Maternal Vascular Physiology in Preeclampsia

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Preeclampsia is a systemic syndrome that occurs during pregnancy and postpartum and affects 3% to 8% of pregnancies. It is one of the leading causes of maternal and neonatal mortality and morbidity worldwide. The American College of Obstetricians and Gynecologists and the International Society for the Study of Hypertension in Pregnancy have set the following criteria for the clinical diagnosis of preeclampsia: de novo maternal hypertension (>140/90 mm Hg) with proteinuria (0.3 g per 24 hours) after 20 weeks of gestation or hypertension combined with hematologic complications, impaired renal and liver function, neurological symptoms, or uteroplacental dysfunction. This broad definition reflects the heterogeneity in clinical presentation of preeclampsia, which suggests heterogeneity in the pathogenesis of this syndrome.

Maternal vascular dysfunction and abnormal hemodynamics are common features of preeclampsia and may be evident in both reproductive and nonreproductive vascular beds. Components of aberrant vascular physiology in preeclampsia include impaired vascular endothelial function, incomplete uterine artery remodeling, augmented vasoconstriction, vascular oxidative stress, and inflammation. Studies using flow-mediated dilation have shown that women who had preeclampsia had lower flow-mediated dilation before clinical diagnosis of preeclampsia, at the time of preeclampsia, and for 3 years postpartum, suggesting that vascular dysfunction may play a role in the pathogenesis of preeclampsia and may be a link between preeclampsia and high risk for cardiovascular disease later in life.

The main objective of this brief review is to discuss the molecular mechanisms underlying aberrant maternal vascular physiology in reproductive and nonreproductive vascular beds in preeclampsia. Evidence from studies in experimental animals and in humans will be discussed. Currently, there is lack of evidence that species other than humans spontaneously develop preeclampsia. Therefore, animal models resembling preeclampsia-like features that are induced by experimentation will be referred as models of experimental preeclampsia.

Systemic Maternal Vascular (Patho) Physiology in Preeclampsia

Increases in cardiac output, expansion of plasma volume, and reduction in total vascular resistance comprise major systemic hemodynamic adaptations in normal pregnancies. Systemic maternal arteries show reduced vascular tone, which contributes to reduced peripheral vascular resistance. In contrast to normal pregnant women, systemic maternal arteries from women with preeclampsia show endothelial dysfunction that is characterized by endothelial injury, reduced dilatory responses, and imbalance in the bioavailability of endothelium-derived vasoactive substances. Glomerular endotheliosis is also observed in preeclamptic women. These abnormalities lead to renal injury and microalbuminuria that is sustained for up to 2 to 4 months after delivery. The following sections will focus on how changes in the bioavailability of vasodilator and action of main endothelium-derived products contribute to abnormal systemic vascular function in preeclampsia. The contribution of vascular smooth muscle–specific pathways to systemic maternal vascular dysfunction will also be considered. The role of circulating angiogenic factors and circulating inflammatory factors as mediators of endothelial activation in preeclampsia has been extensively addressed in previous reviews and will not be covered herein.

