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Recent insights into the pathophysiology of preeclampsia

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Abstract

Preeclampsia, characterized by new-onset gestational hypertension and proteinuria, is a common and serious complication of pregnancy. Evidence from both animal and human studies has implicated placental ischemia and hypoxia as a central causative factor in the etiology of the disorder. The ischemic placenta in turn initiates a cascade of secondary effector mechanisms, including altered proangiogenic and antiangiogenic factor balance, increase in maternal oxidative stress and endothelial and immunological dysfunction. The full elucidation of these mechanisms will hopefully lead to a more complete understanding of the etiology of preeclampsia and lead to successful therapeutic intervention through the targeted disruption of new and novel pathways.

Keywords

heme oxygenase-1; immunological dysfunction; placental ischemia; preeclampsia; reduced uterine perfusion pressure; sVEGF R1; VEGF

Preeclampsia is a pregnancy-specific disorder that is characterized by new-onset hypertension, proteinuria and vascular dysfunction presenting after the 20th week of gestation [1,2]. It remains a leading cause of maternal and fetal morbidity and mortality worldwide, and has been recognized as a contributor to future cardiovascular and metabolic dysfunction in affected offspring [3–5]. Currently, up to 15% of preterm births can be attributed to preeclampsia [6]. The incidence of preeclampsia is approximately 8%, although certain subpopulations experience much higher incidence rates, and the majority of cases occur in previously healthy nulliparous women, although multiparous women pregnant from a new partner have a similar incidence rate to nulliparous women [7,8]. Several of the known risk factors for preeclampsia are common with cardiovascular disease, such as chronic hypertension, renal disease and obesity [9,10], pointing to pre-existing vascular or endothelial dysfunction as a possible factor in at least a subset of affected women.

It is recognized that the source for the underlying pathophysiology of the disease is the placenta, as delivery of the placenta is the only effective intervention to reverse the syndrome, and there are reported cases in which delivery of the fetus alone failed to resolve the disorder [11,12]. The onset of the disease is postulated to occur in two stages. The first is

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a poorly understood error in the normal placentation process, which is maternally asymptomatic. The second is a widespread maternal multisystem disorder, which constitutes the symptomatic phase of the disease [13–15]. Recent research into both of these stages has revealed glimpses into the underlying origins of the disease and the mechanisms of the resulting maternal symptoms.

One important central mechanism of preeclampsia has been hypothesized to be placental ischemia/hypoxia. This in turn induces the effector mechanisms responsible for the maternal cardiovascular dysfunction, most notably oxidative stress, immunological dysfunction and an imbalance between proangiogenic and antiangiogenic factors.

Placental ischemia/hypoxia

In normal placentation, extensive angiogenesis is necessary to ensure adequate blood supply to the placenta and developing fetus. Fetal-derived extravillous trophoblasts invade the uterine arteries, undergo a shift from an epithelial phenotype to a more endothelial phenotype and, in the process, make direct contact with the maternal blood [16]. This in turn leads to conversion of the maternal spiral arterioles from small, high-resistance vessels into dilated, high-capacitance vessels [17,18]. During preeclampsia, examination of the placenta typically reveals shallow trophoblast invasion, and insufficient remodeling of the spiral arterioles [19,20]. In turn, the preeclamptic placenta, which is at least initially a hypoxic environment under normal circumstances, begins to exhibit overexpression of a number of hypoxia-regulated genes [21–23]. This has been linked in some studies to the failure of the trophoblasts to convert to an endothelial phenotype and express requisite cell-surface adhesion molecules, although other studies failed to observe this effect [16,24]. In turn, placental insufficiency and inadequate blood supply to the placenta and developing fetus can result [25].

It is unclear whether inadequate vascular remodeling is a primary or secondary cause of preeclampsia. Similar histological findings are seen in cases of placental insufficiency that do not lead to preeclampsia, so it is an open question as to what pre-existing conditions must be present for the manifestation of the maternal disorder [26]. In addition, although the mechanisms governing trophoblast differentiation and migration are becoming more clearly elucidated (for a review, see [27]), the reasons for trophoblast deficiency in preeclampsia remain obscure. Whatever the cause, it is generally accepted that the release of factors in response to insufficient placental perfusion is an important event in the manifestation of maternal symptoms [28].

One methodology that has proven to be of great use in investigating the role of placental ischemia and hypoxia in the pathophysiology of preeclampsia is that of reduced uterine perfusion. Early studies in dogs demonstrated that partial occlusion of the utero-ovarian arteries resulted in hypertension only upon pregnancy, which subsided postpartum [29]. Subsequent similar studies in rabbits demonstrated another hallmark of preeclampsia, increased peripheral resistance [30]. Most promisingly, a number of separate studies in the baboon and rhesus monkey have shown that in response to reduced uterine perfusion, primates also demonstrate hypertension, proteinuria and glomerular endotheliosis [31–34]. Recent use of rat models of placental insufficiency have also demonstrated its importance in the etiology of preeclampsia. Artificial restriction of uterine blood flow in rats by surgically constricting vessels feeding the uteroplacental unit results in hypertension, proteinuria, endothelial dysfunction and reductions in glomerular filtration rate [35,36]. It is clear, therefore, that placental ischemia/hypoxia is an important step in the pathophysiological manifestation of preeclampsia. These models provide a valuable tool for the identification of

pathological factors that are released in response to placental ischemia and underlie the symptomatic phase of the disorder.

Oxidative stress

Oxidative stress is known to affect the placenta during preeclampsia [37–39]. It is known that the imbalance of pro- and antioxidant factors during oxidative stress can result in severe endothelial dysfunction, either directly or indirectly through reduction in vasoactive mediators [40]. Human studies indicate that the decidua in preeclamptic women has significantly higher levels of lipid hydroperoxides and free isoprostane, a byproduct of free-radical peroxidation of arachidonic acid [41,42]. A number of oxidative stress markers have also been reported systemically in preeclamptic women, among these peroxynitrite. Peroxynitrite levels in the vascular endothelium were found at much higher levels in preeclamptic women versus normal gestation, concurrent with decreased superoxide dismutase (SOD) and nitric oxide synthase [43]. A separate study also demonstrated decreases in both SOD levels and activity in both neutrophils and placentas of preeclamptic women, indicating an overall decrease in antioxidant protection in preeclampsia [40].

In the reduced uterine perfusion pressure (RUPP) rat hypertensive model, there is also an increase in oxidative stress during gestation, suggesting a link between placental ischemia/hypoxia and the production of reactive oxygen species (ROS). Surprisingly, treatment with two different antioxidants, vitamins C and E, had no effect on gestational hypertension. The SOD mimetic drug Tempol, however, led to significant attenuation of the hypertensive response [44]. In a related study, administration of the NADPH oxidase inhibitor apocynin also significantly attenuated RUPP-induced gestational hypertension, implicating that enzyme as an important source of pathogenic ROS in the RUPP animal. Failure of the drug to fully normalize blood pressure, however, leaves open the possibility that alternative ROS production pathways are at work in the RUPP model [45]. Further studies into the mechanism of ROS production in animal models of preeclampsia should help shed further light on the importance of oxidative stress in the etiology of preeclampsia. It remains to be seen whether ROS production is a primary or secondary cause of preeclampsia pathophysiology, and how effective manipulation of the system will be in the search for effective therapies.

