Preeclampsia: Linking Placental Ischemia with Maternal Endothelial and Vascular Dysfunction

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Abstract

Preeclampsia (PE), a hypertensive disorder, occurs in 3% to 8% of pregnancies in the United States and affects over 200,000 women and newborns per year. The United States has seen a 25% increase in the incidence of PE, largely owing to increases in risk factors, including obesity and cardiovascular disease. Although the etiology of PE is not clear, it is believed that impaired spiral artery remodeling of the placenta reduces perfusion, leading to placental ischemia. Subsequently, the ischemic placenta releases antiangiogenic and pro-inflammatory factors, such as cytokines, reactive oxygen species, and the angiotensin II type 1 receptor autoantibody (AT1-AA), among others, into the maternal circulation. These factors cause widespread endothelial activation, upregulation of the endothelin system, and vasoconstriction. In turn, these changes affect the function of multiple organ systems including the kidneys, brain, liver, and heart. Despite extensive research into the pathophysiology of PE, the only treatment option remains early delivery of the baby and importantly, the placenta. While premature delivery is effective in ameliorating immediate risk to the mother, mounting evidence suggests that PE increases risk of cardiovascular disease later in life for both mother and baby. Notably, these women are at increased risk of hypertension, heart disease, and stroke, while offspring are at risk of obesity, hypertension, and neurological disease, among other complications, later in life. This article aims to discuss the current understanding of the diagnosis and pathophysiology of PE, as well as associated organ damage, maternal and fetal outcomes, and potential therapeutic avenues.

Introduction

Hypertensive disorders of pregnancy, including preeclampsia (PE), are the leading cause of premature births and maternal/fetal morbidity and mortality (282). In addition to elevated

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blood pressure, PE is characterized by proteinuria and/or other system disturbances caused primarily by the release of placental factors into the maternal circulation (25, 163, 184, 188, 215, 360). The American College of Obstetrics and Gynecology (ACOG) recommends diagnosis based on the following criteria: new-onset hypertension after 20 weeks of gestation and one of the following: proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms (Table 1) (282).

PE can present with varying features and a combination of symptoms based on time of onset, severity, and any preexisting diseases in the mother. Fetal growth restriction is a well-described feature of PE but is no longer a diagnostic criterion based on ACOG guidelines. The International Society for the Study of Hypertension (ISSHP) continues to recognize fetal growth restriction as a diagnostic feature, which likely contributes to some discrepancy in the incidence of disease (370). Women with preexisting hypertension and presenting with other *de novo* features of PE are diagnosed with superimposed PE. The diagnostic criteria outlined in Table 1 can also be used to differentiate between PE and gestational hypertension, which presents after 20 weeks of gestation but is not usually associated with disturbances in other organ systems. In severe cases, women with PE experience HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), which can be considered a subtype of PE (282). HELLP syndrome is a severe but relatively rare complication of PE that necessitates delivery in 70% of cases, of which 15% are preterm (6, 56, 347, 348). Based on the ACOG guidelines, the terms "mild PE" and "severe PE" should no longer be used but rather "PE with or without severe features", as detailed in Table 2.

Timing of PE Onset and Symptoms

Timing of PE onset can play a role in the degree whereby maternal symptoms arise in this disorder. Early-onset PE typically occurs <34 weeks of gestation, which is associated with more severe symptoms, and often necessitates preterm delivery that carries a much greater risk of fetal death (195). Late-onset PE develops >34 weeks of gestation and does not usually require early delivery. Outcomes for both early- and late-onset PE can vary; however, it is widely accepted that early-onset PE carries more adverse risk for both mother and baby during gestation and postpartum (370). In particular, incidence of growth restriction, hemolysis, neurological, and cardiorespiratory complications are far more common in early-onset PE (370). Although PE typically occurs during gestation, some cases of postpartum PE have been reported and are diagnosed by onset of hypertension and organ disturbances similar to gestational PE (84, 120, 278, 282). Reports of *de novo* postpartum PE have occurred between 48 h and 12 weeks postpartum despite the absence of the placenta by this time. It is possible that subclinical PE was present in these patients during gestation or that vascular and organ dysfunction was mild during gestation and is exacerbated and diagnosed postpartum. Postpartum PE is typically not associated with headaches and should not be mistaken for eclampsia. Eclampsia has more severe and potentially terminal outcomes for the patient due to seizures (306).