Endothelium-Derived Vasodilators

Nitric Oxide

Vascular endothelial cells from preeclamptic women and endothelial cells exposed to serum from preeclamptic pregnancies produce less nitric oxide (NO). Further, agonist-stimulated NO production is reduced in isolated umbilical arteries from women with preeclampsia. Phosphorylation of endothelial NO synthase and changes in intracellular Ca2+ concentrations in endothelial cells are the main determinants of NO production. Previous studies reported increased expression of NO synthase in endothelial cells stimulated with plasma from preeclamptic women. Reduced NO bioavailability in the presence of increased NO synthase expression may be explained by increased scavenging of NO by superoxide. NADPH oxidase and NOS uncoupling because of l-arginine deficiency contribute to superoxide generation in endothelial cells. Treating human endothelial cells with l-arginine, Sankaralingam et al demonstrated that in the presence of superoxide formation, l-arginine supplementation led to formation of peroxynitrite, which has been shown to be increased in the vasculature of women with preeclampsia. In contrast, l-arginine supplementation after inhibition of oxidative stress did not result in peroxynitrite formation, indicating that the oxidant status of the maternal environment may determine the efficacy of certain therapeutic interventions. In addition to superoxide-mediated NO scavenging, increased activity of endogenous NO-negative regulators could also contribute to reduced NO bioavailability. Indeed, expressions of arginase and asymmetrical dimethyl arginine...
are increased in placental and vascular tissues from women with preeclampsia. Systemic pharmacological inhibition of NOS with nitroarginine methyl ester (L-NAME) during pregnancy induced preeclampsia-like features (ie, hypertension, proteinuria, thrombocytopenia, and intrauterine growth restriction) in mice and rats.26–28 These findings underline the significance of NO in the pathophysiology of preeclampsia.

**Prostacyclin**

Prostacyclin (PGI2) is a cyclooxygenase-derived product with potent vasodilatory properties. PGI2 has a short half-life, and thus, indirect measurements of its stable metabolite 6-keto-PGF2α are usually performed. Early studies showed that concentrations of PGI2 metabolites were increased in urine of healthy pregnant compared with healthy nonpregnant women.29 It is likely that this is because of a pregnancy-mediated upregulation of cyclooxygenase enzyme activity in endothelial cells, which has been previously reported in pregnant ewes.30 Pregnancy-mediated changes in cyclooxygenase expression in vascular tissues have not been reported. In preeclampsia, PGI2 metabolites are decreased,31 and this is evident in various vascular beds, plasma, and urine from patients with preeclampsia.31,32 Women who developed hypertension in late pregnancy had also a 50% reduction in urine PGI2 metabolites compared with healthy pregnant women.29 The reduction in PGI2 production may be because of impaired endothelial Ca2+ signaling as determined in intact umbilical vein endothelium from patients with preeclampsia.19 Reactive oxygen species may also contribute to inhibition of PGI2 production.33

**Endothelium-Derived Hyperpolarization**

Endothelium-dependent vasodilation does not depend solely on NO and PGI2. We now know that >1 factor(s) and processes contribute to non-NO, non-PGI2 endothelium-derived vascular smooth muscle hyperpolarization (EDH) and relaxation.34 EDH contribution to relaxation responses varies with vascular bed, vessel size, species, and disease state. EDH contributes to relaxation responses in omental arteries from normal pregnant women. Activation of small-conductance Ca2+-activated K+ channels (SKca) and intermediate-conductance Ca2+-activated K+ channels (IKca) in endothelial cells is the underlying mechanism of this response.19 In many but not all vessels, the endothelial and vascular smooth muscle cells are coupled electrically via myoendothelial gap junctions (MEGJs).35 SKca and IKca-induced hyperpolarization spreads via these junctions to induce vascular smooth muscle cell relaxation. MEGJs and the gap junction protein, Cx43 (connexin 43), are the primary mechanisms underlying EDH in small resistance arteries isolated from subcutaneous fat biopsies from normal pregnant women.37,38 The function of MEGJ was deficient in arteries from women with preeclampsia, contributing to reduced EDH involvement in dilatory responses to bradykinin.39 Total relaxation to bradykinin, however, did not differ between normal pregnant and preeclamptic women.39 Expression of Cx43 did not differ between omental arteries from pregnant women with preeclampsia and normal pregnant women.40 The activity of Cx43 in systemic maternal arteries from pregnancies with preeclampsia has not been characterized. It has been recently suggested that growth factors and cytokines involved in preeclampsia may mediate endothelial dysfunction via closure of Cx43 because of inhibitory phosphorylation of this gap junction protein.41 It is likely that the role of Cx43 is important in all Ca2+-sensitive processes affecting endothelial function, including NO and PGI2 production.