Immunological dysfunction

There is now a growing awareness that immunological dysfunction is an important factor in the pathogenesis of preeclampsia [46,47]. Several empirical lines of evidence suggest the possibility that autoimmunity might play a role in the etiology of the disorder. The first line of evidence is that nulliparous women are at a significantly higher risk of exhibiting preeclampsia than multiparous women [48]. There is also evidence suggesting that repeated exposure to paternal antigens from fetal or sperm cells creates immunological tolerance and reduces the risk of preeclampsia, but only if the subsequent pregnancies are produced with the same partner [49,50].

One of the most fascinating recent avenues of study in preeclampsia is the altered maternal inflammatory response. While it is well established that pregnancy alone sets off an increased maternal inflammatory response, in preeclamptic women the secretion of inflammatory cytokines is markedly increased [51,52]. In our RUPP model, we have demonstrated that circulating levels of IL-6 and TNF- α are elevated, results which are consistent with data from human subjects [53,54]. Furthermore, we have demonstrated that infusion of IL-6 or TNF- α to levels consistent with those seen in preeclamptic women lead to gestational hypertension in rats, with the latter possibly acting through induction of endothelin (ET)-1 expression [53,55,56]. We further showed that TNF- α blockade by the

soluble TNF- α receptor etanercept in the RUPP model partially abrogated the associated hypertension, and reduced tissue expression of ET-1 [54]. Together, these studies demonstrate the importance of the maternal inflammatory response in preeclampsia symptoms, and indicate an important class of targets for potential therapeutics. Recent work has demonstrated that the production of TNF- α and other inflammatory cytokines can be primed by circulating syncytiotrophoblast microparticles, which are elevated in preeclamptic women [57]. This provides yet another mechanism by which the maternal inflammatory response can be upregulated in pregnancy-induced hypertension.

Another interesting recent development in our understanding of the role of immunity in the pathophysiology of preeclampsia is the identification of a circulating angiotensin-1 receptor autoantibody (AT1-AA). The AT1-AA was found in the circulation of preeclamptic patients, and its epitope eventually mapped to the second extracellular loop of the AT1 receptor [58]. *In vitro* experiments indicated that the AT1-AA could induce ROS production through NADPH activation, and correlations exist between AT1-AA levels and circulating soluble fms-like kinase 1 (sFlt-1) in preeclamptic women [59,60]. This latter finding is in agreement with other studies indicating that AT1-AA signaling is an important regulator of sFlt-1 production [61].

In our own rat models, we have demonstrated that in response to our RUPP gestational hypertension model, AT1-AA is produced to levels comparable to those seen in preeclamptic women [62]. This effect was shown to be at least partially dependent on TNF- α , as the TNF- α -induced hypertension model also resulted in AT1-AA production. Blockade of the AT-1 receptor in both RUPP- and TNF- α -induced hypertension rats resulted in significant attenuation of the blood pressure increase. Furthermore, chronic administration of the purified autoantibody to normal pregnant rats to levels seen in pregnant women and RUPP rats resulted in concurrent increases in blood pressure of approximately 20% and dramatic increases in tissue expression of ET-1. ET receptor type A blockade completely normalized the AT1-AA-induced hypertension, indicating an important pathway for AT1-AA to be involved in the pathophysiology of preeclampsia [63]. One particularly promising recent study from Zhou *et al.* demonstrated that administration of the heptapeptide AT1-AA epitope could bind the free antibody and prevent the pathophysiological effects of its infusion in pregnant mice, offering an intriguing possible therapeutic approach for neutralizing AT1-AA's effects in preeclampsia [64]. Future research into the autoimmune aspects of preeclampsia, both the maternal inflammatory response and the AT1-AA, are sure to be a valuable addition to our understanding of the disorder.

Soluble fms-like kinase-1 & VEGF

One of the most promising avenues of research in the last decade has been into the interplay between pro- and antiangiogenic factors in the etiology of preeclampsia. It is now well established that in response to ischemic or hypoxic conditions, the placenta releases a number of vasoactive factors that are believed to be responsible for the widespread endothelial cell dysfunction prominent in preeclampsia [65–67]. One that has received a great deal of attention in recent years is the sFlt-1. sFlt-1 is a splice variant of the longer VEGF receptor-1 cell surface receptor in which the cytoplasmic and transmembrane domains have been post-transcriptionally excised [68], and has been shown to be produced by placental trophoblasts [69,70]. Tellingly, circulating levels of sFlt-1 appear in preeclamptic women as early as 3 months prior to the onset of symptoms [71]. There are several lines of evidence that permit the possibility that abnormal sFlt-1 expression could be at least partially responsible for abnormal placentation. Both VEGF and PlGF, antagonistic targets of sFlt-1, are expressed in invasive cytotrophoblasts, and are important for the proper vascular development of the placenta, and expression of both signaling proteins is

significantly altered in preeclampsia [72]. In its soluble form, sFlt-1 acts as an antagonist for the proangiogenic proteins VEGF and PlGF by sequestering free protein in the plasma, making them unavailable for receptor binding [73]. Furthermore, levels of sFlt-1 in both placenta and plasma are elevated in preeclamptic women compared with women during normal pregnancy [73]. Tellingly, circulating sFlt-1 levels can predict subsequent preeclampsia prior to disease manifestation [74].

The details of the alternative splice sites of sFlt-1 have recently been characterized, but the details of its regulation remain obscure [75]. Two factors known to induce sFlt-1 production are hypoxia and oxidative stress, two conditions known to exist in the ischemic placenta [38,76]. Placental trophoblasts cultured under low oxygen concentrations *in vitro* were shown to produce excessive sFlt-1 [77]. Similar results were later obtained utilizing human placental villous explants, and implicated the hypoxic stress response protein HIF-1 α as a key regulator [78,79]. A second possible pathway for sFlt-1 regulation in the ischemic placenta is the inflammatory cytokine TNF- α , which has been shown to be elevated in the plasma of preeclamptic women [80]. Exogenous TNF- α treatment of placental villous explants is also capable of inducing sFlt-1 release *in vitro*, in the absence of oxygen tension [78]. There are, then, two distinct mechanisms by which sFlt-1 could be upregulated in the ischemic placenta.

