Published in final edited form as:

Curr Hypertens Rep. 2011 August ; 13(4): 269–275. doi:10.1007/s11906-011-0204-0.

Mechanisms and Potential Therapies for Preeclampsia

Eric M. George and Joey P. Granger

Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA

Abstract

Preeclampsia is a pregnancy-induced hypertensive disorder found most commonly in nulliparous women. Recent research performed in animal models of the disease has revealed some of the underlying mechanisms of preeclampsia. Specifically, placental insufficiency and the resulting hypoxia/ischemia have been shown to be crucial to disease progression. In response to placental hypoxia/ischemia, several pathways are activated, which contribute to the clinical manifestations of the disease: increased circulating levels of the anti-angiogenic protein sFlt-1, activation of the maternal inflammatory response, suppressed nitric oxide production, enhanced endothelin-1 production, and induction of reactive oxygen formation. Despite advances in the understanding of the disorder, therapeutic approaches to the treatment of preeclampsia are severely limited. New lines of research, however, indicate some possible new therapeutic approaches for the management of preeclampsia and offer hope for an effective pharmacologic intervention.

Keywords

Preeclampsia; Placental ischemia; Placental hypoxia; VEGF; sFlt-1; Heme oxygenase-1; Endothelin-1; Sildenafil; Hypertension; Pregnancy; Treatment

Introduction

Despite increased awareness and aggressive management, preeclampsia remains an extremely common pregnancy complication, which occurs in approximately 8% of all pregnancies, with significantly higher rates in certain subpopulations [1]. It remains one of the leading causes of maternal and fetal morbidity and mortality. Disease manifestation typically occurs after 20 weeks gestation. Historically, diagnosis has been based on a combination of hypertension, proteinuria, and edema, but edema has now been removed as a required symptom, and there is significant debate over the proper role for proteinuria as a diagnostic measure [2]. The cause of preeclampsia and the initiating mechanisms in its development are poorly understood. It is clear, however, that the central organ of dysfunction is the placenta, as the only truly definitive intervention is delivery of the placenta, after which the symptoms of the disorder begin to remit. Treatment varies by severity, but commonly magnesium sulfate is administered as a prophylactic measure to prevent the seizures seen in the later stage of the disease. Any number of antihypertensive agents may be administered, with the ultimate goal of maintaining pregnancy until 37 weeks of gestation, when labor is typically induced to fully remit the disorder. In the severest forms

of preeclampsia, labor is often induced earlier in gestation, leading to increased risk of complications in the newborn [3].

The disease is postulated to occur in two distinct phases. The first consists of a maternally asymptomatic phase in which an error in placental development leads to placental insufficiency and hypoxia. The second phase is the clinically relevant maternal symptomatic phase, consisting of widespread maternal endothelial dysfunction that leads to a number of cardiovascular effects, including increased vascular resistance and increased sensitivity to vasoconstrictor molecules [4]. It is only recently that the mechanisms that connect these two disparate phases have begun to be elucidated. The mechanisms uncovered in these studies have provided new targets for pharmacologic intervention in preeclampsia.

Placental Ischemia and Hypoxia

During normal placental development, extensive vascular remodeling takes place at the maternal/fetal interface [5]. This remodeling is necessary to ensure an adequate supply of blood to the placenta and by extension, to the developing fetus. The maternal spiral arteries, which begin as muscular, high-resistance, low-capacity vessels, are invaded by invasive cytotrophoblasts of fetal origin. These cells integrate into the vessel lining and transform from an epithelial phenotype into an endothelial-like phenotype. In the process, they convert the artery into a high-capacitance, low-resistance, elastic vessel, promoting greater delivery of oxygenated blood to the placenta. Early evidence demonstrated that placentas harvested from preeclamptic women often had poorly remodeled spiral arteries, which retain their high-resistance, muscular morphology [6]. It is believed that this pattern is a direct result of shallow trophoblast invasion of the maternal spiral arteries, though the reason behind this failure to adequately remodel the spiral arteries is not known. There is some evidence that it is due to failure of the invading trophoblasts to express the necessary endothelial surface adhesion molecules, but this effect has not been universally observed [7].