The contribution of EDH has been examined in the context of the potent endothelium-dependent vasodilation conferred by placental growth factor. Placental growth factor, which binds to the vascular endothelial growth factor receptor-1, induced endothelial cell hyperpolarization via activation of SKca channels in mesenteric arteries from pregnant rats.42 This hyperpolarization was independent from NO and PGI2, and was spread to the vascular smooth muscle cells via large-conductance calcium-activated potassium channels (BKca) that were activated by an unknown diffusible factor.42 The authors posited that in preeclampsia, attenuation of placental growth factor–induced EDH contributes to impaired function of resistance arteries and leads to maternal hypertension.42 Recent studies suggest the involvement of hydrogen sulfide, a gaseous signaling molecule that induces EDH,43 in preeclampsia-associated vascular dysfunction. Circulating hydrogen sulfide is reduced in pregnant women with preeclampsia,44 and expression of cystathionine-β-synthase, the enzyme that is involved in desulfuration of l-cysteine into hydrogen sulfide, is attenuated in endothelial cells stimulated with plasma from pregnancies with preeclampsia.45 Holwerda et al reported that the cystathionine-β-synthase tag single nucleotide polymorphism rs11203172 is associated with a significantly reduced risk to develop early-onset preeclampsia.46 Contribution of EDH to vasodilation is not affected in some models of experimental preeclampsia. Dams treated with testosterone propionate in the third trimester exhibited high blood pressure, endothelial dysfunction, reduced uterine blood flow, and attenuated uterine artery remodeling. In this model, reduced vasodilatory responses to acetylcholine in mesenteric arteries were NO-dependent but independent from PGI2 and EDH.47

In summary, mechanisms underlying reduced vasodilatory responses in maternal arteries from preeclamptic pregnancies include (1) reduction in NO bioavailability and PGI2 production, (2) increase in vascular oxidative stress, and (3) modification in the contribution of NO, PGI2, and EDH relaxation components to total relaxation. Disruption of MEGJs and ion channels, changes in intracellular Ca2+ concentrations, and upregulation of negative regulators of vasodilatory processes contribute to the impaired vasodilatory processes in preeclampsia.

**Endothelium-Derived Vasoconstrictors**

**Thromboxane A2**

Thromboxane A2 (TXA2) is a constrictor prostanoid that is produced from arachidonic acid metabolism in endothelial cells and in platelets.48 The TXA2 metabolite TXB2 is increased in the circulation and urine from women with preeclampsia, implicating TXA2 in the pathophysiology of this disorder.49 In omental arteries from women with preeclampsia, reduced DNA methylation of the promoter of the thromboxane synthase gene (TXAS1) was correlated with increased expression of thromboxane synthase.50,51 Increased expression of thromboxane synthase was found in vascular smooth muscle...
cells, endothelial cells, and neutrophils. Thus, it is likely that epigenetic mechanisms underlie the increased expression of thromboxane synthase in systemic maternal arteries in preeclampsia.

TXA₂ binds the TP (TXA₂ receptor) in vascular smooth muscle cells to induce constriction via multiple mechanisms. In isolated mesenteric arteries from pregnant rats, contractile responses to a TXA₂ mimetic (U46619) are mediated by second messengers—Rho kinase, PKC (protein kinase C), and MAPKs (mitogen-activated protein kinases)—and are inhibited by NO. Using pregnant rats, we recently showed that release of TxB₂ (TXA₂-stable metabolite) from mesenteric arteries was increased in rats with gestational hypertension induced by exposure to an immunogenic stimulus. In addition to its direct constrictor effects, TXA₂ potentiates contractions induced by angiotensin II and ET-1 (endothelin-1). These data indicate that the contribution of TXA₂ to enhanced vasoconstriction in pregnancies with preeclampsia are because of the independent effects of TXA₂ via TP activation but also via its ability to potentiate the actions of other potent constrictors.

