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Endothelial dysfunction; an important mediator in the Pathophysiology of Hypertension during Preeclampsia

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Abstract

Preeclampsia is defined as new onset hypertension with proteinuria during pregnancy. It affects approximately 5% of pregnancies in the US with a subset of those progressing into more severe forms of the disease, known as HELLP or eclampsia. Preeclampsia is associated with intrauterine growth restriction, chronic immune activation and multi-organ endothelial dysfunction thus contributing to the clinically visible elevation in maternal blood pressure. The end result is increased infant and maternal morbidity and mortality thereby contributing to the gross health care expenditure nationwide. Although the underlying cause of this disease still unknown, the most well accepted hypothesis is that placental ischemia/hypoxia results from inadequate uteroplacental vascular remodeling, which leads to a decrease in placental blood flow. The ischemic placenta releases factors such as the soluble VEGF receptor-1 (sFlt-1), the angiotensin II type-1 receptor autoantibody (AT1-AA), and cytokines such as TNF-α and Interleukin 6 which cause maternal endothelial dysfunction characterized by elevated circulating endothelin (ET-1), reactive oxygen species (ROS), and enhanced vascular sensitivity to angiotensinII. These factors act in concert to decrease renal function and cause hypertension during pregnancy. Understanding the link between placental ischemia, endothelial dysfunction and hypertension during pregnancy will lend to better prediction, prevention and treatment strategies for women and children stricken by this devastating disease.

Introduction

Most recently exciting new insights have been gained into potential mechanisms underlying the pathogenesis of hypertension and local endothelial dysfunction during preeclampsia. While numerous factors including genetic, immunological, behavioral, and environmental influences have been implicated in the pathogenesis of preeclampsia, the main focus of this review of the most recent obstetric literature is to highlight studies that link endothelial dysfunction and hypertension in preeclampsia (1–11). The pathophysiologic processes that underlie preeclampsia was proposed by Roberts and colleagues to occur in two stages: stage 1, reduced placental perfusion, and stage 2, the maternal clinical syndrome (1,4). Placental ischemia/hypoxia is believed to result in the release of a variety of factors that have profound effects on endothelial function and arterial blood flow and blood pressure regulation (1, 4, 10, 11). This review will highlight old and new players in the pathology of endothelial dysfunction during preeclampsia as well as review the role of these players to mediate pathophysiology observed in the preeclampsia rat model of reduced placental perfusion (RUPP).

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Previously defined factors include a host of molecules such as the soluble VEGF receptor-1 (sFlt-1), soluble endoglin, the angiotensin II type-1 receptor autoantibody (AT1-AA), and cytokines such as TNF-α which in turn generate widespread dysfunction of the maternal vascular endothelium (1–11). More recent players are thought to include metabolic and dietary factors, hypoxia stimulated COMT or 2ME and/or HO-1 deficiency and increased immune cells and molecules. Endothelial dysfunction manifests as enhanced formation of factors such as endothelin, reactive oxygen species (ROS) and increased vascular sensitivity to angiotensin II (1–11). In addition, preeclampsia is also associated with decreased formation of vasodilators such as nitric oxide and prostacyclin (1–11). These alterations in vascular function not only lead to hypertension but multi-organ dysfunction, with the potential to progresses into eclampsia or HELLP syndrome (1,4, 11–20). Identifying the connection between placental ischemia/hypoxia and maternal cardiovascular abnormalities remains an important area of investigation as preeclampsia, HELLP or eclampsia are the leading cause of maternal death and perinatal morbidity (1,10,11–21).

Endothelial dysfunction of the vasculature, liver and brain during preeclampsia

The maternal vascular endothelium appears to be an important target of factors triggered during preeclampsia (1, 2, 4, 10, 11). Both endothelium-derived relaxing and contractile factors play an important role in the regulation of arterial compliance, vascular resistance and blood pressure. When abnormalities in the production or action of these factors occur, the vasculature is predisposed to vasoconstriction, leukocyte adherence, oxidative stress and vascular inflammation (1, 2, 4). Once immune cells adhere to the activated vascular endothelium a series of cellular interactions occur inducing junction widening between cells and allowing immune cell infiltration into the vascular wall thereby invading local tissues(13). As a result the endothelium becomes leaky allowing for extravasation of fluid, recognized clinically as edema. Therefore, markers of endothelial dysfunction may serve as predictors of the syndrome in women that develop preeclampsia since many are often elevated weeks prior to observance of clinical manifestations (5–9, 14). Such markers include Endothelin-1, soluble vascular adhesion molecule and interleukin-8, ELAM-, or endothelial leukocyte adhesion molecule-1.

