Recent Advances in the Understanding of the Pathophysiology of Preeclampsia

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Preeclampsia, a pregnancy-specific disorder, is typically defined as new-onset hypertension presenting after the 20th week of gestation with proteinuria. The overall prevalence in the United States is 3% to 8% with higher incidence in specific ethnic subpopulations, notably blacks. Preeclampsia is a major source of maternal and neonatal morbidity and mortality. Moreover, women who endure preeclampsia are at greater risk of cardiovascular diseases later in life. Studies published in Hypertension and other journals during the last few years have provided new insights not only into potential mechanisms underlying the pathophysiology of preeclampsia but also into the identification of potential biomarkers for the early diagnosis of preeclampsia. Although numerous factors have been implicated in the pathophysiology of preeclampsia, the main focus of this Recent Advances article is to review recent studies that link placental ischemia, endothelial and vascular dysfunction, and hypertension in preeclampsia.

Biomarkers for the Diagnosis of Preeclampsia

Despite intense research into the identification of molecular markers of preeclampsia, a reliable and accurate marker for the early diagnosis of preeclampsia remains elusive. A number of recent articles have suggested markers that could prove useful in the diagnosis of the disorder. With the growing interest in autoimmunity in preeclampsia, several studies have looked at immune factors in the maternal circulation as possible biomarkers. For instance, Siddiqui et al. found widespread (95%) presence of agonistic autoantibodies to the angiotensin type-1 receptor (AT1-AA). Additionally, the levels of these autoantibodies correlated well with the degree of disease severity, suggesting potential use in diagnosis. In a related study, Jensen et al. found that CD19(+)CD5(+) B-cell populations, a potential source for the AT1-AA, are significantly elevated in the maternal circulation of patients with preeclampsia during late gestation when compared with normal-pregnant controls at the same gestational stage.

One of the most active areas of research in preeclampsia is angiogenic imbalance, principally driven by the production of soluble fms-like tyrosine kinase-1 (sFlt-1), the soluble vascular endothelial growth factor (VEGF), and placental growth factor (PIGF) receptor antagonist. Since the initial studies in which sFlt-1 was proposed as a biomarker for the diagnosis of preeclampsia, a number of groups have investigated the use of angiogenic factors as reliable diagnostic markers. Two recent studies have lent credence to this approach. In the first study, Ohkuchi et al. found that the sFlt-1/PIGF ratio was a useful component for predicting preeclampsia when measured at 26 to 31 weeks of gestation. Likewise, Perni et al. examined angiogenic factors in patients who had preexisting hypertension with superimposed preeclampsia, and found higher circulating levels of sFlt-1 before the 20th week of gestation in patients with preeclampsia versus pregnant women who had preexisting hypertension but did not develop preeclampsia.

Although these studies, along with other recent work, suggest that angiogenic balance could be a reliable marker of preeclampsia and allow detection before the onset of patient symptoms, others have argued that angiogenic factors may be better markers of intrauterine growth restriction without the required presence of preeclampsia. However, Romero et al. recently reported that changes in the maternal plasma concentration of soluble endoglin, sFlt-1, and PIGF precede the clinical presentation of preeclampsia, but only changes in soluble endoglin and PIGF precede the delivery of a small for gestational age neonate.

In a recent expert opinion article in Hypertension, Staff et al. argued that the classic definitions of preeclampsia, based on concepts that are now >50 years old, have become outdated and that the definition could be modernized to take account of our current understanding of disease pathophysiology. They proposed that the definition of preeclampsia includes the placental biomarker PIGF. They also suggested that the definition may need to be expanded in the future to include other factors, such as the antiangiogenic factors, sFlt, and soluble endoglin. Sugulle et al. also recently reported that the midregional proatrial natriuretic peptide may represent another novel biomarker in preeclampsia. Changes in midregional proatrial natriuretic peptide likely reflect the hemodynamic and cardiovascular alterations and endothelial dysfunction in preeclampsia. The authors also suggested that midregional proatrial natriuretic peptide could represent a supplement to the well-established biomarkers of preeclampsia of predominantly placental origin.
Another potential approach to the early diagnosis of preeclampsia is through a multifactorial molecular screen. To this end, Kenny et al. used mass spectrometry–based prospective metabolomic screening of plasma from patients with preeclampsia at 15 weeks of gestation to identify 14 distinct metabolites that, when measured in concert, provided positive predictive value for the development of preeclampsia. Meanwhile, Carty et al. used mass spectrometry–based proteomics to examine the urinary protein profile of patients with preeclampsia. The authors identified a panel of 50 peptides, including uromodulin, collagen fragments, and fibrinogen, which at gestational week 28 were associated with the development of preeclampsia. Taken together, these studies suggest that a combination of immune and angiogenic factors, possibly coupled with mass spectrometry–based profiling of proteins and small molecule metabolites, could provide a definitive diagnostic tool to identify patients at high risk for the development of preeclampsia.