There is currently no therapy that can prevent or cure PE. Low-dose aspirin (60–80 mg) has been reported to delay onset of PE and improve perinatal outcomes (282) but is still only used in high-risk patients. Current management regimens for PE involve use of pregnancy-

safe antihypertensive pharmacotherapy. Identifying mechanistic pathways that can be targeted to prevent and/or treat PE is an active area of research that will be discussed later in this article.

Historical Perspective

Some of the first records of convulsions during child birth date back to 3000 B.C. and were not isolated to a single geographical area with reports from China, India, Europe, and Africa (54). Observations made from that time included convulsions, presenting almost exclusively in first pregnancies or death, in about one-third of the women. We now know that these convulsions were most likely eclampsia—new onset of seizures during or shortly after pregnancy. The association between eclampsia, edema, and proteinuria, linking eclampsia to some form of renal disease, was made in the 1840s; however, blood pressure measurement was not commonplace as it is today (52, 54, 285). Still, physicians recognized that delivery reduced convulsions and improved disease state in the mother (54). In the early 1900s, following the invention of the inflatable armband to measure blood pressure, physicians quickly noticed that pregnant women with eclampsia had markedly increased blood pressure. In fact, blood pressure was increased prior to delivery and preceded development of convulsions and seizures, hence the origin of the term "preeclampsia" (52, 285). In the 1970s, Brosens et al. (51) found that spiral artery remodeling is deficient in PE and proposed that perhaps hypertension is a compensatory mechanism to ensure sufficient nutrient delivery to the baby (50, 264). A significant advance in the understanding of the pathogenesis of PE was made in the late 1980s, when Roberts, Taylor, and Redman published that endothelial dysfunction plays a central role in the maternal syndrome (277, 283, 284). They noted that symptoms associated with PE are consistent with endothelial cell injury, particularly in the renal glomerulus, liver, and brain.

In the 1990s, it was established that an uncomplicated first pregnancy reduces the likelihood that a subsequent pregnancy will be complicated by PE, assuming the same male partner. If the female changes partner, she carries the same risk as a primiparous woman, suggesting this is an immunological disease (208, 287) that could be triggered by the immunological properties of semen. Subsequent studies confirmed that natural killer (NK) cells, which play a role in regulating placentation and spiral artery remodeling, could recognize complexes of fetal origin from the paternal contribution as foreign and trigger an immune response (70, 189, 343).

It is now well established that PE is a multifaceted and multiorgan disease. While there is certainly an immunological component, there is also evidence for maternal, genetic, and environmental contributors to the etiology of PE. In the early 2000s, it was established that antiangiogenic factors in the maternal circulation contribute to the clinical manifestation of PE (215), and that these antiangiogenic and pro-inflammatory factors are released in response to placental ischemia. The specific role of these factors and their impact on different organ systems will be discussed in this article. Despite profound advances in our understanding of the pathogenesis of PE, a definitive etiology and treatment strategy remains elusive.

Epidemiology

Incidence of PE

Hypertensive pregnancy disorders, including PE, affect more than 10% of pregnancies and are a major contributor of maternal and fetal morbidity and mortality. PE alone impacts 3% to 8% of pregnancies (22, 88, 151, 346). Worldwide, PE is associated with 70,000 to 80,000 maternal deaths and >500,000 infant mortalities per year (87, 146, 243, 282). There is a notable racial disparity in prevalence of this disease. In one study, hospitalizations with PE delivery (per 100) were 3.4 among African-American women compared to 1.7 among Caucasian women (331). In the United States and most developed countries, the incidence of late-onset PE accounts for 90% of cases, as compared to 70% of cases in developing countries (54, 286). However, rates of PE with severe features have increased dramatically in the past 40 years (Figure 1) (22). While changes to the diagnostic criteria may have impacted the number of patients diagnosed with PE, the overall rise in the incidence of PE is most likely due to a significant increase in the risk factors associated with the disease, such as obesity and preexisting cardiovascular and metabolic diseases (358).