NO and PGI₂ negatively regulate TXA₂-induced contractions by TP desensitization. Given that NO and PGI₂ are reduced in preeclampsia, it is reasonable to suggest that negative regulation of TP is also impaired. Animal studies have confirmed this hypothesis. Contractile responses to TP activation were increased in resistance mesenteric arteries in a rat model with gestational hypertension, and inhibition of NOS did not have any effect on these responses. In contrast, inhibition of NOS potentiated these contractions in normal pregnant rats, indicating loss of the NO inhibitory effects in the experimental group.

Low-dose aspirin treatment is currently recommended in women at high risk of developing preeclampsia. Inhibition of TXA₂ production is one of the primary actions of aspirin. In women with preeclampsia, initiation of aspirin treatment (50–150 mg/d) before 16 weeks of gestation results in a dose-response reduction in the incidence of preeclampsia. In experimental studies, low-dose aspirin treatment during pregnancy attenuated systemic and vascular production of TxB₂ in a rat model with gestational hypertension but did not improve blood pressure and vascular reactivity.

**Endothelin-1**

ET-1 is produced in endothelial cells and interacts with (1) ETₐ receptors in vascular smooth muscle cells to induce vasoconstriction, and (2) ETₐ receptor in endothelial cells to trigger the production of endothelium-derived vasodilators. ET-1 concentrations are increased in the circulation of women with preeclampsia as compared with healthy pregnant women and are greatest at the later stages of preeclampsia, indicating that ET-1 may be involved in the pathophysiology but not in the pathogenesis of preeclampsia. Increases in ET-1 production, downregulation of ETₐ receptor in endothelial cells, and upregulation of ETₐ and ETₐ receptors in vascular smooth muscle cells may all contribute to reduced relaxation and increased vasoconstriction in pregnancies with preeclampsia. In an animal model of experimental preeclampsia that is induced by surgical reduction of uterine blood flow, ET-1-induced constriction is increased in resistance arteries. This increase is associated with ET-1-induced increases in calcium influx. Pharmacological inhibition of ETₐ receptors reduces preeclampsia-like symptoms in various models of experimental preeclampsia, indicating that the ET-1 contribution to preeclampsia is ETₐ dependent. ETₐ receptors are also involved in experimental preeclampsia. Expression and activity of endothelial ETₐ receptors were reduced in rats with preeclampsia-like features (ie, hypertension, intrauterine growth restriction, proteinuria, renal dysfunction) induced by surgical reduction of uterine blood flow as compared with sham controls. Others have shown that contractile responses to inactive precursor big ET-1 were increased in mesenteric arteries from this experimental model and that inhibition of matrix metalloproteinase, an enzyme that catalyzes the conversion of big ET-1 to ET-1, abolished the enhanced contractile responses.

Collectively, studies on endothelium-derived constrictors suggest that TXA₂ and ET-1 contribute to maternal vascular dysfunction in women with preeclampsia and in animal models with experimental preeclampsia. Neither the human nor the animal investigations, however, provide any insight into whether changes in TXA₂ and ET-1 production and actions contribute to the pathogenesis of preeclampsia or are consequences of the syndrome.

**Angiotensin II**

Angiotensin II (Ang II) is a potent constrictor that is implicated in increased vascular tone in preeclampsia. Circulating Ang II is not increased in women with preeclampsia; however, the sensitivity of their vascular system to Ang II is exaggerated as compared with normal pregnant women. Ang II induces its constrictor effects through binding of the Ang II receptor type 1 that has increased expression in pregnancies with preeclampsia. Previous studies reported that agonistic autoantibodies are present in the circulation of women with preeclampsia, and this may further enhance Ang II signaling in this population. Interestingly, women with a history of preeclampsia had augmented microvascular constrictor responses to Ang II, indicating that preeclampsia-associated vascular dysfunction persist postpartum. Phosphorylation of ERK1/2 (extracellular signal-regulated kinase 1/2), induction of NADPH oxidase, phosphorylation of NF-κB (nuclear factor kappa light chain enhancer of activated B cells), and promoter activation in the nucleus have been all implicated in Ang II hypersensitivity in preeclampsia. Studies in rats treated with L-NAME during pregnancy suggest that hypersensitivity to Ang II may be because of oxidative stress and reduced NO bioavailability.