Observations from a number of animal models of preeclampsia also implicate sFlt-1 as an important factor in the pathology of the disorder. Adenovirus vector expression of sFlt-1 in pregnant rats produced a preeclampsia-like phenotype, with increased arterial pressure, glomerular endotheliosis and proteinuria [73]. Mimicry of sFlt-1 increase by infusion of VEGF antibodies has been shown to cause glomerular endothelial damage in mice, again demonstrating the importance of proper pro- and antiangiogenic factor balance for endothelial cell survival [81]. In an intriguing recent study, Byers *et al.* showed that sFlt-1-induced hypertension significantly altered the vascular function of affected offspring into adulthood [82]. Furthermore, our own group has demonstrated that placental ischemia induced by reductions in uterine perfusion pressure in rats resulted in increased plasma and placental sFlt-1 concentrations, results confirmed in a nonhuman primate model of placental ischemia by Makris *et al.* [34,83]. Chronic infusion of sFlt-1 into rats to circulating levels mimicking those seen in preeclamptic women leads to significant increases in maternal blood pressure, with concomitant decreases in fetal weight and increases in both placental and vascular ROS, an important factor in endothelial dysfunction [84]. Chronic sFlt-1 infusion was also found to upregulate cortical ET. The role of ET in sFlt-1-induced hypertension proved to be crucial, as coadministration of ET receptor type A antagonist completely abolished the blood pressure response [85].

VEGF, a target for sFlt-1, is a powerful proangiogenic and pro-mitogenic factor that is essential for endothelial integrity. The net ratio between sFlt-1 and VEGF has been proposed to mediate the pathophysiology of preeclampsia [86]. It has been hypothesized that decreases in free VEGF are responsible for the glomerular endotheliosis and proteinuria associated with preeclampsia [87]. Several lines of evidence support the importance of VEGF in maintaining normal renal function. VEGF is known to be important in the maintenance of glomerular ultrastructure and preservation of fenestrated endothelium [88]. In transgenic mice with glomerular podocyte-specific VEGF knockout, proteinuria and glomerular endotheliosis result [81]. Finally, administration of anti-VEGF antibody cancer therapies have produced hypertension and proteinuria [89]. It is evident that maintenance of circulating VEGF levels is necessary for proper endothelial and renal function.

The net ratio between sFlt-1 and VEGF has been proposed to mediate the pathophysiology of preeclampsia [86]. Supporting that view, Li *et al.* demonstrated that, when pregnant rats

treated with a retrovirus causing them to overexpress sFlt-1 were treated chronically with recombinant VEGF 121, the observed preeclampsia-like symptoms were significantly attenuated, results that were later confirmed in a similar mouse model of sFlt-1-induced preeclampsia [90,91]. Detailed examination by Bergmann *et al.* demonstrated that coexpression of VEGF in sFlt-1-induced hypertension in mice acted to protect the glomerular fenestrated endothelium from the effects of sFlt-1 overproduction [92]. In a separate rat model, Gilbert *et al.* have recently demonstrated that increase in arterial pressure, decreased renal function and vascular activity brought on by placental ischemia in response to reduced uterine perfusion pressure could all be significantly restored by chronic infusion of recombinant VEGF [93]. The balance of sFlt-1 and VEGF is thus an important mediator in the pathophysiology of preeclampsia. These studies provide a promising avenue for possible future therapeutic approaches in its treatment.

Placental growth factor

Another, less thoroughly understood target for sFlt-1 is the proangiogenic protein PlGF. PlGF is a powerful proangiogenic protein with strong homology to VEGF, and has been shown to be produced by both villous trophoblasts and the placental vasculature [94–96]. A number of clinical studies have indicated that, along with increased sFlt-1 and decreased VEGF, a decrease in circulating levels of PlGF are strongly correlated in preeclamptic women [74,97]. Despite its homology to VEGF, PlGF elicits its effects only through the Flt-1 receptor, as it does not bind the VEGF receptor Flk-1 [98]. Interestingly, PlGF appears to have relatively minor effects on its own, but importantly has the ability to enhance the actions of VEGF, possibly through binding to the Flt-1 receptor, sequestering those binding sites and forcing VEGF to bind to Flk-1 instead [99]. This is biologically important, as the Flk-1 receptor has been shown to be responsible for the vast majority of VEGF's proliferative activity [100]. One recent observation from mouse transgenic PlGF knockout lines indicates that PlGF has some role in the proper maturation of uterine natural killer cells, which are involved in placental vascular remodeling during normal placentation [101], although further work still needs to be done to understand the mechanisms behind this phenomena and whether it is physiologically relevant in preeclampsia.

In an elegantly designed study, Maynard *et al.* demonstrated the importance of both VEGF and PlGF in the pathology of preeclampsia. Retroviral delivery of soluble Flk-1 (sFlk-1) protein, which binds VEGF but not PlGF, produced no appreciable phenotype in pregnant rats. The explanation for this direct contrast to the sFlt-1-induced models of hypertension is that sFlt-1 is known to bind both VEGF and PlGF [73]. More recently, in a mouse model of adenoviral-delivered sFlt-1-induced hypertension, it was demonstrated that coexpression with either VEGF or PlGF had the ability to significantly reduce the resulting hypertension, although neither had an appreciable effect on proteinuria [91]. It is clear, therefore, that PlGF has an important role in the pathophysiology of preeclampsia. Much work, however, remains to be done to elucidate the mechanisms involved.

Soluble endoglin

Much recent attention has centered on the protein soluble endoglin (sEng). An extracellular domain fragment of a TGF- β 1 and TGF- β 3 coreceptor, sEng is believed to act antagonistically to TGF- β 1 binding, and is highly expressed in both vascular endothelium and syncytiotrophoblasts [102,103]. Like sFlt-1, the appearance of circulating sEng precedes the onset of the symptomatic phase of preeclampsia [71]. *In vitro* studies have demonstrated that sEng is a powerful inhibitor of endothelial cell proliferation and tube formation. The same study demonstrated that adenoviral-mediated overexpression of sEng in pregnant rats induced mild preeclampsia-like symptoms. Coadministration of both sFlt and sEng,

however, led to a severe preeclamptic phenotype; fetal growth restriction, proteinuria and hypertension. There was even evidence of low platelet levels and elevated lactate dehydrogenase, both hallmarks of the severe form of preeclampsia known as 'hemolytic anemia, elevated liver enzymes, low platelet count' (HELLP) syndrome [104].

Reduced uterine perfusion pressure in the rat was also shown to stimulate sEng and placental endoglin production, pointing to placental ischemia/hypoxia as a factor in sEng release during preeclampsia, although the exact mechanistic pathways involved are not clear [105]. Also recently, it was shown that infusion of the AT1-AA into pregnant mice, but not nonpregnant mice, led to increased sEng levels. This was further shown to be mediated through induction of TNF- α . Most importantly, the mice demonstrated abnormalities in placental vascularization, although whether this was directly caused by sEng production is unclear [106]. It is suggested that since sFlt-1 and sEng act through independent mechanisms, the two factors together may both be responsible for much of the pathophysiology of preeclampsia.