An important marker of endothelial activation is an endothelial-derived factor that may play a role in preeclampsia is the vasoconstrictor, endothelin-1 (ET-1). While some studies have reported no significant changes in circulating levels of ET-1 during moderate forms of preeclampsia, a possible role for ET-1 in preeclampsia remains worthy of consideration (11,12,14–16). Since ET-1 is released towards the vascular smooth muscle changes in plasma levels of ET may not reflect its local production thereby making it difficult to ascertain whether preeclampsia is associated with altered ET production. However, local synthesis of ET has been assessed in preeclamptic women and investigators have found preproendothelin mRNA to be elevated in a variety of tissues (11,12,14–16). Because of the limitations of clinical studies utilizing selective ET type A receptor antagonists in pregnant women, the importance of locally produced ET in the pathophysiology of preeclampsia remains unclear, however in multiple animal models emulating preeclampsia which will be discussed in this review, the ET-1 system appears to be a common pathway linking endothelial dysfunction with elevation in blood pressure during pregnancy (17–23).

Vascular manifestations of endothelial dysfunction may also affect the maternal liver and brain in severe forms of the disease(24–29). Approximately 20 % of preeclamptic patients develop HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). These women present with abdominal pain, nausea, vomiting, elevated liver enzymes and examination of the liver indicates periportal and sinusoidal fibrin deposits (24). More extreme cases present

with placental abruption, hepatic infarction, rupture, hemorrhage and necrosis, acute renal failure and intra-abdominal bleeding, thereby resulting in maternal death. Management of HELLP is prophylactic magnesium sulfate.

Brain injury which occurs in eclampsia is defined by the presence of seizures (25–29). Eclampsia is characterized by vascular spasm throughout the body, decreased liver function and kidney output, extreme hypertension and in severe cases progresses to coma. Eclampsia is associated with edema and posterior reversible encephalopathy syndrome (PRES). These cerebral manifestations include hemorrhage and stroke which cause of the majority of eclamptic deaths. We have recently investigated the efficacy of various therapeutic agents facilitating patient recovery and have found a trend toward shorter recovery times when corticosteroids were used to supplement magnesium sulfate, suggesting a role for steroids to facilitate healing in eclamptic PRES patients (28,29).

Renal dysfunction is the underlying cause of increased blood pressure and proteinuria during hypertensive disorders. Normal pregnancies progress with increased renal blood flow in order to excrete excess fluid volume doubling during development of uteroplacental unit. However, during preeclampsia both renal blood flow and glomerular filtration rate are decreased. The renal pathology of preeclampsia and the more severe forms of the disease are characterized by thickening of the renal glomerular tufts with protein deposits in the basement membrane and accumulation of extracellular fluid. This leads to an increased blood pressure in attempts maintain body fluid homeostasis and begins a vicious cycle characterized by protein in the urine, hypertension, endothelial dysfunction and edema in the preeclamptic woman(1–16).

Important mediators of endothelial dysfunction during preeclampsia

Inflammatory mediators of Endothelial dysfunction

CD4+ T helper lymphocytes—Preeclampsia is associated with chronic immune activation and many of these factors have been shown to play a role in mediating endothelial dysfunction during pregnancy(10, 11, 18–21, 23, 30–39). Most recently we have demonstrated a role for $CD4^+$ T cells to be important players in the development of endothelial dysfunction in response to placental ischemia induced by reductions in uterine perfusion pressure (RUPP) (33, 34). We have recently shown that RUPP induced CD4+ Tcells adoptively transferred into normal pregnant rats increase blood pressure and decrease glomerular filtration rate (34). Furthermore, this hypertension is accompanied by elevated TNFα and sFlt-1 and AT1-AA in normal pregnant recipient rats of RUPP $CD4^+$ T cells (33, 34). Previous studies have shown an important role for ET_A receptor blockade in attenuating hypertension in response to placental ischemia, and elevated TNFα, sFlt-1 and AT1-AA (17,18,20–23,35,36,37). Furthermore, in unpublished data, by administrating an ET_A receptor antagonist to NP recipient rats of RUPP $CD4^+$ T cells we were able to attenuate the elevated blood pressure increase, indicating the importance of activation of the endothelin-1 system to mediate hypertension in response to inflammatory CD4+ T cells (37). We found that circulating factors were released in response to adoptive transfer of RUPP $CD4^+$ T cells that stimulated vascular ET-1 from endothelial cells similar to what as had been previously shown in RUPP controls and in preeclamptic women (18,37,38,39). These data suggest that circulating factors in response to elevated CD4+ Tcells activated during placental ischemia may be important in causing endothelial cells to secrete ET-1, a marker of endothelial activation and dysfunction, similarly to that of sera from RUPP rats or preeclamptic women.