**Vascular Smooth Muscle Cell Physiology**

The majority of studies on maternal vascular physiology in preeclampsia have been focused on the vascular endothelium, and only few investigations have addressed the contribution of vascular smooth muscle to maternal vascular dysfunction. This evidence suggests deficiencies in both vasodilatory (ie, soluble guanylyl cyclase [sGC]-cyclic guanosine monophosphate [cGMP] pathway) and constrictor (ie, Ca²⁺ signaling) mechanisms.

To examine the dilatory responses of vascular smooth muscle cells in the presence of preeclampsia, Turgut et al assessed the vascular effects of sGC stimulators and NO.
donors in pregnant rats treated with suramin that exhibit preeclampsia-like features such as hypertension, proteinuria, and intrauterine growth restriction. In these rats, relaxation responses to sGC stimulators and NO donors were diminished because of a reduction in sGC stimulation and cGMP content.

The enzymes phosphodiesterases regulate cGMP, which is downstream of the interaction of NO with sGC in vascular smooth muscle cells. Serum phosphodiesterases is increased, and cGMP concentrations are attenuated in pregnancies with preeclampsia. Sildenafil, a phosphodiesterases-5 inhibitor, has been used in various experimental and clinical settings to overcome the increased phosphodiesterases activity and improve pregnancy outcomes in preeclampsia. Sildenafil improved maternal and fetal outcomes and reduced oxidative stress and ET-1 in models of experimental preeclampsia. Release of Ca2+ from intracellular stores and entry of Ca2+ from the extracellular space cause an increase in intracellular Ca2+ concentrations, which trigger the contraction of vascular smooth muscle. Incubation of human umbilical smooth muscle cells cocultured with umbilical endothelial cells with serum from women with preeclampsia increased intracellular Ca2+ concentrations and PKC-α (second messenger) activation. In cultured rat aortic vascular smooth muscle cells, 4-hour incubation with serum from patients with preeclampsia had no effect on basal intracellular Ca2+ concentrations but reduced hormonally mediated Ca2+ transients. Basal and agonist-stimulated intracellular calcium concentrations were increased in smooth muscle cells isolated from renal interlobular arteries of L-NAME-treated pregnant rats.

In summary, changes in the sGC/cGMP pathway, intracellular Ca2+ concentrations, and sensitivity to Ca2+ possibly underline dysfunction in the vascular smooth muscle cell layer in arteries with women with preeclampsia.

**Uterine Arterial Adaptations and Responses in Preeclampsia**

**Spiral Artery Remodeling**

The term uterine artery remodeling often refers to spiral artery remodeling, although structural changes are seen in uterine vessels of varying sizes during pregnancy. Remodeling of the spiral arteries involves derangement of their vascular smooth muscle layer and loss of their endothelial lining. This results in conversion of the spiral arteries from tightly coiled vessels to low resistance, wide-bore conduits that are not tonically active. In preeclampsia, spiral artery remodeling is incomplete, with some vessels retaining portions of their smooth muscle and others being totally unmodified. Incomplete transformation of the spiral arteries to low-resistance vessels decreases uterine blood flow and blood supply to the growing fetus.

Spiral artery remodeling is a well-coordinated process that is mediated by several factors, including hormonal influences, immune cells, and extravillous trophoblasts. The significance of trophoblastic invasion in spiral artery remodeling is highlighted by evidence that in placental bed biopsies from pregnancies with preeclampsia obtained during cesarean sections, trophoblastic invasion was absent in the majority of samples, indicating that failure of trophoblastic invasion is associated with the placental pathology of preeclampsia. Trophoblasts invade the spiral arteries starting at 6 to 8 weeks of human gestation and complete their task by 20 weeks of gestation. The attracted trophoblast cells downregulate the production of epithelial-like molecules and upregulate the release of endothelial-specific adhesion molecules. In preeclampsia, invasive trophoblast cells fail to express endothelial markers, such as integrin, cadherin, and the Ig superfamily members.