Risk factors for PE

A number of risk factors have been identified that contribute to the development of PE, including but not limited to, genetic susceptibility, primiparity, history of PE, preexisting cardiovascular-renal disease, multiple gestations, obesity, and advanced age (Table 3) (40, 276, 282). In addition, risk for early-onset PE in the United States has been linked to African-American race and chronic hypertension, while late-onset PE is associated with younger maternal age, multifetal pregnancy, and diabetes mellitus (195, 325).

Some evidence suggests a genetic predisposition to PE (44, 148, 172) and increased susceptibility to PE (63, 94, 123, 218). This concept was first postulated in the 1960s when Chesley, Annitto, and Cosgrove noted that close relatives, including sisters, daughters, and even granddaughters, presented to the hospital with PE and eclampsia (61). To date, the most supportive data suggests a susceptibility locus near the *FLT1* gene in neonates from PE pregnancies, which encodes the protein sFlt-1—a pathologic antiangiogenic factor in PE (54, 218). These findings highlight the importance of considering fetal and maternal genetics in the development of PE, particularly because the fetus dictates the genotype of the placenta. Also, there is evidence to suggest that the male partner could play a role in the development of PE. One study showed that advanced paternal age (>45 years old) further increases the likelihood of PE by 14%, based on assessment of >40 million births (168).

PE is characterized by a robust inflammatory and hypercoagulable state, thus, preexisting conditions that inappropriately activate these systems likely increase risk for this disorder. Autoimmune diseases, such as systemic lupus erythematosus and antiphospholipid syndrome (54, 62), and blood disorders such as thrombophilia (41, 97) significantly increase the risk for PE. Overwhelming data also exists to support that cardiovascular and metabolic diseases, including obesity, are major risk factors for PE (318). In an analysis of live births between 1989 and 2005, one study found that increasing body mass index (BMI, kg/m^2) is associated with greater risk for both early- and late-onset PE significantly (216).

Additionally, the incidence of PE is increased when obesity is combined with other risk factors such as advanced maternal age, nulliparity, and diabetes mellitus (216). In another study of prepregnancy obesity (BMI >30) in primiparous women, incidence of PE was 14.5% and superimposed PE was 2.6% compared to women with BMI <30. Furthermore, severity of PE in these women was greater when the degree of obesity is greater (322, 376). It is important to note that not all women with obesity develop PE; thus, understanding the difference between these two cohorts may be important in unraveling the pathophysiology of this disease.

In contrast to factors that increase the risk of PE, improved maternal nutrition has been associated with reduced incidence (75). Specifically, greater intake of vegetables and plant-based foods (47), dietary fiber (268), and essential micronutrients (217, 372) has been inversely related to the development of PE, particularly when these behaviors are initiated preconception and in early pregnancy. Supplementation of antioxidant nutrients and coefficients, such as vitamin D and magnesium, to restore low levels seen in PE is an active area of research (75, 173, 377). However, clinical studies have had conflicting results attributed to variation in timing of intervention, dose, severity of disease, and sample size, among other factors (75, 80, 145, 166, 222, 334).

Maternal Hemodynamic Adaptations During Normal Pregnancy and PE

The systemic hemodynamic changes that occur during the course of a normal pregnancy have been extensively reviewed (13, 68, 117, 132, 296, 330, 340). During the typical 40 weeks of gestation, extracellular fluid volume increases and systemic vascular resistance decreases, leading to greater venous return to the right atrium. In turn, this causes an increase in stroke volume and maternal cardiac output (by approximately 40%–50%), which typically reaches its peak during the middle of the third trimester (Figure 2) (37, 288, 295). During pregnancy, increased circulating levels of progesterone, prostaglandins, and relaxin are most likely responsible for decreased vascular resistance through the production of nitric oxide (NO), which is a gaseous molecule produced by healthy endothelial cells. A single layer of endothelial cells forms the endothelium and lines the lumen of all blood vessels. NO stimulates pathways in the underlying smooth muscle to promote vasorelaxation (263, 312). It is important to note that, although systemic resistance decreases during pregnancy, mean arterial pressure (MAP) is only slightly reduced (5–10 mmHg) or remains constant because of the concomitant increase in cardiac output. Furthermore, reduced MAP in normal pregnant women is associated with greater reductions in diastolic pressure rather than systolic, which reaches its lowest point by midgestation (28, 233). During the third trimester, pressure begins to rise toward prepregnancy levels (Figure 2). Ultimately, these hemodynamic changes create an environment that meets the metabolic demands of both the mother and baby.