Endothelin

One promising target in the study of preeclampsia pursued by our group in recent years is the potent vasoconstrictor peptide ET. First identified over 20 years ago, ET is produced by a two-stage proteolytic degradation of the protein preproET into the active 21-amino acid peptide [107,108]. The majority of clinical studies that have investigated ET have identified elevated levels in preeclamptic women compared with healthy controls, although the effect is not universally observed [109–112]. In our rat model of TNF- α -induced hypertension during pregnancy, which achieves TNF- α levels seen in preeclamptic women, we observed an increase in the transcriptional activation of preproET in the placenta, aorta and kidney. Furthermore, the hypertension induced by TNF- α infusion could be completely abrogated by pretreatment with an ET receptor type A antagonist [56]. Later studies demonstrated that pharmacological blockade of TNF- α in the rat reduced uterine perfusion model produced a concomitant decrease in tissue levels of ET-1 and a normalization of blood pressure [54].

Later studies utilizing the AT1-AA infusion rat model of preeclampsia again demonstrated an elevation in tissue ET production. Administration of ET-A-specific antagonists again blunted the hypertension associated with this model [63]. Finally, the sFlt-1 infusion hypertension model also showed significant elevations in cortical ET transcription, and normalization of blood pressure in response to ET-A receptor blockade [85]. The elevation of ET in response to these varied models of preeclampsia argues for an important role in the pathophysiology of preeclampsia. More importantly, the ability of ET-A receptor blockade to normalize many of the symptoms displayed in these models suggests a possible target in the treatment of preeclampsia. Future studies into the safety and efficacy of targeted ET-A suppression for the treatment of preeclampsia should be enlightening.

Heme oxygenase-1: a possible therapeutic target

Heme oxygenase (HO)-1 is an inducible protein found in the normal heme salvage pathway, catalyzing the conversion of heme to biliverdin, the rate-limiting step in the pathway. More recently, however, HO-1 has been recognized for the ability of it and its byproducts to assist in normalizing blood pressure during pathophysiological states [113]. During normal pregnancy, placental HO-1 levels are known to increase throughout gestation [114,115]. In addition, HO activity also increases throughout the placenta [116]. The exact role that HO-1 plays in the placenta during normal gestation, however, is not clear [117].

In fact, the exact mechanisms for HO-1's beneficial effects on hypertension are not entirely clear, but are believed to be mediated through the byproducts of heme degradation; namely

the vasodilatory actions of carbon monoxide (CO) and the antioxidant properties of bilirubin [118]. As placental vessels are maintained at near maximal dilation to facilitate perfusion, and it was shown that CO is capable of reducing perfusion pressure in the isolated human placenta, it has been hypothesized that CO could be an important regulator of that vasodilation [119]. In addition, it has recently been hypothesized that HO-1-derived CO might be an important signal in the initiating trophoblast invasion of the spiral arteries, suggesting a possible role in the pathogenesis of the disorder [114]. The role of oxidative stress in the etiology of preeclampsia has been previously discussed at length, so it is important to note the antioxidant activity of bilirubin, another HO-1 byproduct. In addition, placental bilirubin/biliverdin levels have been shown to positively correlate with advancing gestation in normal pregnancy, possibly playing an important physiological role as an antioxidant agent [120].

Studies looking at the placental expression of HO-1 during preeclampsia have been mixed, with some reporting significant increases, and others seeing no change at all [114,121]. Studies of this kind are further complicated by the fact that HO-1 activity decreases with decreasing oxygen content, meaning that correlations with levels and activity in hypoxic/ischemic tissues such as preeclamptic placentas are not always linear [122]. In our own RUPP model of placental ischemia, we have shown increases in HO-1 production in ischemic placentas, but relatively minor increases in HO activity [105]. The exact role of HO-1 in both normal pregnancy and preeclampsia are still very much a matter of debate, although future studies utilizing animal models of each should help to elucidate its function.

Recent studies have demonstrated that expression of HO-1 in a number of animal models of hypertension causes decreases in blood pressure. In the spontaneously hypertensive rat, for instance, a recent study indicated that overexpression of HO-1 by chronic administration of the inducer hemin caused a total normalization of blood pressure. Remarkably, although hemin was administered for only 3 weeks, blood pressure normalization persisted for up to 9 months after cessation of treatment, possibly owing to vascular remodeling and long-term changes in inducible nitric oxide synthase expression [123]. It will be interesting to see if increases in HO-1 expression or activity by pharmacological or transgenic means will demonstrate a similar effect on the various animal models of preeclampsia, providing a new and exciting target for the treatment of the disorder.

Expert commentary

Despite recent advances into the factors behind the pathophysiology of preeclampsia, there are still many unanswered questions. The initiating events that eventually manifest the disorder remain essentially unknown. While insufficient placental remodeling is clearly the earliest identifiable cause, the underlying mechanisms remain obscure. The identification of spontaneous animal models of preeclampsia would be most beneficial to the elucidation of these early events, although to date, no widely available model exists.

Placental ischemia, a central player in the pathogenesis of preeclampsia, has multiple effects on the fetal and maternal environment. As seen in Figure 1, ischemia-mediated increases in AT1-AA, TNF- α , HIF-1 α and sEng subsequently detrimentally affect several downstream targets. The succeeding dysregulation of pro- and antiangiogenic factors such as sFlt-1, VEGF and PlGF and the increased production of ROS lead to the subsequent maternal endothelial dysfunction. As a result, increased ET-1 production and the decreased bioavailability of nitric oxide lead to the characteristic hypertension observed in this disorder.

We now stand in the midst of a dizzying number of factors that have been implicated in the pathology of the disease, each of which interplays into the regulation and signaling pathways of the others. Currently, the relative importance of each of these factors needs to be ascertained, and a network of crossregulation that governs them needs to be fully elucidated. Unfortunately, there are currently no pharmacological agents that can safely target any of these newly identified factors in the pregnant human, although current studies to further our understanding of the systemic effects of preeclampsia, specifically systemic inflammation, might provide more general targets for candidate therapies.

Five-year view

There are a number of exciting new fields in the area of preeclampsia research. The continued exploration of autoimmunity as a factor, either primary or secondary in the etiology of preeclampsia, is likely to present a number of new potential therapies and avenues of research. Continued investigations into the various soluble factors released from the preeclamptic placenta and understanding their regulation and mechanistic effects will identify new regulatory pathways for potential manipulation. The continued development of animal models to address each of these issues will provide powerful experimental tools for the investigation of the pathophysiology and treatment of one of the most challenging obstetrical disorders today. Finally, experimental therapeutic interventions that target placental perfusion in animal models should also be pursued.

