consideration. We recently examined the role of endothelin in mediating the hypertension in response to chronic reductions in uterine perfusion pressure in conscious, chronically instrumented pregnant rats (5). Renal expression of preproendothelin was significantly elevated in both the medulla and in the cortex of the pregnant rats with chronic reductions in uterine perfusion pressure compared with control pregnant rats. Chronic administration of the selective endothelin type A receptor antagonist (ABT-627, 5 mg·kg\(^{-1}\)·day\(^{-1}\) for 10 days) markedly attenuated the increase in mean arterial pressure observed in the pregnant rats with chronic reductions in uterine perfusion pressure (Fig. 3). However, endothelin type A receptor blockade had no significant effect on blood pressure in the normal pregnant animals. These findings suggest that endothelin plays a major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure in pregnant rats.
in uterine perfusion pressure in pregnant rats (2). Chronic oral administration of a converting enzyme inhibitor (Enalapril, 250 mg·l⁻¹·day⁻¹ for 6 days) decreased mean arterial pressure to a similar extent in pregnant rats with reduced uterine perfusion pressure and normal pregnant rats. Blockade of the renin-angiotensin system, however, had no significant effect on the blood pressure response to chronic reductions in uterine perfusion pressure since the differences in blood pressures between the normal pregnant rats and rats with reduced uterine perfusion pressure were similar in control and converting enzyme inhibitor-treated groups. These findings suggest that the renin-angiotensin system does not play a major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure in pregnant rats (2).

Is maternal endothelial activation/dysfunction in preeclampsia due to enhanced cytokine production in response to placental ischemia?

Although reductions in blood flow to the uteroplacental unit are known to result in cardiovascular and renal abnormalities consistent with the pathophysiological features of human preeclampsia, the physiological mechanisms linking placental ischemia with abnormalities in the maternal circulation are unclear (6, 16). 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 tumor necrosis factor-α (TNF-α) (9). TNF-α is an inflammatory cytokine that has been shown to induce structural and functional alterations in endothelial cells (17). TNF-α also enhances formation of a number of endothelial cell substances such as endothelin and reduces acetylcholine-induced vasodilatation (9). TNF-α has been shown to directly induce 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 because 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 in women with preeclampsia by about twofold (9). Furthermore, interleukin-6, which is activated by TNF-α, is also elevated in preeclamptic women (9). Although high levels of TNF-α, as observed during septic shock or after lipopolysaccharide (LPS) administration, activate gene expression of inducible NO synthase, modest levels of TNF-α have been shown to destabilize the mRNA of endothelial NO synthase (9).

Whether chronic and modest increases in plasma TNF-α can activate the endothelium during pregnancy and lead to reduced kidney function, high blood pressure, and other features of preeclampsia is unknown. Consistent with a potential role of cytokine activation in preeclampsia is a recent study demonstrating that an intravenous infusion of a very low dose of LPS resulted in significant and long-term increases in blood pressure and urinary albumin excretion and significant platelet aggregation in conscious pregnant rats (12). Although LPS is known to activate TNF-α, it is unclear whether the effects of low-dose LPS on cardiovascular and kidney function were

FIGURE 4. Potential mechanism whereby chronic reductions in uteroplacental perfusion may lead to hypertension. ET, endothelin; TBX, thromboxane; NO, nitric oxide; PG, prostaglandin; ANG, angiotensin.
mediated via TNF-α and/or interleukin-1 since these cytokines were not measured in that study.

Although plasma levels of TNF-α are elevated by two- to threefold in women with preeclampsia, the importance of TNF-α in mediating the systemic and renal hemodynamic changes associated with this disease is unclear. To determine the long-term effects of a two- to threefold elevation in plasma TNF-α on renal and systemic hemodynamics in pregnant rats, we recently infused TNF-α for 5 days at a rate of 50 ng/day during days 14–19 of gestation in pregnant rats (13). Plasma levels doubled in the TNF-α-treated pregnant rats. Arterial pressure was significantly higher in the TNF-α-treated pregnant rat compared with pregnant controls at day 19 of gestation. A twofold elevation in plasma TNF-α in pregnant rats also caused a significant reduction in renal hemodynamics. These data suggest that elevated plasma levels of TNF-α observed in preeclamptic women may play an important role in the pathogenesis of preeclampsia.

Although these preliminary findings with TNF-α support the cytokine hypothesis, 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 placenta of women with preeclampsia and in animal models of chronic reductions in uterine perfusion pressure should provide new insights into the link between placental ischemia 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.

References