Studies have also focused on changes that occur in specific organ systems over the course of a normal pregnancy. During pregnancy, uterine blood flow is markedly increased and accounts for approximately 25% of cardiac output (340). Uterine artery blood flow can be measured by Doppler ultrasound to assess whether there is adequate blood supply to the fetus. During a normal pregnancy, uterine artery resistance is low, and the Doppler pattern

exhibits a high peak flow during systole that rapidly falls during diastole (Figure 3) (119, 219). As discussed below, impaired uterine hemodynamic function has important functional consequences during preeclamptic pregnancy.

The kidneys have a central role in the chronic control of blood pressure through sodium and water homeostasis. Given that the kidneys receive 20% of the cardiac output, dilation of the renal vasculature during pregnancy is an important contributor to reduced systemic vascular resistance, which, in part, is controlled by elevated circulating levels of progesterone. Another important hormone involved in renal vasodilation, during early gestation, is relaxin, which is produced by the corpus luteum and stimulated by human chorionic gonadotropin (73, 92, 106). Decreased vascular resistance caused by these hormonal factors results in a compensatory activation of the renin angiotensin aldosterone system and subsequent increase in extracellular fluid volume associated with pregnancy (296). In addition, due to vasodilation of both the afferent and efferent arterioles during pregnancy, there is a significant increase in renal plasma flow and glomerular filtration rate, by approximately 30% to 50%, and minimal changes in glomerular capillary pressure (224). These renal adaptations during normal pregnancy are important for maintaining plasma volume, blood pressure, and overall body fluid homeostasis.

In contrast to the hemodynamic changes expected in normal healthy pregnancy, PE is associated with increased MAP and total peripheral resistance along with reduced cardiac output, renal plasma flow, and glomerular filtration. In addition, uterine blood flow is significantly reduced in PE, which can be observed using Doppler ultrasound. Specifically, peak flow during systole is reduced, followed by a sharp fall and a more pronounced notch in the descending wave form (Figure 3). The differences between Doppler waveforms in normal pregnancy versus PE indicate a marked decrease in blood flow in PE (particularly during diastole) and greater uterine artery resistive index (UARI). Among the consequences of inadequate uterine blood flow is poor perfusion of the placenta and insufficient nutrient supply to the fetus. The underlying mechanisms and impact of placental ischemia for the mother will be discussed in detail in the subsequent sections, including experimental animal models that have been utilized to study and expand our understanding of PE.

Animal models: A critical tool in understanding the pathogenesis of PE

Our current understanding of the pathogenesis of PE would be limited without the use of appropriate animal models. In fact, this multisystem disease necessitates the use of the integrated systems that whole-animal models provide. Such studies coupled to *in vitro* and *ex vivo* preparations have greatly expanded our knowledge of PE. The reduced uterine perfusion pressure (RUPP) model is a well-established animal model of PE that has been extensively studied and utilized in multiple species, including nonhuman primate (UPI; uteroplacental ischemia) (23, 59), dog (143), rabbit (4), mice (154), and the rat (16, 34, 116, 159, 185, 192, 291, 299, 329). In this model in the rat, placental ischemia is induced by placing silver clips on the abdominal aorta and branches of the ovarian artery to reduce blood flow to the uterine horns, placenta, and fetuses by approximately 40%. This procedure mimics the impaired uterine hemodynamics and placental ischemia-induced production of many of the circulating factors that occur in women with PE (117). While the RUPP model

has been a powerful tool to understand the impact of placental factors on the development of PE and the associated hemodynamic changes, it is not without limitations. Due to the surgical restriction of blood flow, the RUPP model cannot be used in studies to pharmacologically promote uterine blood flow. The hypertensive Dahl Salt-Sensitive rat has been shown to spontaneously develop a PE-like phenotype, including mimicking the altered uterine artery Doppler waves in PE patients (Figure 3), without the need of surgical manipulation of the uterine vessels. It represents an excellent model of superimposed PE (119).