The immediate result of this failure to remodel the maternal arteries is that the placenta, which is mildly hypoxic even in normal pregnancy, becomes severely hypoxic, resulting in chronic placental ischemia. It is at this stage that great progress has been made in the elucidation of preeclampsia mechanisms. A preponderance of evidence now indicates that, as a result of placental ischemia, the placenta produces a number of soluble factors, which are released into the maternal circulation and elicit many of the symptoms characteristic of preeclampsia. Several pathways recently elucidated are altered angiogenic balance, increased maternal inflammation and immunologic dysfunction, creation of harmful reactive oxygen species, suppression of nitric oxide (NO) production, and enhanced endothelin-1 (ET-1) production.

Angiogenic Factors

One of the most intensely studied pathways activated by placental ischemia is alteration in circulating levels of pro-angiogenic and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) is a powerful angiogenic factor. Tellingly, it is crucial for endothelial cell maintenance, and as the symptomatic phase of preeclampsia is marked by systemic endothelial dysfunction, it was a logical target for investigation. Indeed, reduction of VEGF levels by transgenic knockout in mouse models or pharmacologic reduction by administration of anti-VEGF monoclonal antibodies results in hypertension, proteinuria, and glomerular endotheliosis, all common findings in preeclampsia [8].

Perhaps the most important breakthrough in understanding the role of angiogenic factors in the development of preeclampsia was the identification of a naturally occurring VEGF antagonist known as soluble fms-like tyrosine kinase-1 (sFlt-1), an inducible splice variant

of the VEGF receptor flt-1. Although the exact mechanisms that regulate sFlt-1 expression are not clear, it appears to be upregulated by hypoxia through the actions of hypoxia-inducible factor-1 (HIF-1), and has been shown to be secreted by placental tissue in vitro when exposed to low oxygen tension. This variant expresses no transmembrane domain and as a result is secreted and remains soluble in the circulation. In its soluble form, sFlt-1 binds to circulating VEGF and renders it unavailable for receptor binding, effectively acting as a competitive inhibitor of the protein [9]. Importantly, in preeclamptic patients, circulating sFlt-1 levels were significantly higher than in normal pregnant women, sometimes well before the symptomatic phase of the disease [10].

Several experimental models of preeclampsia lend credence to the causative role of sFlt-1 in the pathology of preeclampsia. Ectopic administration of sFlt-1 to pregnant rodents by either retroviral delivery or direct infusion leads to a preeclampsia-like phenotype, including the characteristic hypertension and proteinuria [11, 12]. Experimental animal models of placental hypoxia/ischemia have demonstrated increased production of sFlt-1 by the placenta and resulting increases in maternal circulating levels of sFlt-1 [13]. Finally, several laboratories, using a diverse selection of animal models of preeclampsia, have demonstrated that administering VEGF, or binding peptides that sequester sFlt-1 and render it incapable of binding VEGF, reverses many of the symptoms associated with preeclampsia [14, 15]. It is clear that hypoxia-induced sFlt-1 derived from the placenta is an important pathologic factor in the development of preeclampsia, and that manipulation of the levels of sFlt-1, VEGF, or both is a promising target for therapeutic intervention.

The Maternal Inflammatory and Immune Response

A second major pathway activated by the ischemic placenta is the induction of maternal inflammation. It is well established that the maternal inflammatory response is heightened even during normal pregnancy. In preeclampsia, this effect seems to be exaggerated. Levels of inflammatory cytokines such as IL-6 and TNF- α are markedly higher than levels in women undergoing healthy pregnancies, and the same findings are seen in experimental animal models of placental ischemia. Administration of either of these cytokines in rodent models of pregnancy induces a gestational hypertension similar to that seen in placental ischemic models. Intriguingly, administration of the soluble TNF- α receptor etanercept in a rodent model of placental ischemia blunted the hypertension associated with the model, possibly by reducing the production of the vasoconstrictor endothelin-1 (ET-1) [16].