Abnormal Implantation and Vasculogenesis in Preeclampsia

To ensure adequate oxygen and nutrient delivery to the developing uteroplacental unit during normal pregnancy, fatally derived cytotrophoblasts invade and remodel the maternal uterine spiral arteries. This complex process results in the conversion of the high-resistance, small-diameter spiral arteries into high-capacitance, low-resistance vessels. During preeclampsia, it is thought that poor cytotrophoblast invasion leads to abnormal vascular remodeling and inadequate oxygen delivery to the developing uteroplacental unit. The exact mechanisms responsible for the abnormal placental trophoblast invasion and vascular remodeling in preeclampsia are unclear, but a number of recent studies have increased our understanding of potential mechanisms that may lead to maladaptations. For example, Hering et al. recently reported that local tissue angiotensin-II (Ang II) stimulates trophoblast invasion in vivo in the rat and in vitro in human cells. The authors suggested that upregulation of tissue Ang II in the maternal part of the placenta represents an important growth factor for trophoblast migration and invasion, and abnormalities in this system may play a role in the pathophysiology of preeclampsia.

The Notch signaling pathway is thought to play an important role in vasculogenesis by modulating differentiation and function during cell–cell contact. The main pathway consists of 4 transmembrane receptors (NOTCH1–4) and 5 ligands (DLL1/3/4 and JAG1/2). Binding of receptors and ligands on adjacent cells triggers serial proteolytic cleavage of the receptor, releasing the Notch intracellular domain that subsequently translocates to the nucleus to bind to transcription factors and induce downstream targets. Supporting a role for Notch signaling in vascular remodeling is a recent report by Hunkapiller et al. where the absence of Notch2 in mice is associated with reduced vessel diameter and placental perfusion. Additional findings that perivascular and endovascular cytotrophoblasts often fail to express the Notch ligand, JAG1, in preeclampsia provide further evidence that defects in Notch signaling may be an important part of the pathogenesis of this pregnancy complication.

Another recently described molecular pathway implicated in placental vascular development is the transcription factor storkhead box 1 (STOX1), a member of the winged helix transcription factor family. STOX1 was originally implicated in an epidemiological study that suggested increased rates of STOX1 mutation in women who experienced preeclampsia. A recent report from Doridot et al. demonstrated that transgenic overexpression of STOX1 in the mouse leads to a phenotype that mimics preeclampsia in several key ways, most notably, a dramatic rise in systolic blood pressure during gestation, proteinuria, and elevated maternal circulating levels of sFlt-1 and soluble endoglin. Although these data are intriguing, much work remains to be done to elucidate the causative and symptomatic role of STOX1 in the development of preeclampsia.

Angiogenic Factors

There is strong evidence that an imbalance between proangiogenic and antiangiogenic factors exists in preeclampsia favoring the antiangiogenic agents, such as sFlt-1. sFlt-1 is a soluble splice variant of the VEGF receptor-1 that is able to prevent the actions of proangiogenic molecules, such as VEGF and PIGF in target tissues. Additional alternatively spliced Flt-1 transcripts have been identified, and Jubbink et al. found that preeclamptic placentas have a 3-fold higher expression of all mRNA variants compared with controls, with a slight shift to the sFlt-1_v1.