Trophoblastic invasion of spiral arteries had been initially suggested as the primary mechanism responsible for the transformation of the spiral arteries. Observations in intrauterine decidual samples from tubal pregnancies and early terminations, however, showed that early vascular changes occur in the absence of invading trophoblasts, indicating that other cell populations are also involved. Studies in human decidua basalis samples demonstrated that vascular infiltration of spiral arteries by natural killer cells and decidual macrophages precedes trophoblastic invasion. Desialized immune cells secrete chemoattractants that aid in the recruitment of trophoblast cells. Chemotraction of trophoblast cells by decidual natural killer cells was reduced in pregnancies, with high uterine artery resistance index. These measurements were obtained from pregnancies before early termination that were not diagnosed with preeclampsia. Given that pregnancies with preeclampsia are associated with high uterine resistance index, these data suggest that impaired interaction between fetal trophoblast cells and uterine leukocytes may lead to poor spiral artery remodeling in preeclampsia.

Poor spiral artery remodeling is primarily seen in early-onset (delivery at <34 weeks) compared with late-onset (delivery at >34 weeks) preeclampsia. Cytokines produced within the uterine environment play a regulatory role in trophoblast function and may explain the heterogeneity in the presentation of spiral artery transformation between different subtypes of the syndrome. IL-11, a member of the gp130 family, has been shown to inhibit extravillous trophoblastic invasion and spiral artery remodeling. Circulating IL-11 is significantly increased, and placental IL-11 is upregulated in women with early-onset versus late-onset preeclampsia. Pregnant mice treated with IL-11 exhibit preeclampsia-like features.

**Main Uterine, Arcuate, and Radial Artery Remodeling**

The main uterine, arcuate, and radial arteries undergo remodeling during normal pregnancy, but it is unknown whether the mechanisms underlying their adaptation are trophoblast dependent or trophoblast mediated. Remodeling of these arteries refers to increases in their lumen (outward remodeling) and in their length (elongation). In pregnant rats, the
internal diameter of the main uterine artery increases, and the extent of this adaptation differs between the ovarian (30% increase) and cervical origins (80% increase) of the artery.\textsuperscript{95} Pregnancy-associated changes in the lumen of the vascular wall have been attributed to vascular smooth muscle cell axial hypertrophy and hyperplasia.\textsuperscript{94,96} Elongation of the main uterine, arcuate, and radial arteries is evident in various species. In pregnant rats, the length of the main uterine artery at term is 2- to 3-fold greater compared with the length of the uterine artery from nonpregnant rats.\textsuperscript{94} Pregnant rats with hypertension, vascular dysfunction, and proteinuria because of testosterone treatment had reduced radial artery diameter and length, diminished uterine blood flow, and elevated markers of hypoxia in placental tissues.\textsuperscript{97} Reduced placental perfusion in eNOS knockout mice was associated with a 30% reduction in uterine and radial arteries.\textsuperscript{99} This model does not exhibit gestational hypertension and proteinuria but shows systemic vascular dysfunction and placental hypoxia,\textsuperscript{99} which are also features of preeclampsia.