Key issues

- Preeclampsia is a significant cause of maternal and fetal morbidity and mortality.
- Recent evidence indicates a central role for placental ischemia and hypoxia in the pathophysiology of the disease.
- Placental ischemia causes secondary maternal effects responsible for the symptomatic phase of the disorder, notably oxidative stress, immunological dysfunction, angiogenic imbalance and endothelial dysfunction.
- Two prominent mechanisms of immunological dysfunction are enhanced maternal inflammatory response through upregulation of inflammatory cytokines, and production of the angiotensin-1 receptor autoantibody.
- The change in the balance between the proangiogenic protein VEGF and the antiangiogenic protein sFlt-1 in the maternal circulation is a major factor in the disease pathophysiology.
- Exogenous expression of the protein heme oxygenase-1, which has been shown to be an effective intervention in several animal models of hypertension, is an intriguing prospect for therapeutic treatment in preeclampsia, as it possesses both antioxidant activity and produces the potentially vasodilatory carbon monoxide molecule as a byproduct.

References

1. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet* 2001;357(9249):53–56. [PubMed: 11197372]
2. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA. Pathophysiology of preeclampsia: linking placental ischemia/hypoxia with microvascular dysfunction. *Microcirculation* 2002;9(3): 147–160. [PubMed: 12080413]

3. Zandi-Nejad K, Luyckx VA, Brenner BM. Adult hypertension and kidney disease: the role of fetal programming. *Hypertension* 2006;47(3):502–508. [PubMed: 16415374]
4. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;365(9461):785–799. [PubMed: 15733721]
5. Harskamp RE, Zeeman GG. Preeclampsia: at risk for remote cardiovascular disease. *Am J Med Sci* 2007;334(4):291–295. [PubMed: 18030186]
6. Meis PJ, Goldenberg RL, Mercer BM, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal–Fetal Medicine Units Network of the National Institute of Child Health and Human Development. *Am J Obstet Gynecol* 1998;178(3):562–567. [PubMed: 9539527]
7. Roberts JM, Pearson GD, Cutler JA, Lindheimer MD. Summary of the NHLBI working group on research on hypertension during pregnancy. *Hypertens Pregnancy* 2003;22(2):109–127. [PubMed: 12908996]
8. Caritis S, Sibai B, Hauth J, et al. Predictors of pre-eclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal–Fetal Medicine Units. *Am J Obstet Gynecol* 1998;179(4):946–951. [PubMed: 9790376]
9. Sibai BM, Ewell M, Levine RJ, et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. *Am J Obstet Gynecol* 1997;177(5):1003–1010. [PubMed: 9396883]
10. Mostello D, Catlin TK, Roman L, Holcomb WL Jr, Leet T. Preeclampsia in the parous woman: who is at risk? *Am J Obstet Gynecol* 2002;187(2):425–429. [PubMed: 12193937]
11. Hladunewich M, Karumanchi SA, Lafayette R. Pathophysiology of the clinical manifestations of preeclampsia. *Clin J Am Soc Nephrol* 2007;2(3):543–549. [PubMed: 17699462]
12. Shembrey MA, Noble AD. An instructive case of abdominal pregnancy. *Aust N Z J Obstet Gynaecol* 1995;35(2):220–221. [PubMed: 7677698]
13. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynecol* 1999;180(2 Pt 1):499–506. [PubMed: 9988826]
14. Roberts JM, Pearson G, Cutler J, Lindheimer M. Summary of the NHLBI working group on research on hypertension during pregnancy. *Hypertension* 2003;41(3):437–445. [PubMed: 12623940]
15. Roberts JM, Gammill HS. Preeclampsia: recent insights. *Hypertension* 2005;46(6):1243–1249. [PubMed: 16230510]
16. Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? *J Clin Invest* 1997;99(9):2152–2164. [PubMed: 9151787]
17. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstet Gynecol Annu* 1972;1:177–191. [PubMed: 4669123]
18. Karimu AL, Burton GJ. The effects of maternal vascular pressure on the dimensions of the placental capillaries. *Br J Obstet Gynaecol* 1994;101(1):57–63. [PubMed: 8297870]
19. Lim KH, Zhou Y, Janatpour M, et al. Human cytotrophoblast differentiation/invasion is abnormal in pre-eclampsia. *Am J Pathol* 1997;151(6):1809–1818. [PubMed: 9403732]
20. Damsky CH, Fisher SJ. Trophoblast pseudo-vasculogenesis: faking it with endothelial adhesion receptors. *Curr Opin Cell Biol* 1998;10(5):660–666. [PubMed: 9818178]
21. Rodesch F, Simon P, Donner C, Jauniaux E. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. *Obstet Gynecol* 1992;80(2):283–285. [PubMed: 1635745]
22. Rajakumar A, Doty K, Daftary A, Harger G, Conrad KP. Impaired oxygen-dependent reduction of HIF-1 α and -2 α proteins in pre-eclamptic placentae. *Placenta* 2003;24(2–3):199–208. [PubMed: 12566247]
23. Rajakumar A, Whitelock KA, Weissfeld LA, et al. Selective overexpression of the hypoxia-inducible transcription factor, HIF-2 α , in placentas from women with preeclampsia. *Biol Reprod* 2001;64(2):499–506. [PubMed: 11159352]
24. Lyall F, Greer IA, Boswell F, et al. Expression of cell adhesion molecules in placentae from pregnancies complicated by pre-eclampsia and intrauterine growth retardation. *Placenta* 1995;16(7):579–587. [PubMed: 8577657]