Another interesting, though less thoroughly understood, aspect to the maternal immune component of preeclampsia is the identification in preeclamptic women of circulating agonistic autoantibodies to the angiotensin type 1 receptor (AT1-AA), an antibody also identified in experimental animal models of preeclampsia. Besides its proposed role in activating the AT1 receptor, there appears to be a significant correlation between AT1-AA levels and the production of sFlt-1 [17]. Infusion of the purified antibody into pregnant rodents leads to a gestational hypertension similar to that seen in placental ischemia models. The hypertensive response can be blocked by concurrent infusion of a synthetic heptapeptide, which mimics the antibody's natural epitope on the AT1 receptor [18]. This offers yet another intriguing possibility for a novel therapeutic agent for the treatment of preeclampsia.

Reactive Oxygen Production

Another factor known to be increased in response to placental ischemia is the production of reactive oxygen species. Reactive oxygen is a well defined factor in endothelial dysfunction, either by direct action on the endothelium or through a secondary pathway by the downregulation of vasoactive signaling molecules. In preeclamptic placentas, elevated levels

of a number of different markers of oxidative stress have been identified, specifically free isoprostane and hydroperoxides [19], and there is evidence that this translates to higher systemic levels of reactive oxygen in the maternal endothelium. This could be an additional mechanism, in addition to reduced bioactive VEGF, for maternal endothelial dysfunction.

In our rodent model of placental ischemia, we demonstrated increased superoxide in the placenta. Use of the superoxide dismutase mimetic compound Tempol significantly attenuated the hypertension associated with the model. Furthermore, similar results were obtained by pharmacologic inhibition of NADPH oxidase, indicating a possible important role for that enzyme in the production of reactive oxygen in placental ischemia [20]. This increase in reactive oxygen production, coupled with the reported suppression of maternal antioxidant activity during preeclampsia, could be a powerful factor in the maternal phase of the disorder. Further research into the manipulation of reactive oxygen production should help determine whether it is in fact a useful target in the search for new therapeutic agents.

Reduced Nitric Oxide Availability

During normal pregnancy, changes in vascular reactivity are believed to result, at least in part, from increased levels of NO derived from endothelial cells [21]. Increased synthesis of nitric oxide synthase (NOS) in the uterine artery has been reported during normal human gestation, along with increased circulating levels and excretion of the NO secondary messenger cGMP [22]. Further studies in animals have also demonstrated that increased vasorelaxation in late pregnancy is mediated by endothelium-derived NO, with concurrent upregulation of tissue NOS synthesis and NO production [23, 24].

As NO has been shown to be important for the vasodilatation seen during pregnancy, it has been hypothesized that reduced NO bioavailability could be a major factor in the increase in peripheral resistance seen in preeclamptic women. In an animal model, inhibition of NOS by the L-arginine derivative L-NAME leads to a preeclampsia-like state in pregnant rats, which exhibit an enhanced hypertensive response when compared with virgin controls also given L-NAME [23]. Among the symptoms expressed by these animals are enhanced renal vasoconstriction, proteinuria, and fetal growth restriction. In this experimental model, there are also significant increases in vascular reactivity to phenylephrine compared with normal pregnant controls [23]. The levels of NO-derived metabolites have been measured in the umbilical vein blood and amniotic fluid of pregnant women and have been shown to be significantly decreased in preeclamptic cases, but findings of reduced NO bioavailability in women with preeclampsia have not been equivocal [25, 26].

Endothelin: A Common Link?

Another pivotal factor implicated in the characteristic maternal endothelial dysfunction associated with preeclampsia is elevated levels of the signaling peptide endothelin-1 (ET-1). First identified over 20 years ago as the most potent known vasoconstrictor, ET-1 is produced by a two-step proteolytic degradation of the precursor molecule preproET-1 into the active 21-amino acid final product [27–29]. Most published studies indicate that circulating endothelin is significantly increased in preeclamptic women compared with nonpregnant controls, and this increase returns to normal levels directly after delivery, consistent with clinical resolution of preeclampsia [30–32]. It should be noted, however, that there are conflicting reports in the literature [33].