Infusion of individual mediators (such as chronic infusion of a particular placental-ischemic factor to mimic circulating levels encountered in PE) allows for assessment of its specific impact on symptoms of PE. For example, infusion of specific pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and angiotensin II type 1 receptor autoantibody (AT1-AA) increases blood pressure in the pregnant rodents and has widespread implications in the mother (182, 183). Other examples of animal models include genetic mouse models, such as BPH/5, which is mildly hypertensive while nonpregnant and exhibits a PE-like phenotype during pregnancy (79). Rat models overexpressing components of the renin angiotensin system have also been shown to produce a PE-like phenotype during pregnancy (139). The L-NAME (L-N^G-nitro arginine methyl ester) model, where an NO synthase inhibitor is administered, produces elevated blood pressure, proteinuria, and reduced fetal weight (53). Another model involves administration of extremely low doses of bacterial lipopolysaccharide (LPS) to pregnant mice and rats to induce a pro-inflammatory profile similar to PE. The LPS model is associated with increased blood pressure, proteinuria, low platelet count, glomerular injury, and brain abnormalities (96). The critical impact that these animal models and others have had on our understanding of PE will be discussed throughout this article.

Pathogenesis of Placental Ischemia in PE

Evidence supports theories of genetic, environmental, and autoimmune origins for the development of PE. While the etiology is not completely understood, it is generally accepted that the pathogenesis of PE occurs in two phases; (1) abnormal placentation and impaired spiral artery remodeling and (2) subsequent clinical manifestations of the disorder. To understand the mechanisms by which abnormal placentation leads to PE, it is important to first understand the anatomy, development, and function of a healthy human placenta and what we have learned about mechanisms of placentation from studies in rodent uteroplacental tissue. We then discuss disturbances to these pathways that lead to lack of spiral artery remodeling in PE.

Placental vascular anatomy

The mature placenta is a complex organ composed of fetal and maternal tissue of varying cell types and three different layers. The outermost layer is the maternal decidua. The decidua is the uterine endometrial lining that has been transformed during implantation and pregnancy. Rodent and human placentas are similar, making these animals useful in the study of pregnancy (Figure 4). In both cases, proper development of the decidua, which

contains the endometrial vessels, is critical (157, 276). The spiral arteries, an important target for vascular remodeling during pregnancy, are found in this layer. The innermost, or "fetal", layer is termed the labyrinth in rodents and the villous layer in humans. This layer is composed of specialized trophoblasts that form a large surface area important in nutrient/gas exchange between the fetus and mother. The middle layer is a transitional, or junctional, layer between the "maternal" and "fetal" portions of the placenta. One difference in vascular anatomy between rodents and humans is that in the human, the spiral arteries drain directly into the intervillous spaces. However, in the rat, the spiral arteries converge onto one or more canals that pass through the junctional zone to the base of the villous layer and then branch out to feed the sinusoid/intervillous spaces where nutrient/gas exchange between maternal and fetal circulations occurs (Figure 4). Following, deoxygenated blood moves through the labyrinth, converging on smaller channels that cross the junctional zone and deliver blood to lacunae or small pools of blood in the decidual layer and then to maternal uterine veins.

Cytotrophoblast cell differentiation and proliferation

During the luteal phase of the menstrual cycle, blood flow is increased to the endometrium via the spiral arteries to become receptive to implantation of the early embryo (blastocyst). The blastocyst consists of an inner cell mass, which will become the embryo, and an outer trophectoderm layer of stem cells. In humans and rats, the trophectoderm gives rise to various trophoblast cell lineages that form the placental layers and line the maternal vessels. However, the names of these cells differ between human and rat (314). In humans, the trophectoderm gives rise to cytotrophoblasts and the primitive syncytium (107). The latter assists in early invasion of the blastocyst into the uterus and early formation of individual lacunae that fill with blood from uterine capillaries, which will eventually become the continuous intervillous space where maternal blood surrounds the placental villi (58). Proliferation of cytotrophoblasts in the initial stages of placental formation occurs in very low oxygen tensions. The introduction and delivery of oxygenated maternal blood flow generates oxidative stress and activates signaling pathways in the differentiation of these cells from a proliferative to an invasion phenotype (177, 368). Proliferative cytotrophoblasts push through the primitive syncytium to form the placental villi (176). The villous cytotrophoblasts fuse with the preexisting syncytium to form the multinucleated syncytiotrophoblasts that line the intervillous space to serve as the interface between maternal blood and the underlying villi (386). The proliferative cytotrophoblasts also create columns to anchor the placenta to the decidua. From these anchoring structures, cytotrophoblasts can differentiate into one of two phenotypes; invasive extravillous trophoblasts that reside in the interstitium to interact with decidual stromal cells, such as decidual natural killer (dNK) cells (as detailed below); or endovascular trophoblasts that invade and remodel the maternal spiral arteries (Figure 5). In rodents, the extravillous trophoblast cells are termed trophoblast giant cells (193). Distinct subtypes of trophoblast giant cells, classified by their location, function, and gene expression, line the lumen of vessels including the central canal, maternal blood sinusoids, and spiral arteries (310, 311). It is important to mention these cells in rats, because rodents have proven to be useful tools to study mechanisms of trophoblast invasion of the placenta and the dramatic uteroplacental vascular remodeling that occurs during normal pregnancy (313, 320). Cytotrophoblasts and