Alterations in angiogenic factors are detectable before the clinical diagnosis of preeclampsia, including women with chronic hypertension, who developed subsequently superimposed preeclampsia, and women after 5 to 8 years of delivery. Besides single determinations of plasma sFlt-1 concentration and sFlt-1/PIGF ratio, Woodham et al. suggested that the combination of midpregnancy 25 hydroxyvitamin D level with sFlt-1/PIGF ratio is a better tool to predict the development of severe preeclampsia. Siddiqui et al. also found that the titer of AT1-AA is significantly correlated with sFlt-1. Interestingly, a pilot study in extracorporeal removal of sFlt-1 from women with very preterm preeclampsia revealed that dextran sulfate apheresis can lower circulating sFlt-1 levels, reduce proteinuria, and stabilize blood pressure without adverse maternal and fetal outcomes.

Recent in vitro studies have focused on mechanisms whereby sFlt-1, which is strongly bound to the extracellular matrix, gains access to the maternal circulation. Al-Ani et al. demonstrated in human umbilical vein endothelial cells that this process may occur through activation of endothelial Proteinase–Activated Receptor-2 leading to increased sFlt-1 release. Gould et al. reported that urotensin-II, a vasoconstrictor and proangiogenic agent elevated in preeclampsia, is associated with increased sFlt-1 secretion from placental explants under hypoxic conditions. In addition, the authors showed that hypoxia augments the levels of urotensin-II receptors in syncytiotrophoblasts, and the urotensin-II receptor expression is upregulated in preeclamptic placentas compared with controls. Another study from Rajakumar et al. revealed that the syncytiotrophoblast layer forms abundant knots enriched with sFlt-1 during preeclampsia. The easy detachment of these knots from the placenta produces free, transcriptionally active
syncytial aggregates that can become an autonomous source of sFlt-1 delivery into the circulation.

Placental ischemia in rats, as a result of reduced uterine perfusion pressure (RUPP), results in increased sFlt-1 and decreased free VEGF levels in the circulation.27–29 In addition to the RUPP model, the BPH/5 mouse and other published models have disrupted angiogenic balance.25–29 A number of studies have recently demonstrated that restoration of free VEGF levels in animal models of preeclampsia results in significant improvement in renal function and blood pressure. Gilbert et al30 reported that chronic infusion of VEGF(121) into placental ischemic rats restores their glomerular filtration rate and endothelial function, resulting in a reduction of the high blood pressure associated with placental ischemia. Using BPH/5 mice, Woods et al11 found that adenoviral-mediated delivery of VEGF(121) prevented the late-gestational elevation of blood pressure and proteinuria, and reduced the incidence of fetal reabsorptions. These interesting results suggest that VEGF(121) may be a candidate pharmacotherapy for preeclampsia.

In an attempt to elucidate the mechanisms whereby the enhanced sFlt-1 production seen in preeclampsia leads to hypertension during pregnancy, Murphy et al34 showed that exogenous sFlt-1 administration into pregnant rats results in high arterial blood pressure and elevated renal preproendothelin mRNA expression. The simultaneous administration of a selective endothelin type A receptor antagonist brought the blood pressure to normal-pregnant range, suggesting that endothelin-1, via endothelin type A receptor, is an important mediator of the hypertension secondary to excess sFlt-1 in pregnancy.32 Li et al35 also recently reported that reduced maternal endothelial NO synthase/NO exacerbates the sFlt1-related preeclampsia-like phenotype through activation of the endothelin system. Other processes in which angiogenic factors may play a role include the following: relaxin-induced vasodilatation during normal pregnancy36 and increased sensitivity to Ang II postpartum in preeclamptic women with low-sodium balance.37

### Immune Factors and Inflammation in Preeclampsia

The immune system and inflammatory factors are thought to play an important role in the pathophysiology of preeclampsia. Redman et al38 have suggested that the inflammatory response is triggered by placental debris or particles, ranging from large deported multinuclear fragments to subcellular components, shed from the syncytiotrophoblast surface of the human placenta. Using nanoparticle tracking analysis to measure the size and concentration of syncytiotrophoblast vesicles obtained by placental perfusion, they recently found that vesicles range in size from 50 nm to 1 μm with the majority being <500 nm. The authors speculated that changes in the number and size of beneficial syncytiotrophoblast exosomes and harmful microvesicles may be important in the maternal syndrome of preeclampsia.