Several animal models of pregnancy-induced hypertension have also implicated ET-1 as an important factor in the pathology of preeclampsia. In the reduced uterine perfusion pressure (RUPP) model in rats, cortical and medullary preproET-1 levels are significantly elevated when compared with normal pregnant controls. Critically, the hypertension associated with

this experimental model was significantly decreased with administration of an endothelin type-A (ET_A) antagonist [34]. In the TNF- α infusion model of pregnancy-induced hypertension, which raises TNF- α levels to those seen in pregnant women, preproET-1 levels were again elevated in the kidney, the aorta, and the placenta. In this model, ET_A blockade completely normalized the associated hypertension [35]. In a follow-up study linking these two pieces of data, blockade of TNF- α by the soluble receptor etanercept in the RUPP model led to a significant decrease in the levels of tissue ET-1, and again the associated hypertension was completely normalized [36]. Crucially, the ability of ET-1 to induce hypertension experimentally has been shown to be based at least partially on the production of reactive oxygen, as Tempol is again able to attenuate the hypertensive response to ET-1 infusion in rodents [37].

In the sFlt-1 infusion model of pregnancy-induced hypertension discussed previously, mean arterial pressure is elevated about 15 mm Hg in pregnant rats but not in virgin control rats. In response to elevated sFlt-1, cortical preproET-1 mRNA levels were significantly increased, and again ET_A receptor blockade totally normalized the hypertension [38]. Finally, ET-1 has also been demonstrated to have a significant role in the pathophysiology of the AT1-AA infusion model. When these antibodies are administered experimentally in a rat model, symptoms mimicking preeclampsia are observed. As with the other experimental models mentioned above, significant elevations in tissue preproET-1 are observed. And as seen before, administration of an ET_A receptor antagonist significantly blunts the associated hypertension in this model [39]. This ability of ET_A blockade to blunt the hypertension associated with several diverse models of pregnancy-induced hypertension argues for a very important role for ET-1 in the pathologic manifestations of hypertension in preeclampsia.

Potential New Therapies for Preeclampsia

Although awareness of the dangers of preeclampsia has been growing, clinicians are hampered by the dearth of treatment options once a diagnosis is made. Traditional antihypertensives are relatively ineffective in many cases, and disease management focuses on prolonging gestation as long as possible with restrictive bed rest and anticonvulsives, because only delivery of the baby and placenta fully remediates the disorder. The result is often early delivery by induction or surgery. The identification of new therapies for preeclampsia would be a valuable addition to the obstetric arsenal. The recent advances in our understanding of the mechanisms involved in the development of preeclampsia have presented a number of promising therapeutic avenues, and various new approaches for therapeutic intervention have been proposed in recent years.

One of the most interesting candidates is manipulation of the heme oxygenase-1 (HO-1) enzyme pathway. HO-1 is normally a constituent of the heme degradation pathway, and two of its byproducts produced in the degradation of heme are carbon monoxide (CO) and bilirubin. CO, though toxic at high levels, acts as a potent vasodilator and has been hypothesized to play an important role in maintaining normal vasodilatation in placental vessels [40]. The actions of CO are similar to those of NO, which is postulated to play an important role in the development of preeclampsia. Extra production of CO by induced HO-1 production thus could improve endothelial and vascular function, increase vasodilatation, and reduce hypertension. Additionally, it has recently been shown that in culture, HO-1 and CO can negatively regulate sFlt-1 expression, providing an additional mechanism through which HO-1 could be beneficial in preeclampsia.

Bilirubin, the major end product of HO-1, is a powerful antioxidant agent, and as previously discussed, oxidative stress is an important mediator of pregnancy-induced hypertension. Increasing HO-1 activity may then reduce vascular oxidative stress and improve endothelial

dysfunction. Supporting this concept, beneficial effects of HO-1 induction have been demonstrated in a number of experimental models of hypertension that share many of the same mechanistic pathways as preeclampsia [41••, 42, 43]. Future studies into the expression of HO-1 or the administration of CO, bilirubin, or both should help indicate whether this is a viable pathway for the treatment of preeclampsia.