Activating autoantibodies to the angiotensin II type I receptor

Recent studies in preeclamptic women demonstrate increased circulating concentrations of an agonistic autoantibody to the angiotensin type 1 receptor (AT1-AA) (40–47). In addition to being elevated during preeclampsia, the AT1-AA has also been reported to be increased in postpartum women. Hubel and colleagues demonstrated that the AT1-AA does not regress completely after delivery and that the increase in AT1-AA correlated with insulin resistance and sFlt-1 (43). The importance of AT1-AA after preeclampsia, especially in the context of increased cardiovascular risk, remains to be determined.

Interestingly, the AT1-AA appear to be responsible for a variety of effects in several different tissues ranging from increased intracellular Ca^{++} mobilization to monocyte activation and stimulation of IL-6 production from mesangial cells (40–42). Another effect that has recently been attributed to the AT1 receptor is stimulation of sFlt-1 expression from trophoblast cells (40–42). While 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 increases blood pressure during pregnancy remain unclear.

Dechend and colleagues (42, 44) used the cardiomyocyte contraction assay to detect the presence of AT1 agonistic antibody in pregnant transgenic rats overexpressing components of the human renin angiotensin system. Peptide competition experiments showed that the antibody interacted with the same seven amino acid epitope on the second extracellular loop of the AT1 receptor defined by AT1-AA obtained from women with preeclampsia.

We have shown that placental ischemia in pregnant rats is associated with increased circulating levels of the AT1-AA (48,49) and that chronic elevation of TNF alpha or IL-6 in pregnant rats stimulates increased production of the AT1-AA, however have no effect in non pregnant rats (48–50). Moreover, we found that the hypertension in response to placental ischemia, elevated TNF alpha or IL-6 in pregnant rats was markedly attenuated by antagonism of the AT1 receptor.

Furthermore, we have demonstrated that increasing levels of AT1-AA to levels observed in preeclamptic women and in placental ischemic rats, increased mean arterial pressure (MAP) in pregnant rats by activation of the endothelin system (23). We reported that infusion of purified rat AT1-AA into normal pregnant rats, increased serum AT1-AA, blood pressure, and tissue levels of preproendothelin. Furthermore, AT1-AA-induced hypertension in pregnant rats was attenuated by either oral administration of the AT1 receptor antagonist losartan or an ET type A receptor antagonist. In addition, the increase in endothelin transcript in response to AT1-AA induced hypertension was abolished by administration of an AT1 receptor antagonist. In a follow up study we examined the effect of the chronic AT1-AA to cause renal endothelial dysfunction in the renal interlobar artery (51). We found significant endothelial dysfunction that was prevented by chronic ETA receptor blockade. These studies we demonstrate that administration of the AT1-AA to pregnant rats significantly increased ET-1 levels in renal cortices and placenta of pregnant rats and causes endothelial dysfunction in the kidney as mechanisms of hypertension during pregnancy.

Most recently, we utilized the technique of B cell depletion (Rituximab) to suppress lymphocyte entry into the circulation and as a direct result, suppression of AT1-AA production in response to placental ischemia (49). RUPP rats treated with Rutiximab and having suppressed AT1-AA exhibited less blood pressure increase in response to induced placental ischemia. Furthermore, B cell depleted RUPP rats had lower tissue ET-1 transcript in renal cortices and placentas compared to RUPP control rats. Importantly, endothelial cells exposed to serum from B cell depleted, AT1-AA suppressed RUPP rats, secreted less ET-1

than endothelial cells exposed to control RUPP serum. Collectively, these data indicate an important role for AT1-AA stimulated in response to placental ischemia to contribute to the renal, placental and vascular endothelial dysfunction that we know to occur during hypertension during preeclmpasia.