Maternal immune tolerance involves crucial interactions between regulatory CD4+ T cells and uterine natural killer cells recognizing and accepting the fetal antigens and facilitating placental growth. Abnormalities in this process have been proposed to lead to poor placentation, reduced placental perfusion and stress, and chronic immune activation. Preeclamptic women27 and placental ischemic rats have a decrease in circulating regulatory CD4+ T cells.38 T helper 17 cells, which are upregulated in a variety of autoimmune disorders, are also increased in preeclamptic women and in placental ischemic rats.39 Although these data support the hypothesis that hypertension in response to placental ischemia represents a shift from the normal anti-inflammatory state of pregnancy to a proinflammatory state, the quantitative importance of CD4+ T cells and T helper 17 cells in the pathophysiology of preeclampsia remains to be determined.

Another area related to the immune component of preeclampsia is research on the AT1-AA. These autoantibodies, isolated over a decade ago in preeclamptic women, have been studied more intensively recently, including their identification in the circulation of rats undergoing placental ischemia. LaMarca et al40 recently reported the role of B-lymphocyte activation in the production of AT1-AA in placental ischemic rats. They found that B-cell depletion resulted in reductions in AT1-AA and was associated with decreases in blood pressure and tissue endothelin-1 levels. Wenzel et al40 recently generated and purified activating antibodies against the AT1 receptor (AT1-AB) by immunizing rabbits against the AFHYESQ epitope of the second extracellular loop, which is the binding epitope of endogenous activating AT1-AA from patients with preeclampsia. They reported that the AT1-ABs increase Ang II sensitivity, possibly explaining the increased Ang II sensitivity observed in patients with preeclampsia. They also found that passive transfer of AT1-ABs alone into pregnant rats did not induce a preeclamptic syndrome. However, the combination of AT1-ABs and Ang II produced hypertension, proteinuria, abnormal placental vascular remodeling, and intrauterine growth restriction. Additionally, AT1-AB plus Ang II induced hypoxia inducible factor 1, which was associated with arteriolar sclerotic lesions in the spiral arteries and altered trophoblast invasion. Finally, they also found that the AT1-AB enhanced Ang II-induced endothelin-1 expression.40 Taken together, these data demonstrate the important roles that B-lymphocyte activation and AT1-AA play in the pathophysiology of hypertension in response to placental ischemia.

Proinflammatory and anti-inflammatory cytokines are also involved in the pathogenesis of preeclampsia. Proinflammatory cytokines, such as tumor necrosis factor and interleukin (IL)-6, are elevated in preeclamptic women and in placental ischemic rats. These proinflammatory cytokines have not only been shown to stimulate the production of reactive oxygen species, endothelin-1, and the AT1-AA but also play an important role in increasing blood pressure in response to placental ischemia in pregnant rats. Loss of anti-inflammatory actions may also be important in preeclampsia. Chatterjee et al41 reported that absence of IL-10 exacerbated the hypertension and endothelial dysfunction in a mouse model of preeclampsia caused by Toll-like receptor 3 activation during pregnancy. Moreover, they reported that exogenous IL-10 treatment had beneficial effects on endothelial function in the model and suggested that IL-10 therapy may be beneficial for women with preeclampsia.
Heme Oxygenase in Pregnancy and Preeclampsia

One system that has received great attention in recent years is the heme oxygenase-1 (HO-1) system, which has been shown to be important for normal placental vascular function.\(^42\)\(^{-}44\) Induction of HO-1 has been shown to be a potent antihypertensive agent in several forms of experimental hypertension.\(^45\)\(^{-}49\) The precise mechanisms that govern HO-1 antihypertensive effects are still under investigation, but are hypothesized to function in part through the actions of its biologically active metabolites CO, a potent vasodilator and inhibitor of sFlt-1 production, and bilirubin, which has powerful antioxidant properties.\(^45\)\(^)\(^50\)