Another pharmacologic intervention that has been suggested for treatment of preeclampsia is administration of the phosphodiesterase type 5 (PDE5) inhibitor sildenafil citrate. PDE enzymes catalyze the degradation of the NO secondary messenger cGMP, and thus antagonize vasodilatation. Preliminary work in sheep has demonstrated that PDE5 is localized in the maternal portion of the uteroplacental unit [44]. Furthermore, endothelium-dependent relaxation of myometrial arteries taken from preeclamptic women or women whose pregnancies were complicated by fetal growth restriction was enhanced by the inhibition of PDE5 [45, 46]. Phase 2 clinical trials have been reported on the safety of sildenafil during pregnancy, but no beneficial effect was observed in preeclamptic women [47]. However, sildenafil was only administered late in the affected pregnancies, and objections have been raised as to the design of the study [48]. Future research into the feasibility of treating preeclampsia with PDE5 inhibitors is needed to firmly establish whether this therapy will be effective in a clinical setting.

Finally, it seems clear that endothelin-1, acting through the ET_A receptor, is a pivotal pathway in the etiology of preeclampsia. In every experimental model of preeclampsia examined, administration of an ET_A antagonist significantly improved the associated symptoms. Unfortunately, clinical administration of an ET_A antagonist has been largely rejected, as ET_A knockout causes birth defects and neonatal death in mice [49]. However, follow-up pharmacologic antagonism of ET_A receptors pinpointed specific windows of gestation that were responsible for the birth defects and death. All of these windows occurred with administration in early to mid gestation, leaving open the possibility that ET_A receptor antagonists could be an effective intervention for the treatment of preeclampsia in late gestation [50]. Further research into the safety and efficacy of ET_A receptor antagonists is certainly warranted.

Conclusions

The past two decades have greatly increased our understanding of the mechanisms underlying preeclampsia. Though the initiating cause remains unknown, we now know that placental ischemia is a central agent in producing many of the detrimental symptomatic effects seen in the disorder. Experimentally, placental ischemia has been shown to lie at the root of changes in angiogenic balance, increases in oxidative stress, increases in maternal inflammatory responses, decreases in NO availability, and increased production of ET-1. Together, these pathways are responsible for much of the pathology associated with preeclampsia.

The lack of effective pharmacologic therapeutic approaches for the management of preeclampsia is a serious health concern in clinical obstetrics. New potential therapies focusing on manipulating these newly defined pathologic pathways provide a tantalizing subject for future research. As can be seen in Fig. 1, multiple identified pathways leading from placental ischemia to hypertension provide distinct and intriguing therapeutic targets for the management of preeclampsia. Research looking into the use of HO-1, sildenafil, and ET_A receptor blockade is an important first step in identifying a useful intervention for the treatment of preeclampsia.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. 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):109–27. [PubMed: 12908996]
2. Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a more pathophysiological approach. *Obstet Gynecol*. 2010; 115(2 Pt 1):365–75. [PubMed: 20093912]
3. Turner JA. Diagnosis and management of pre-eclampsia: an update. *Int J Womens Health*. 2010; 2:327–37. [PubMed: 21151680]
4. Gant NF, Daley GL, Chand S, et al. A study of angiotensin II pressor response throughout primigravid pregnancy. *J Clin Invest*. 1973; 52(11):2682–9. [PubMed: 4355997]
5. Khong Y, Brosens I. Defective deep placentation. *Best Pract Res Clin Obstet Gynaecol*. 2010 in press.
6. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstet Gynecol Annu*. 1972; 1:177–91. [PubMed: 4669123]
7. Lim KH, Zhou Y, Janatpour M, et al. Human cytotrophoblast differentiation/invasion is abnormal in pre-eclampsia. *Am J Pathol*. 1997; 151(6):1809–18. [PubMed: 9403732]
8. 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):186–93. [PubMed: 17261421]
- 9•. Wu FT, Stefanini MO, Mac Gabhann F, et al. A systems biology perspective on sVEGFR1: its biological function, pathogenic role and therapeutic use. *J Cell Mol Med*. 2010; 14(3):528–552. [PubMed: 19840194] [This review exhaustively examines the molecular mechanisms of the actions of sFlt-1 and the available physiological data about its role in human disease.]
10. 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]
11. 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):649–58. [PubMed: 12618519]
12. 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):564–8. [PubMed: 19265787]
13. 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):1142–7. [PubMed: 17923588]
14. 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):380–5. [PubMed: 20026764]
15. 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*. 2010; 14(6B):1857–67. [PubMed: 19538465]
- 16••. 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):H541–550. [PubMed: 18055511] [This review thoroughly covers the evidence indicating the central role of placental ischemia in the development of preeclampsia. The evidence for multiple pathways leading to the hypertensive state is covered in detail.]
17. 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):1010–9. [PubMed: 18259044]