25. Macara L, Kingdom JC, Kohnen G, et al. Elaboration of stem villous vessels in growth restricted pregnancies with abnormal umbilical artery Doppler waveforms. *Br J Obstet Gynaecol* 1995;102(10):807–812. [PubMed: 7547738]
26. Sheppard BL, Bonnar J. An ultrastructural study of utero–placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. *Br J Obstet Gynaecol* 1981;88(7):695–705. [PubMed: 7248226]
27. Knofler M. Critical growth factors and signalling pathways controlling human trophoblast invasion. *Int J Dev Biol* 2010;54(2–3):269–280. [PubMed: 19876833]
28. Lindheimer MD, Taler SJ, Cunningham FG. ASH position paper: hypertension in pregnancy. *J Clin Hypertens (Greenwich)* 2009;11(4):214–225. [PubMed: 19614806]
29. Hodari AA. Chronic uterine ischemia and reversible experimental ‘toxemia of pregnancy’. *Am J Obstet Gynecol* 1967;97(5):597–607. [PubMed: 6018981]
30. Losonczy G, Brown G, Venuto RC. Increased peripheral resistance during reduced uterine perfusion pressure hypertension in pregnant rabbits. *Am J Med Sci* 1992;303(4):233–240. [PubMed: 1562040]
31. Cavanagh D, Rao PS, Tsai CC, O’Connor TC. Experimental toxemia in the pregnant primate. *Am J Obstet Gynecol* 1977;128(1):75–85. [PubMed: 403766]
32. Cavanagh D, Rao PS, Tung KS, Gaston L. Eclamptogenic toxemia: the development of an experimental model in the subhuman primate. *Am J Obstet Gynecol* 1974;120(2):183–196. [PubMed: 4606463]
33. Combs CA, Katz MA, Kitzmiller JL, Brescia RJ. Experimental preeclampsia produced by chronic constriction of the lower aorta: validation with longitudinal blood pressure measurements in conscious rhesus monkeys. *Am J Obstet Gynecol* 1993;169(1):215–223. [PubMed: 8333460]
34. Makris A, Thornton C, Thompson J, et al. Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. *Kidney Int* 2007;71(10):977–984. [PubMed: 17377512]
35. Granger JP, LaMarca BB, Cockrell K, et al. Reduced uterine perfusion pressure (RUPP) model for studying cardiovascular–renal dysfunction in response to placental ischemia. *Methods Mol Med* 2006;122:383–392. [PubMed: 16511995]
36. Sholook MM, Gilbert JS, Sedeek MH, et al. Systemic hemodynamic and regional blood flow changes in response to chronic reductions in uterine perfusion pressure in pregnant rats. *Am J Physiol Heart Circ Physiol* 2007;293(4):H2080–H2084. [PubMed: 17644567]
37. Burton GJ, Jauniaux E. Placental oxidative stress: from miscarriage to preeclampsia. *J Soc Gynecol Investig* 2004;11(6):342–352.
38. Hung TH, Burton GJ. Hypoxia and reoxygenation: a possible mechanism for placental oxidative stress in preeclampsia. *Taiwan J Obstet Gynecol* 2006;45(3):189–200. [PubMed: 17175463]
39. Hung TH, Skepper JN, Charnock-Jones DS, Burton GJ. Hypoxia–reoxygenation: a potent inducer of apoptotic changes in the human placenta and possible etiological factor in preeclampsia. *Circ Res* 2002;90(12):1274–1281. [PubMed: 12089065]
40. Walsh SW. Maternal–placental interactions of oxidative stress and antioxidants in preeclampsia. *Semin Reprod Endocrinol* 1998;16(1):93–104. [PubMed: 9654611]
41. Staff AC, Ranheim T, Khoury J, Henriksen T. Increased contents of phospholipids, cholesterol, and lipid peroxides in decidua basalis in women with preeclampsia. *Am J Obstet Gynecol* 1999;180(3 Pt 1):587–592. [PubMed: 10076133]
42. Staff AC, Halvorsen B, Ranheim T, Henriksen T. Elevated level of free 8-iso-prostaglandin F2 α in the decidua basalis of women with preeclampsia. *Am J Obstet Gynecol* 1999;181(5 Pt 1):1211–1215. [PubMed: 10561647]
43. Roggensack AM, Zhang Y, Davidge ST. Evidence for peroxynitrite formation in the vasculature of women with preeclampsia. *Hypertension* 1999;33(1):83–89. [PubMed: 9931086]
44. Sedeek M, Gilbert JS, LaMarca BB, et al. Role of reactive oxygen species in hypertension produced by reduced uterine perfusion in pregnant rats. *Am J Hypertens* 2008;21(10):1152–1156. [PubMed: 18670418]
45. Sedeek MW, Wang YP, Granger JP. Increased oxidative stress in a rat model of preeclampsia. *Am J Hypertens* 2004;17(142A)

46. Xia Y, Kellems RE. Is preeclampsia an autoimmune disease? *Clin Immunol* 2009;133(1):1–12. [PubMed: 19501024]
47. Herse F, Staff AC, Hering L, et al. AT1-receptor autoantibodies and uteroplacental RAS in pregnancy and pre-eclampsia. *J Mol Med* 2008;86(6):697–703. [PubMed: 18398593]
48. Campbell DM, MacGillivray I, Carr-Hill R. Pre-eclampsia in second pregnancy. *Br J Obstet Gynaecol* 1985;92(2):131–140. [PubMed: 3970893]
49. Saito S, Shiozaki A, Nakashima A, Sakai M, Sasaki Y. The role of the immune system in preeclampsia. *Mol Aspects Med* 2007;28(2):192–209. [PubMed: 17433431]
50. Robillard PY, Hulse TC, Alexander GR, et al. Paternity patterns and risk of preeclampsia in the last pregnancy in multiparae. *J Reprod Immunol* 1993;24(1):1–12. [PubMed: 8350302]
51. Schiessl B. Inflammatory response in preeclampsia. *Mol Aspects Med* 2007;28(2):210–219. [PubMed: 17532463]
52. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response – a review. *Placenta* 2003;24(Suppl A):S21–S27. [PubMed: 12842410]
53. Gadonski G, LaMarca BB, Sullivan E, et al. Hypertension produced by reductions in uterine perfusion in the pregnant rat: role of interleukin 6. *Hypertension* 2006;48(4):711–716. [PubMed: 16940225]
54. LaMarca B, Speed J, Fournier L, et al. Hypertension in response to chronic reductions in uterine perfusion in pregnant rats: effect of tumor necrosis factor- α blockade. *Hypertension* 2008;52(6):1161–1167. [PubMed: 18981324]
55. Alexander BT, Cockrell KL, Massey MB, Bennett WA, Granger JP. Tumor necrosis factor- α -induced hypertension in pregnant rats results in decreased renal neuronal nitric oxide synthase expression. *Am J Hypertens* 2002;15(2 Pt 1):170–175. [PubMed: 11863253]
56. LaMarca BB, Cockrell K, Sullivan E, Bennett W, Granger JP. Role of endothelin in mediating tumor necrosis factor-induced hypertension in pregnant rats. *Hypertension* 2005;46(1):82–86. [PubMed: 15928030]
57. Germain SJ, Sacks GP, Sooranna SR, Sargent IL, Redman CW. Systemic inflammatory priming in normal pregnancy and preeclampsia: the role of circulating syncytiotrophoblast microparticles. *J Immunol* 2007;178(9):5949–5956. [PubMed: 17442979]
58. Wallukat G, Homuth V, Fischer T, et al. Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. *J Clin Invest* 1999;103(7):945–952. [PubMed: 10194466]
59. Dechend R, Viedt C, Muller DN, et al. AT1 receptor agonistic antibodies from preeclamptic patients stimulate NADPH oxidase. *Circulation* 2003;107(12):1632–1639. [PubMed: 12668498]
60. Stepan H, Faber R, Wessel N, et al. Relation between circulating angiotensin II type 1 receptor agonistic autoantibodies and soluble fms-like tyrosine kinase 1 in the pathogenesis of preeclampsia. *J Clin Endocrinol Metab* 2006;91(6):2424–2427. [PubMed: 16569734]
61. Zhou CC, Ahmad S, Mi T, et al. Autoantibody from women with preeclampsia induces soluble Fms-like tyrosine kinase-1 production via angiotensin type 1 receptor and calcineurin/nuclear factor of activated T-cells signaling. *Hypertension* 2008;51(4):1010–1019. [PubMed: 18259044]
62. LaMarca B, Wallukat G, Llinas M, et al. Autoantibodies to the angiotensin type I receptor in response to placental ischemia and tumor necrosis factor α in pregnant rats. *Hypertension* 2008;52(6):1168–1172. [PubMed: 18852381]
63. LaMarca B, Parrish M, Ray LF, et al. Hypertension in response to autoantibodies to the angiotensin II type I receptor (AT1-AA) in pregnant rats: role of endothelin-1. *Hypertension* 2009;54(4):905–909. [PubMed: 19704104]
64. Zhou CC, Zhang Y, Irani RA, et al. Angiotensin receptor agonistic autoantibodies induce pre-eclampsia in pregnant mice. *Nat Med* 2008;14(8):855–862. [PubMed: 18660815]
65. Mutter WP, Karumanchi SA. Molecular mechanisms of preeclampsia. *Microvasc Res* 2008;75(1):1–8. [PubMed: 17553534]
66. LaMarca BD, Alexander BT, Gilbert JS, et al. Pathophysiology of hypertension in response to placental ischemia during pregnancy: a central role for endothelin? *Gend Med* 2008;5(Suppl A):S133–S138. [PubMed: 18395679]