Several recent articles have suggested a potential role of the HO-1 system in the management of preeclampsia in both in vivo animal models and in the human population. Wikström et al\(^51\) investigated the effect of cigarette smoking on the incidence of preeclampsia in a Swedish population. Women who smoked in mid- to late gestation had up to 50% lower incidence of preeclampsia when compared with women using no tobacco products or snuff alone, with degree of use positively correlating with greater protection. From this, the authors concluded that the combustion products of tobacco, which include CO, are responsible for the decreased incidence of preeclampsia in this population. In a subsequent study, we investigated the effects of HO-1 induction in the RUPP rodent model of placental ischemia–induced hypertension.\(^29\) Induction of HO-1 by Cobalt Protoporphyrin led to≈50% attenuation of the RUPP-induced hypertension on gestational day 19. More interestingly, this was accompanied by improvements in angiogenic balance in both the placenta itself and an increase in bioavailable VEGF in the maternal circulation. In addition, the placental oxidative stress, characteristic of both patients with preeclampsia and the RUPP rat, was significantly attenuated by HO-1 induction, presumably by enhanced bilirubin production. As a result, the increase in the production of vascular preproendothelin-1 seen in this model was significantly reduced. Following studies also demonstrated attenuation of sFlt-1–induced hypertension, again accompanied by enhanced free VEGF in the maternal circulation and suppression of vascular preproendothelin-1 expression.\(^52\)

Two related studies by McCarthy et al\(^53\)\(^,\)\(^54\) also suggest a possible role for HO-1 in both the development and treatment of preeclampsia. Using the rodent RUPP model, McCarthy et al\(^53\) demonstrated that the peroxisome proliferator–activated receptor-\(\gamma\) (PPAR-\(\gamma\)) agonist rosiglitazone could ameliorate many of the pathological manifestations in response to placental ischemia, including hypertension and vascular dysfunction. Furthermore, the beneficial effects of rosiglitazone treatment were dependent on HO-1, as coadministration of the HO inhibitor, SnMP, significantly blocked the effects of rosiglitazone. In a subsequent study, the same group found that administration of a PPAR-\(\gamma\) antagonist in rodents during pregnancy mimicked several features of preeclampsia, including hypertension, endothelial dysfunction, and fetal growth restriction. Interestingly, and perhaps counterintuitive to the earlier work, PPAR-\(\gamma\) antagonism resulted in a significant increase in the levels of circulating and placental HO-1 despite worsening angiogenic balance and hypertension.

Although some of the studies described above provide potential support for the HO-1 system as a therapeutic target in preeclampsia, more work is still needed. In this respect, statins have been shown to stimulate HO-1 expression and inhibit sFlt-1 release in vivo and in vitro; thus, they have the potential to ameliorate early onset preeclampsia. The Study to Ameliorate early onset Preeclampsia (StAmP) trial is currently addressing this potential therapeutic intervention and, if positive, statins may be adopted as a therapeutic intervention to prolong affected pregnancies.\(^55\)

Endothelial and Vascular Dysfunction in Preeclampsia

The vascular endothelium has many important functions, including control of smooth muscle tone through release of vasoconstrictor and vasodilatory substances, and regulation of anticoagulation, antiplatelet, and fibrinolysis functions via release of different soluble factors. The maternal vascular endothelium seems to be an important target for factors that are triggered by placental ischemia/hypoxia in preeclampsia.\(^29\)\(^,\)\(^30\)\(^,\)\(^38\)\(^,\)\(^39\)\(^,\)\(^53\)

An important link between placental ischemia and vascular function was established in a recent study showing that treatment of small mesenteric arteries from normal-pregnant rats with serum from placental ischemic rats attenuates endothelial-dependent relaxation via reduced NO synthase function.\(^56\) NO not only causes vasodilation but also has anti-inflammatory and antioxidant actions in blood vessels.\(^57\)\(^,\)\(^58\) Interestingly, there is increased endothelial adherence and infiltration of neutrophils in omental arteries from preeclamptic compared with normal pregnant women.\(^59\) This study showed that reactive oxygen species derived from neutrophils augment Ang II–induced vasoconstriction in omental arteries from normal-pregnant women, and this effect was exacerbated in endothelium-denuded artery preparations. These data suggest that reduced endothelial NO synthase function in preeclampsia increases susceptibility to inflammation-induced vascular dysfunction. The need for proper anti-inflammatory mechanisms in normal pregnancy was further demonstrated by the finding that aortic endothelial dysfunction and hypertension in pregnant mice have concomitant deficiency of IL-10 and activation of toll-like receptor 3.\(^31\)\(^,\)\(^60\) Reduced action of the transcription factor peroxisome proliferator–activated receptor PPAR-\(\gamma\) is found in RUPP rats.\(^53\)\(^,\)\(^54\)\(^,\)\(^59\)