- 18*. 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] [In this paper, Zhou et al. demonstrate the importance of the AT1-AA in the development of preeclampsia-like symptoms. More importantly, they demonstrate that an epitope mimetic hepta peptide, which neutralizes the antibody, is capable of attenuating its effects. This finding suggests an intriguing target for therapeutic intervention.]
19. 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):587–92. [PubMed: 10076133]
20. 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):1152–6. [PubMed: 18670418]
21. Anumba DO, Robson SC, Boys RJ, Ford GA. Nitric oxide activity in the peripheral vasculature during normotensive and preeclamptic pregnancy. *Am J Physiol.* 1999; 277(2 Pt 2):H848–854. [PubMed: 10444514]
22. Nelson SH, Steinsland OS, Wang Y, et al. Increased nitric oxide synthase activity and expression in the human uterine artery during pregnancy. *Circ Res.* 2000; 87(5):406–11. [PubMed: 10969039]
23. Khalil RA, Crews JK, Novak J, et al. Enhanced vascular reactivity during inhibition of nitric oxide synthesis in pregnant rats. *Hypertension.* 1998; 31(5):1065–9. [PubMed: 9576115]
24. Alexander BT, Kassab SE, Miller MT, et al. Reduced uterine perfusion pressure during pregnancy in the rat is associated with increases in arterial pressure and changes in renal nitric oxide. *Hypertension.* 2001; 37(4):1191–5. [PubMed: 11304523]
25. Lyall F, Young A, Greer IA. Nitric oxide concentrations are increased in the fetoplacental circulation in preeclampsia. *Am J Obstet Gynecol.* 1995; 173(3 Pt 1):714–8. [PubMed: 7573231]
26. Lyall F, Greer IA. The vascular endothelium in normal pregnancy and pre-eclampsia. *Rev Reprod.* 1996; 1(2):107–16. [PubMed: 9414447]
27. 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):6964–7. [PubMed: 3045827]
28. Yanagisawa M, Kurihara H, Kimura S, et al. A novel peptide vasoconstrictor, endothelin, is produced by vascular endothelium and modulates smooth muscle Ca²⁺ channels. *J Hypertens Suppl.* 1988; 6(4):S188–191. [PubMed: 2853725]
29. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature.* 1988; 332(6163):411–5. [PubMed: 2451132]
30. 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):1675–7. [PubMed: 2229324]
31. Bernardi F, Constantino L, Machado R, et al. Plasma nitric oxide, endothelin-1, arginase and superoxide dismutase in pre-eclamptic women. *J Obstet Gynaecol Res.* 2008; 34(6):957–63. [PubMed: 19012693]
32. 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):485–8. [PubMed: 19390804]
33. 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]
34. Alexander BT, Rinewalt AN, Cockrell KL, et al. Endothelin type a receptor blockade attenuates the hypertension in response to chronic reductions in uterine perfusion pressure. *Hypertension.* 2001; 37(2 Part 2):485–9. [PubMed: 11230323]
35. LaMarca BB, Cockrell K, Sullivan E, et al. Role of endothelin in mediating tumor necrosis factor-induced hypertension in pregnant rats. *Hypertension.* 2005; 46(1):82–6. [PubMed: 15928030]
36. 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-alpha blockade. *Hypertension.* 2008; 52(6):1161–7. [PubMed: 18981324]
37. Sedeek MH, Llinas MT, Drummond H, et al. Role of reactive oxygen species in endothelin-induced hypertension. *Hypertension.* 2003; 42(4):806–10. [PubMed: 12874096]