Cytokines—Several groups have shown an important role for inflammatory cytokines in the etiology of preeclampsia (19,30–32,39,52,53). Freeman and colleagues examined changes in inflammatory markers prospectively during pregnancy and the current inflammatory status of women who had a pregnancy complicated by preeclampsia 20 years previously against matched controls and found that preeclampsia was associated with short- and long-term changes in inflammatory status (53). Other investigators have shown elevations in autoimmune cytokines such as IL17 and suggest that preeclampsia has similarities to autoimmune diseases (30–32).

While inflammatory cytokines such as IL-6, IL-17, 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 in blood pressure. However, we have shown that chronic infusion of TNF-α 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 (20,21,50,54). In addition, many laboratories have shown that TNF alpha activates endothelial cells in culture causing ET-1 secretion and increased sICAM which would lend to leukocyte adherence and migration into vascular tissues. (55,56)

Most recent studies have shown that that endothelial dysfunction may be induced by CD40/CD40 ligand. The CD40 antigen binds to the CD40 ligand on T cells and is active in B lymphocyte proliferation. A recent study compared the effect of maternal serum from preeclamptic patients and normal pregnant patients to induced apoptosis and CD40/Cd40 ligand expression (57). These authors found altered morphology, decreased cell growth and increased apoptosis with greater CD40/CD40 ligand expression following exposure to preeclamptic sera verses that from healthy normal pregnant women.

Nitric Oxide (NO)—NO production is significantly elevated in normal pregnancy and studies suggest that NO production plays an important role in the cardiovascular adaptations of pregnancy, thereby suggestind that NO deficiency could be playing an important role in disease progression of preeclampsia (11, 12, 27, 38, 33, 58–70). Much of the uncertainty in this area of research originates from the difficulty in directly assessing the NO activity in the clinical setting. Activity of the NO system has been assessed, however, in animal models of placental ischemia and cytokine excess(64–67, 70). Placental ischemia in pregnant rats has no effect on urinary nitrite/nitrate excretion relative to control pregnant rats (64,65). However, basal and stimulated release of nitric oxide from isolated vascular strips were significantly lowered in the RUPP pregnant rat (66). In a recent study by Murphy et al. (70) we examined whether NO availability affected ET synthesis and hypertension in response to excess sFlt-1 during pregnancy. In response to sFlt-1 induced hypertension glomerular NO production was decreased 70% compared to normal pregnant rats. Furthermore, L-Arginine supplementation attenuated the blood pressure response and local ET-1 excess in response to elevated sFlt-1 during pregnancy. These studies suggest that reductions in NO may be one contributor to endothelial activation and dysfunction as indicated by alterations in ET-1 production, during sFlt-1 induced hypertension.

Oxidative Stress—The normal immune response occurs with recruitment of leukocytes such as neutrophils to the site of infection as a major host defense mechanism against extracellular bacteria (13). At the site of recruitment stimulated neutrophilic release of

antimicrobial substances and/or phagocytosis of microbes and dead tissues. Macrophages and neutrophils convert molecular oxygen into reactive oxygen species by the phagocyte oxidase system catalyzed by the enzyme NADPH oxidase. Once neutrophils are activated they can cause injury to normal host tissues, such as the placental unit in the case of pregnancy related illnesses, by the release of lysosomal enzymes, reactive oxygen species or nitric oxide. Many studies have indicated that preeclamptic women have elevated oxidative stress within the placental unit measured by increased NADPH subunits as well as elevated urinary 8 isoprostanes as a measure of whole body oxidative stress (71–73).

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 (74). Interestingly, higher placental NADPH oxidase activity reported in women with early-onset preeclampsia as compared with those with late-onset of disease (74). Thus, there is considerable evidence to suggest that activation of NADPH oxidase plays an important role in the placental oxidative stress associated with preeclampsia.