### Uterine Artery Function

Myometrial arteries from women with preeclampsia had similar myogenic tone with arteries from healthy pregnant women but were unable to develop flow-mediated shear stress–induced relaxation.\textsuperscript{99} In pregnant rats with surgically induced reduced uterine blood flow, uterine resistance arteries had increased myogenic reactivity and decreased vasodilatory responses to methacholine and vascular endothelial growth factor.\textsuperscript{100} Increased receptor-mediated uterine artery constriction has been also reported in models with experimental preeclampsia. Uterine arteries from the catechol-O-methyl transferase (COMT\textsuperscript{−/−}) knockout mouse\textsuperscript{101,102} and the TgA rat (transgenic human angiotensinogen × human renin) exhibited augmented uterine artery responsiveness to phenylephrine and angiotensin II, respectively.\textsuperscript{9}

Reactivity to agonist-induced vasodilation in the main uterine artery relies primarily on NO, although PGI\textsubscript{2} contribution has been reported.\textsuperscript{103–105} In rat uterine arteries, EDH contribution has also been reported.\textsuperscript{103,106} As in systemic arteries, pregnancy mediates the contribution of NO, PGI\textsubscript{2}, and EDH to total vasodilation in uterine arteries as well. In radial arteries from normal pregnant rats, NO contributes 30% and EDH contributes 70%, whereas in arteries from nonpregnant rats, these contributions are 80% and 20%, respectively.\textsuperscript{107} Upregulation of Ca\textsuperscript{2+}-activated K\textsuperscript{+} (K\textsubscript{Ca}) channels via steroid hormone–dependent mechanisms may contribute to pregnancy-mediated increases in EDH-dependent uterine artery dilation.\textsuperscript{108} Gestational hypoxia inhibits BK\textsubscript{Ca} and SK\textsubscript{Ca} channel upregulation,\textsuperscript{109,110} and this may be because of pathways mediated by reactive oxygen species.\textsuperscript{111} Considering that preeclampsia is associated with hypoxia and is a state of oxidative stress, these results may have implications for preeclampsia.\textsuperscript{111} Indeed, a reduction in EDH because of disruption of MEGJs was found in myometrial arteries from women with preeclampsia.\textsuperscript{112} In normal human pregnancy, EDH solely involves MEGJs, but in preeclampsia, multiple pathways contribute to EDH, including MEGJs, hydrogen peroxide, and cytochrome P-450 epoxygenase products of arachidonic acid metabolism.\textsuperscript{112}

Changes in intracellular-free Ca\textsuperscript{2+} concentrations and signaling in vascular cells plays a role in production of NO and PGI\textsubscript{2}, as well as in tonic responses of vascular smooth muscle cells. Mechanisms underlying changes in calcium concentrations involve transient receptor potential vanilloid type 3 and type 4 ion channels, upregulation of transient receptor potential canonical type 3, and upregulation of connexins.\textsuperscript{5,113} Studies on Ca\textsuperscript{2+} entry mechanisms are relatively new and need to be expanded in models of experimental preeclampsia to better understand the pathophysiology of the uteroplacental circulation.

### Conclusions and Perspectives

Aberrant maternal vascular physiology is a main characteristic of preeclampsia and is evident in reproductive and nonreproductive vascular beds (Figure). The mechanisms underlying vascular dysfunction in peripheral (nonreproductive vasculature) and regional (uteroplacental vasculature) vascular beds, and the molecular links between systemic and uteroplacental aberrant vascular physiology in preeclampsia are not well understood. In some cases, the underperfused placenta releases antiangiogenic and immunogenic factors that can act on the maternal circulation, accelerating and potentiating systemic maternal vascular dysfunction.\textsuperscript{4,60} It is possible that maternal factors, such as preexisting low-grade inflammation and exposure to infections, determine maternal propensity to develop vascular dysfunction and to have impaired hemodynamics when the mother faces the physiological cardiovascular stress of normal pregnancy.

The presentation of vascular dysfunction is not homogeneous among cases with preeclampsia. For example, aberrant uterine remodeling and reactivity are not always accompanied by systemic maternal vascular dysfunction and vice versa. Consequently, not all pregnancies with preeclampsia are associated with placental underperfusion and intrauterine...
growth restriction. Understanding the source of this heterogeneity and its implications may shed insight into the differential mechanisms underlying the various subtypes of preeclampsia (ie, early versus late onset; placental versus maternal).  

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