38. 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):394–8. [PubMed: 20026766]
39. 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):905–9. [PubMed: 19704104]
40. Bainbridge SA, Farley AE, McLaughlin BE, et al. Carbon monoxide decreases perfusion pressure in isolated human placenta. *Placenta*. 2002; 23(8–9):563–9. [PubMed: 12361675]
41. Cao J, Inoue K, Li X, et al. Physiological significance of heme oxygenase in hypertension. *Int J Biochem Cell Biol*. 2009; 41(5):1025–1033. [PubMed: 19027871] [This review thoroughly highlights the potentials and pitfalls of using HO-1 in treating hypertension. The roles of the individual metabolic byproducts are thoroughly reviewed.]
42. Sabaawy HE, Zhang F, Nguyen X, et al. Human heme oxygenase-1 gene transfer lowers blood pressure and promotes growth in spontaneously hypertensive rats. *Hypertension*. 2001; 38(2):210–5. [PubMed: 11509478]
43. Yang L, Quan S, Nasjletti A, et al. Heme oxygenase-1 gene expression modulates angiotensin II-induced increase in blood pressure. *Hypertension*. 2004; 43(6):1221–6. [PubMed: 15166181]
44. Coppage KH, Sun X, Baker RS, Clark KE. Expression of phosphodiesterase 5 in maternal and fetal sheep. *Am J Obstet Gynecol*. 2005; 193(3 Pt 2):1005–10. [PubMed: 16157102]
45. Wareing M, Myers JE, O'Hara M, et al. Effects of a phosphodiesterase-5 (PDE5) inhibitor on endothelium-dependent relaxation of myometrial small arteries. *Am J Obstet Gynecol*. 2004; 190(5):1283–90. [PubMed: 15167831]
46. Wareing M, Myers JE, O'Hara M, Baker PN. Sildenafil citrate (Viagra) enhances vasodilatation in fetal growth restriction. *J Clin Endocrinol Metab*. 2005; 90(5):2550–5. [PubMed: 15713717]
47. Samangaya RA, Mires G, Shennan A, et al. A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor sildenafil for the treatment of preeclampsia. *Hypertens Pregnancy*. 2009; 28(4):369–82. [PubMed: 19843000]
48. Downing J. Sildenafil for the treatment of preeclampsia. *Hypertens Pregnancy*. 2010; 29(2):248–50. author reply 251–242. [PubMed: 20367510]
49. Clouthier DE, Hosoda K, Richardson JA, et al. Cranial and cardiac neural crest defects in endothelin-A receptor-deficient mice. *Development*. 1998; 125(5):813–24. [PubMed: 9449664]
50. Taniguchi T, Muramatsu I. Pharmacological knockout of endothelin ET(A) receptors. *Life Sci*. 2003; 74(2–3):405–9. [PubMed: 14607269]

Fig. 1.

A network of mechanisms leads from placental ischemia to hypertension during the development of preeclampsia. This diagram presents three possible therapeutic interventions —heme oxygenase-1 (HO-1), endothelin type-A (ET_A) receptor blockade, and sildenafil—that interact with these pathways at discrete sites and provide exciting avenues for the development of new therapies for the management of preeclampsia. *AT1-AA* agonistic autoantibodies to the angiotensin type 1 receptor, *ET-1* endothelin-1, *HIF-1* hypoxia-inducible factor-1, *NO* nitric oxide, *ROS* reactive oxygen species, *sFlt-1* soluble fms-like tyrosine kinase-1, *TNF-* tumor necrosis factor-, *VEGF* vascular endothelial growth factor