67. LaMarca BD, Gilbert J, Granger JP. Recent progress toward the understanding of the pathophysiology of hypertension during preeclampsia. *Hypertension* 2008;51(4):982–988. [PubMed: 18259004]
68. Banks RE, Forbes MA, Searles J, et al. Evidence for the existence of a novel pregnancy-associated soluble variant of the vascular endothelial growth factor receptor, Flt-1. *Mol Hum Reprod* 1998;4(4):377–386. [PubMed: 9620838]
69. Helske S, Vuorela P, Carpen O, et al. Expression of vascular endothelial growth factor receptors 1, 2 and 3 in placentas from normal and complicated pregnancies. *Mol Hum Reprod* 2001;7(2):205–210. [PubMed: 11160848]
70. Kendall RL, Thomas KA. Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. *Proc Natl Acad Sci USA* 1993;90(22):10705–10709. [PubMed: 8248162]
71. Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006;355(10):992–1005. [PubMed: 16957146]
72. Zhou Y, McMaster M, Woo K, et al. Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome. *Am J Pathol* 2002;160(4):1405–1423. [PubMed: 11943725]
73. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003;111(5):649–658. [PubMed: 12618519]
74. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350(7):672–683. [PubMed: 14764923]
75. Huckle WR, Roche RI. Post-transcriptional control of expression of sFlt-1, an endogenous inhibitor of vascular endothelial growth factor. *J Cell Biochem* 2004;93(1):120–132. [PubMed: 15352169]
76. Soleymanlou N, Jurisica I, Nevo O, et al. Molecular evidence of placental hypoxia in preeclampsia. *J Clin Endocrinol Metab* 2005;90(7):4299–4308. [PubMed: 15840747]
77. Nagamatsu T, Fujii T, Kusumi M, et al. Cytotrophoblasts up-regulate soluble fms-like tyrosine kinase-1 expression under reduced oxygen: an implication for the placental vascular development and the pathophysiology of preeclampsia. *Endocrinology* 2004;145(11):4838–4845. [PubMed: 15284201]
78. Ahmad S, Ahmed A. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. *Circ Res* 2004;95(9):884–891. [PubMed: 15472115]
79. Nevo O, Soleymanlou N, Wu Y, et al. Increased expression of sFlt-1 in *in vivo* and *in vitro* models of human placental hypoxia is mediated by HIF-1. *Am J Physiol Regul Integr Comp Physiol* 2006;291(4):R1085–R1093. [PubMed: 16627691]
80. Heiskanen J, Romppanen EL, Hiltunen M, et al. Polymorphism in the tumor necrosis factor- α gene in women with preeclampsia. *J Assist Reprod Genet* 2002;19(5):220–223. [PubMed: 12099552]
81. Eremina V, Sood M, Haigh J, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. *J Clin Invest* 2003;111(5):707–716. [PubMed: 12618525]
82. Byers BD, Betancourt A, Lu F, et al. The effect of prepregnancy obesity and sFlt-1-induced preeclampsia-like syndrome on fetal programming of adult vascular function in a mouse model. *Am J Obstet Gynecol* 2009;200(4):432.e1–7. [PubMed: 19318153]
83. Gilbert JS, Babcock SA, Granger JP. Hypertension produced by reduced uterine perfusion in pregnant rats is associated with increased soluble fms-like tyrosine kinase-1 expression. *Hypertension* 2007;50(6):1142–1147. [PubMed: 17923588]
84. Bridges JP, Gilbert JS, Colson D, et al. Oxidative stress contributes to soluble fms-like tyrosine kinase-1 induced vascular dysfunction in pregnant rats. *Am J Hypertens* 2009;22(5):564–568. [PubMed: 19265787]
85. Murphy SR, LaMarca BB, Cockrell K, Granger JP. Role of endothelin in mediating soluble fms-like tyrosine kinase 1-induced hypertension in pregnant rats. *Hypertension* 2010;55(2):394–398. [PubMed: 20026766]