Because IL-10 and PPAR-\(\gamma\) positively regulate endothelial NO synthase,\(^61\)\(^,\)\(^62\) failure in these pathways may play a role in the pathophysiology of preeclampsia.

Recent studies identified potential pathways in vascular smooth muscle cells that may fail and promote preeclampsia. Given the importance of adequate placental perfusion, it was demonstrated in uterine arteries from normal, near-term pregnant versus nonpregnant sheep that myogenic tone is reduced; this was mediated by increased expression and activity of large conductance \(\text{Ca}^{2+}\)-activated \(K^+\) (BK\(_{\text{Ca}}\)) channels.\(^63\) This ex vivo study showed that 17\(^\beta\)-estradiol increases BK\(_{\text{Ca}}\) channel activity in isolated uterine arterial vascular smooth muscle cells. Likewise, the novel ovarian hormone relaxin, which promotes \(\text{Ca}^{2+}\) efflux from uterine smooth muscle,\(^64\) mediates reduced myogenic tone of renal arteries during pregnancy.\(^34\)\(^,\)\(^65\) Also
related to the importance of reduced myogenic tone in pregnancy. Xiao et al\textsuperscript{67} demonstrated that actin polymerization is reduced in ovine uterine arteries in normal-pregnant sheep, whereas activity and expression of RhoA kinase, which facilitates Ca\textsuperscript{2+} sensitization of the contractile apparatus and actin polymerization,\textsuperscript{68} is increased in omental arteries from preeclamptic women.\textsuperscript{69} Whether reduced sex hormone regulation of intracellular Ca\textsuperscript{2+} promotes RhoA kinase activation to induce the known increase in uterine artery resistance in RUPP\textsuperscript{70,71} is not defined.

**Cerebrovascular Changes in Pregnancy and Preeclampsia**

As discussed earlier, it is widely established that preeclampsia contributes to gross maternal vascular dysfunction. Specifically, cerebrovascular abnormalities play a significant role in the pathogenesis of preeclampsia/eclampsia. An astounding 39\% of all preeclampsia/eclampsia deaths are because of cerebrovascular events with cerebral hemorrhage contributing 35\%, cerebral edema 3\%, and cerebral embolus 1\% of preeclampsia-related deaths.\textsuperscript{72} Neurological symptoms such as headaches, blurred vision, nausea, drowsiness, and seizures are commonly reported in patients with preeclampsia.\textsuperscript{73} Furthermore, women with preeclampsia/eclampsia are at increased risk of developing stroke during pregnancy and the postpartum year.\textsuperscript{74} Presently, the pathogenesis of preeclampsia-induced cerebrovascular abnormalities is still poorly understood.

MRI and computed tomography scans reveal abnormalities consistent with edema in patients with preeclampsia.\textsuperscript{75,76} Edema forms from either increased water transport into cells (cytotoxic edema) or through the disruption of the blood–brain barrier (vasogenic edema). The blood–brain barrier, formed by the close association of endothelial cells, smooth muscle cells or pericytes (capillaries), and astrocytes, regulates the transport of substances between the blood and brain tissue. Increased permeability of the cerebral vessels has been reported in both normal pregnancy and preeclampsia. For example, plasma from normal-pregnant and preeclamptic women increases permeability of cerebral vessels in an ex vivo model.\textsuperscript{77} This study suggests that pregnancy itself induces changes in the cerebral vasculature, which may be exacerbated in the presence of increased arterial pressure, characteristic of preeclampsia.