In disease states of oxidative stress, an imbalance of pro-oxidant and anti-oxidant forces results in endothelial dysfunction, either by direct actions on the vasculature or through vasoactive mediators (68,69,70–76). During preeclampsia, oxidative stress may result from interactions between the maternal component which may include preexisting conditions such as obesity, diabetes, and hyperlipidemia, and/or the placental component which may involve secretion of lipid peroxides (70–76). Oxidative stress may mediate endothelial cell dysfunction and contribute to the pathophysiology of preeclampsia as there is evidence of increased pro-oxidant activity formation along with decreased anti-oxidant protection in preeclampsia. Superoxide dismutase (SOD) levels are decreased and reduced SOD activity reported in neutrophils and placentas of preeclamptic women (71). These authors emphasize the importance in this study was that diminished SOD occurs within both the maternal and placental components.

Various important anti-oxidants are significantly decreased in women with preeclampsia(68). Vitamin C, vitamin A, vitamin E, β-carotene, and glutathione are lower in the maternal circulation of women with preeclampsia than women with a normal pregnancy. These deficiencies in anti-oxidants may have important vascular effects in preeclampsia. It has been shown that moderate ascorbate deprivation increases mesenteric artery myogenic response during pregnancy which may result from a decrease in nitric oxide-mediated modulation of the myogenic contractile response (76). 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 (74). 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, intrauterine growth restriction, or the risk of death (77). In contrast, supplementation with vitamin C and vitamin E increased the rate of low birthweight babies therefore, the use of high dose vitamin C and vitamin E does not appear to be justified during preeclampsia(78).

Arachidonic acid metabolites—Significant alterations in the vasodilators prostacyclin and thromboxane occur during preeclampsia, (11,12,79). Experimental studies in animals have attempted to determine the role of arachidonic acid metabolites in response to placental ischemia. Hypertension produced by acute placental ischemia in pregnant dogs was prevented by thromboxane receptor antagonism (80). While urinary thromboxane B2 increased in response to RUPP in pregnant rats, acute administration of a thromboxane receptor antagonist failed to alter blood pressure (81). However, inhibition of cytochrome

P450 enzymes with 1-aminobenzotriazole (ABT) attenuated the hypertension, increased renal vascular resistance, 20-HETE formation and CYP4A expression in the renal cortex normally observed in the placental ischemic pregnant rat (82). Recent studies have shown that alteration in CYP4A enzymes effect vitamin D metabolism directly by destabilizing the biologically active form(83). Alterations in vitamin D metabolism have been suggested to play a role in hypertensive disorders of pregnancy. However, recently Powe et al demonstrated no significant differences occur in circulating first trimester Vitamin D or vitamin D binding protien between normal pregnant or preeclamptic patients (84). Nevertheless, the importance of arachidonic acid metabolites in the pathology of the disease or vitamin D metabolism during hypertensive pregnancies has yet to be elucidated.

Renin-Angiotensin System (RAS)—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 (40,85). In contrast, during preeclampsia there appears to be a marked increase in the sensitivity to Ang II (40,85). Although the mechanisms underlying these observations remain unclear, there is growing evidence to suggest that dysregulation of the tissue-based RAS is important in the pathophysiology of preeclampsia (85–87). Recent studies from our group indicate that the AT1-AA is in part responsible for increased endothelial cell and blood pressure sensitivity ANGII sensitivity (88). Endothelial cells increased ET-1 secretion in response to ANGII or to AT1-AA. However, when the AT1-AA and ANGII are combined endothelial cell ET-1 secretion is elevated 200 fold compared to ANGII or AT1-AA alone. Likwise, either ANGII or AT1-AA alone increased blood pressure during pregnancy. In chronic AT1-AA induced hypertensive pregnant rats, a bolus injection of ANGII increased blood pressure 20mmHg above that achieved with normal pregnant control rats. These studies indicate an important role for AT1-AA to enhance both endothelial cell and blood pressure sensitivity to ANGII during pregnancy.