86. Gilbert JS, Ryan MJ, LaMarca BB, et al. Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction. *Am J Physiol Heart Circ Physiol* 2008;294(2):H541–H550. [PubMed: 18055511]
87. Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. *Physiology (Bethesda)* 2009;24:147–158. [PubMed: 19509125]
88. Ballermann BJ. Glomerular endothelial cell differentiation. *Kidney Int* 2005;67(5):1668–1671. [PubMed: 15840009]
89. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007;49(2):186–193. [PubMed: 17261421]
90. Li Z, Zhang Y, Ying Ma J, et al. Recombinant vascular endothelial growth factor 121 attenuates hypertension and improves kidney damage in a rat model of preeclampsia. *Hypertension* 2007;50(4):686–692. [PubMed: 17724276]
91. Suzuki H, Ohkuchi A, Matsubara S, et al. Effect of recombinant placental growth factor 2 on hypertension induced by full-length mouse soluble fms-like tyrosine kinase 1 adenoviral vector in pregnant mice. *Hypertension* 2009;54(5):1129–1135. [PubMed: 19786649]
92. Bergmann A, Ahmad S, Cudmore M, et al. Reduction of circulating soluble Flt-1 alleviates preeclampsia-like symptoms in a mouse model. *J Cell Mol Med* 2009;14(6B):1857–1867. [PubMed: 19538465]
93. Gilbert JS, Verzwylvelt J, Colson D, et al. Recombinant vascular endothelial growth factor 121 infusion lowers blood pressure and improves renal function in rats with placental ischemia-induced hypertension. *Hypertension* 2010;55(2):380–385. [PubMed: 20026764]
94. Maglione D, Guerriero V, Viglietto G, Delli-Bovi P, Persico MG. Isolation of a human placenta cDNA coding for a protein related to the vascular permeability factor. *Proc Natl Acad Sci USA* 1991;88(20):9267–9271. [PubMed: 1924389]
95. Shore VH, Wang TH, Wang CL, et al. Vascular endothelial growth factor, placenta growth factor and their receptors in isolated human trophoblast. *Placenta* 1997;18(8):657–665. [PubMed: 9364601]
96. Khaliq A, Li XF, Shams M, et al. Localisation of placenta growth factor (PlGF) in human term placenta. *Growth Factors* 1996;13(3–4):243–250. [PubMed: 8919031]
97. Lam C, Lim KH, Karumanchi SA. Circulating angiogenic factors in the pathogenesis and prediction of preeclampsia. *Hypertension* 2005;46(5):1077–1085. [PubMed: 16230516]
98. Park JE, Chen HH, Winer J, Houck KA, Ferrara N. Placenta growth factor. Potentiation of vascular endothelial growth factor bioactivity, *in vitro* and *in vivo*, and high affinity binding to Flt-1 but not to Flk-1/KDR. *J Biol Chem* 1994;269(41):25646–25654. [PubMed: 7929268]
99. Ahmed A, Dunk C, Ahmad S, Khaliq A. Regulation of placental vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) and soluble Flt-1 by oxygen – a review. *Placenta* 2000;21(Suppl A):S16–S24. [PubMed: 10831117]
100. Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol* 1995;146(5):1029–1039. [PubMed: 7538264]
101. Tayade C, Hilchie D, He H, et al. Genetic deletion of placenta growth factor in mice alters uterine NK cells. *J Immunol* 2007;178(7):4267–4275. [PubMed: 17371983]
102. Cheifetz S, Bellon T, Cales C, et al. Endoglin is a component of the transforming growth factor- β receptor system in human endothelial cells. *J Biol Chem* 1992;267(27):19027–19030. [PubMed: 1326540]
103. Gougos A, St Jacques S, Greaves A, et al. Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts. *Int Immunol* 1992;4(1):83–92. [PubMed: 1371694]
104. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med* 2006;12(6):642–649. [PubMed: 16751767]
105. Gilbert JS, Gilbert SA, Arany M, Granger JP. Hypertension produced by placental ischemia in pregnant rats is associated with increased soluble endoglin expression. *Hypertension* 2009;53(2):399–403. [PubMed: 19075097]

106. Zhou CC, Irani RA, Zhang Y, et al. Angiotensin receptor agonistic autoantibody-mediated tumor necrosis factor- α induction contributes to increased soluble endoglin production in preeclampsia. *Circulation* 2010;121(3):436–444. [PubMed: 20065159]
107. Yanagisawa M, Inoue A, Ishikawa T, et al. Primary structure, synthesis, and biological activity of rat endothelin, an endothelium-derived vasoconstrictor peptide. *Proc Natl Acad Sci USA* 1988;85(18):6964–6967. [PubMed: 3045827]
108. Yanagisawa M, Kurihara H, Kimura S, Goto K, Masaki T. A novel peptide vasoconstrictor, endothelin, is produced by vascular endothelium and modulates smooth muscle Ca^{2+} channels. *J Hypertens Suppl* 1988;6(4):S188–S191. [PubMed: 2853725]
109. Taylor RN, Varma M, Teng NN, Roberts JM. Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. *J Clin Endocrinol Metab* 1990;71(6):1675–1677. [PubMed: 2229324]
110. Benigni A, Orisio S, Gaspari F, et al. Evidence against a pathogenetic role for endothelin in pre-eclampsia. *Br J Obstet Gynaecol* 1992;99(10):798–802. [PubMed: 1384688]
111. Bernardi F, Constantino L, Machado R, Petronilho F, Dal-Pizzol F. Plasma nitric oxide, endothelin-1, arginase and superoxide dismutase in pre-eclamptic women. *J Obstet Gynaecol Res* 2008;34(6):957–963. [PubMed: 19012693]
112. Nezar MA, el-Baky AM, Soliman OA, et al. Endothelin-1 and leptin as markers of intrauterine growth restriction. *Indian J Pediatr* 2009;76(5):485–488. [PubMed: 19390804]
113. Cao J, Inoue K, Li X, Drummond G, Abraham NG. Physiological significance of heme oxygenase in hypertension. *Int J Biochem Cell Biol* 2009;41(5):1025–1033. [PubMed: 19027871]
114. Ahmed A, Rahman M, Zhang X, et al. Induction of placental heme oxygenase-1 is protective against TNF α -induced cytotoxicity and promotes vessel relaxation. *Mol Med* 2000;6(5):391–409. [PubMed: 10952020]
115. Yoshiki N, Kubota T, Aso T. Expression and localization of heme oxygenase in human placental villi. *Biochem Biophys Res Commun* 2000;276(3):1136–1142. [PubMed: 11027601]
116. McLaughlin BE, Hutchinson JM, Graham CH, et al. Heme oxygenase activity in term human placenta. *Placenta* 2000;21(8):870–873. [PubMed: 11095937]
117. Bainbridge SA, Smith GN. HO in pregnancy. *Free Radic Biol Med* 2005;38(8):979–988. [PubMed: 15780756]
118. Idriss NK, Blann AD, Lip GY. Hemoxygenase-1 in cardiovascular disease. *J Am Coll Cardiol* 2008;52(12):971–978. [PubMed: 18786476]
119. Bainbridge SA, Farley AE, McLaughlin BE, et al. Carbon monoxide decreases perfusion pressure in isolated human placenta. *Placenta* 2002;23(8–9):563–569. [PubMed: 12361675]
120. Qanungo S, Mukherjee M. Ontogenic profile of some antioxidants and lipid peroxidation in human placental and fetal tissues. *Mol Cell Biochem* 2000;215(1–2):11–19. [PubMed: 11204445]
121. Barber A, Robson SC, Myatt L, Bulmer JN, Lyall F. Heme oxygenase expression in human placenta and placental bed: reduced expression of placenta endothelial HO-2 in preeclampsia and fetal growth restriction. *FASEB J* 2001;15(7):1158–1168. [PubMed: 11344084]
122. Appleton SD, Marks GS, Nakatsu K, et al. Heme oxygenase activity in placenta: direct dependence on oxygen availability. *Am J Physiol Heart Circ Physiol* 2002;282(6):H2055–H2059. [PubMed: 12003811]
123. Wang R, Shamloul R, Wang X, Meng Q, Wu L. Sustained normalization of high blood pressure in spontaneously hypertensive rats by implanted hemin pump. *Hypertension* 2006;48(4):685–692. [PubMed: 16940218]

Figure 1. Placental ischemia initiates numerous pathways in the pathophysiology of preeclampsia

AT1-AA: Angiotensin 1 receptor autoantibody; ET-1: Endothelin-1; HIF-1 α : Hypoxia-inducible factor-1 α ; NO: Nitric oxide; ROS: Reactive oxygen species; sEng: Soluble endoglin; sFlt-1: Soluble fms-like tyrosine kinase-1.