Cerebral blood flow is highly regulated and kept relatively constant even with fluctuations in blood pressure. Acute increases in blood pressure activate the vascular myogenic response, protecting neuronal tissue from damage. Women with severe preeclampsia have increased cerebral blood flow and perfusion pressure,\textsuperscript{78} and our laboratory recently demonstrated impaired myogenic tone in the middle cerebral arteries and cerebral edema in placental ischemic rats.\textsuperscript{79} These conditions of increased cerebral blood flow and impaired myogenic reactivity render patients with preeclampsia susceptible to neurological complications with acute increases in blood pressure. This concept is supported by studies demonstrating that during acute hypertension, pregnancy decreases vascular resistance and increases cerebral blood flow,\textsuperscript{79,80} resulting in a rightward shift in the autoregulatory curve,\textsuperscript{81} and cerebral edema.

Although the myogenic response is important during sudden, acute elevations in blood pressure, vascular remodeling occurs during chronic elevations of blood pressure. Pregnancy is associated with outward remodeling of penetrating arterioles and increased cerebral capillary density,\textsuperscript{82} whereas hypertension induces inward remodeling of posterior cerebral arteries.\textsuperscript{82,83} Importantly, pregnancy reverses\textsuperscript{84} or prevents\textsuperscript{85} the inward remodeling of cerebral arteries in hypertensive animals. Together, these studies suggest that failure of the cerebral vasculature to remodel in the presence of decreased vascular resistance and increased cerebral blood flow results in the transmission of pressure to the cerebral microvessels causing blood–brain barrier disruption and edema.

Cerebral arteries (pial arteries) are innervated by both sympathetic and parasympathetic nerves. Although nerve innervation is thought to play a minimal role in the control of cerebral blood flow, nerve density on posterior cerebral innervation is thought to play a minimal role in the control of cerebral blood flow, nerve density on posterior cerebral arteries increases during pregnancy and decreases during pregnancy accompanied by hypertension.\textsuperscript{82} Interestingly, plasma from pregnant rats induces neuronal hyperexcitability and increased microglial activation through tumor necrosis factor-\textgreek{a} activity\textsuperscript{86} thereby demonstrating that circulating factors can exert effects on neurons if they come into direct contact as may occur during cerebral hemorrhage or microbleeds. Because preeclampsia is associated with increased circulating factors, such as vasoactive peptides and inflammatory cytokines, increased cerebral perfusion pressure along with impaired myogenic reactivity could result in blood–brain barrier disruption, cerebral edema, and excitability of neurons, resulting in the neurological symptoms of preeclampsia.

**Concluding Remarks**

Despite recent advances in identifying the factors involved in the pathophysiology of preeclampsia, there are still many unanswered questions. The initiating events that eventually manifest the disorder remain to be fully elucidated. Although abnormal spiral artery remodeling is thought to play a critical role, the underlying cellular and molecular mechanisms remain obscure. As seen in the Figure, abnormal cytotrophoblast invasion and spiral artery remodeling are proposed to lead to ischemia/hypoxia-mediated increases in sFlt-1, AT1-AA, and inflammatory cytokines, resulting in subsequent detrimental effects on several downstream targets. The decrease in proangiogenic factors, such as VEGF and PI GF, and the increased production of reactive oxygen species lead to maternal endothelial dysfunction. As a result, increased endothelin-1 production and the decreased bioavailability of NO lead to the characteristic widespread vascular abnormalities in various organs, such as the kidneys and brain, hypertension, and proteinuria observed in this disorder. Currently, the relative importance of each of these factors needs to be ascertained, and the network of cross-regulation that governs them needs to be fully elucidated. Unfortunately, the lack of effective pharmacological therapeutic approaches for the management of preeclampsia is a serious health concern in clinical obstetrics. The identification of new therapies that focus on manipulating these newly defined pathological pathways is a critical area for future research.
Figure. Schematic representation of the proposed initiating events and factors in the pathophysiology of preeclampsia. ET-1 indicates endothelin-1; GFR, glomerular filtration rate; PlGF, placental growth factor; RBF, renal blood flow; ROS, reactive oxygen species; sFlt-1, soluble fms-like tyrosine kinase-1; and VEGF, vascular endothelial growth factor.

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