Hypoxia stimulated factors causing endothelial dysfunction

Angiogenic factors

Placental hypoxia is thought to be a key player stimulating factors that act upon that maternal endothelium and thereby contribute to the maternal endothelial dysfunction associated with preeclampsia. HIf-1α is a transcription factor stimulated in response to hypoxia to mediate a multitude of hypoxia induced cellular activities (24). One protein regulated by HIf-1α is soluble tyrosine like kinase, sFlt-1, which binds to vascular endothelial growth factor and placental growth factor, having a negative impact on placental vascularity during preeclampsia. Both plasma and amniotic fluid concentrations of sFlt-1 are increased in preeclamptic patients, as well as placental sFlt-1 mRNA (40,89). Recently, studies have reported that increased sFlt-1 may have a predictive value in diagnosing preeclampsia as concentrations seem to increase before manifestation of symptoms (40,89). Several years ago, Maynard et al. (89)reported that exogenous administration of sFlt-1 into pregnant rats via adenoviral 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 (90). Furthermore, recent studies by Murhpy et al, indicate that one mechanism important to sFlt-1 induced hypertension is activation of the local ET-1 system (70). Sflt-1 induced hypertensive pregnant rats have elevated blood pressure and tissue sFlt-1. The blood pressure increase in response to sFlt-1 excess was attenuated by ETA receptor blockade, thereby indicating the importance of ET-1 acitivation and sFlt-1 induced endothelial dysfunction to mediate hypertension in response to elevated sFlt-1 .

An additional anti-angiogenic factor, soluble endoglin (sEng), has also been revealed as a factor in the pathogenesis of preeclampsia (91,92). Endoglin is a component of the 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 anti-angiogenic as it is thought to impair TGF-β1 binding to cell surface receptors. Venkatesha *et al*. 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 protien alone and caused in fetal growth restriction, hypertension and proteinuria, a phenotype similar to HELLP syndrome (92). Moreover, recent clinical evidence also suggests that sEng may also preceed the onset of preeclampsia (92).

An additional ramification of hypoxia following reduced uteroplacental blood flow could be decreased regulators acting on HIf-1α such as 2 methoxyestradiol (2ME) (24). Preeclamptic women exhibit decreased 2ME which could be an indicator of hypoxic events leading to elevated levels of HIf-1α. In a recent study genetically modified knockdown of catechol-O-methyltransferase (COMT) resulted in decreased 2ME during pregnancy thereby emulating preeclampsia. COMT knockout mice developed hypertension, proteinuria, elevated sFlt-1, and placental hypoxia, thereby indicating that altered HIf-1α regulation of hypoxia stimulated proteins leads to symptoms similar to those seen in preeclamptic women.

One additional regulator of sFlt-1 that has gained much attention of late is heme oxygenase (HO-1)(93,94). HO-1 produces two bioactive compounds, bilirubin and carbon monoxide, a powerful antioxidant acting as a vasodilator. In addition HO-1 has been shown to decrease sFlt-1. Studies from George et al demonstrated that HO-1 induction decreased sFlt-1 and oxidative stress in the preeclampsia RUPP rat model (94). In more recent studies by George et al, CO was shown to decrease hypoxia stimulated sFlt-1 and oxidative stress from cultured placental vascular bundles (93). In addition bilirubin significantly decreased hypoxia stimulated sFlt-1 from vascular bundles. Furthermore, addition of bilirubin to explants under either normal or hypoxic conditions decreased superoxide compare to hypoxic stimulated controls. These studies indicate the importance of further examination of HO-1 induced mechanisms as potential therapeutics for preeclampsia.

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 (95–99). 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 (95–99). 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 compared to normal pregnant women (96,97). This significantly increased plasma triglycerides in women with preeclampsia correlates with an increased plasma of concentrations low-density lipoproteins (98). Importantly, elevated LDL can lead to increased vascular oxidative stress and decreased bioavailability of NO. In a recent study by Morton et al tested the importance of LDL in response to placental ischemia (99). The authors found that LOX1 receptor, for LDL-1 was elevated in the RUPP preeclamptic rat model. These increased correlated to decreased vasodilator function in the RUPP thoracic aorta compared to normal pregnant rats. Furthermore, endothelial dysfunction was modestly improved in the presence of oxidized LDL and the LOX-1 receptor inhibitor indicating that this LDL and activation of LOX-1 receptors could contribute to endothelial dysfunction seen in response to placental ischemia.

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Figure 1. Role of reduced uterine blood flow in the development of hypertension during preeclampsia

Immunomodulators and anti-angiogenic factors stimulated in response to placental ischemia play an important role in causing endothelial dysfunction, generation of ROS, and enhanced ET-1 and ANG II sensitivity thereby contributing to the development of hypertension during pregnancy