leukocytes, namely dNK cells, make up the bulk of the placenta and work in concert to regulate appropriate spiral artery remodeling.

Cytotrophoblast-mediated spiral artery remodeling

Early in pregnancy, spiral arteries are high resistance, low capacitance vessels. During normal pregnancy, these arteries undergo trophoblast-mediated remodeling to become high capacitance, low resistance vessels that support proper growth of the fetal-placental unit (60). Within the maternal vascular spaces, the trophoblast cells promote development of the placental vasculature in at least two processes: (i) vasculogenic mimicry and (ii) vascular invasion and endothelial mimicry. Vasculogenic mimicry describes how trophoblast cells can create *de novo* vascular tubes. This process occurs with the formation of the canals, sinusoids/villous space, channels, and lacunae. Vascular invasion and endothelial mimicry describe how trophoblast cells invade into and displace the resident endothelial cells and then alter their morphology to appear more like an endothelial cell (273). This process occurs in spiral arteries in which trophoblasts migrate from the anchoring villi and invade the vasculature intraluminally, termed endovascular invasion, or extraluminally where they colonize the vascular smooth muscle layer (367). In *in vitro* studies, extravillous trophoblasts promote remodeling in non-placental spiral arteries isolated from women at Caesarean section by inducing endothelial and smooth muscle apoptosis through the cell death surface receptor Fas and its interaction with Fas ligand (27). The Fas receptor belongs to the TNF family of receptors and is a classical mode for induction of cell death by cytotoxic immune cells (361). Migration, invasion, and recolonization of vascular cells by trophoblasts is a progressive process that begins around midgestation in rodents and toward the end of the first trimester humans (290). This phenomenon results in normal remodeling of the uterine spiral arteries. Trophoblast-driven vascular remodeling to widen the spiral arteries is considered an important mechanism to increase blood flow to the growing fetus. During pregnancy, spiral arteries widen from a diameter of 200 μm to 2 mm by term (368) and increasing placental blood flow 4.5 to 10-fold reaching approximately 500 to 600 mL/min at term in humans (24, 280).

Hormones, immune cells, and spiral artery remodeling

Several pregnancy hormones and growth factors drive cytotrophoblast invasion and remodeling. Progesterone derived from decidual stromal cells stimulates increases in vascular endothelial growth factor (VEGF)-A and matrix metalloproteinase (MMP)-2 and −9 (109, 174). VEGF serves as a chemoattractant for first-trimester trophoblast cells and promotes migration (187). Relaxin has antiapoptotic effects on extravillous trophoblast cells (197). In a study in baboons, early pregnancy was associated with low levels of estrogen, which permitted cytotrophoblast invasion into spiral arteries (10, 45). When estradiol levels were increased threefold, cytotrophoblast invasion was significantly reduced, suggesting that lower levels of estrogen that exist in early pregnancy could be important to allow proper cytotrophoblast invasion.

dNK cell activity has been well described in pregnancy. These cells differ from systemic NK cells in that they have immunomodulatory properties and are only marginally cytolytic (276). dNK cells recognize maternally and paternally derived major histocompatibility

complexes (MHC). Extravillous trophoblasts of fetal origin express human leukocyte antigen-C (HLA-C) MHC, which combine and produced a unique complex with the maternal killer cell Ig-like receptor (KIR) MHC (228). The introduction of these allogenic HLA-C MHC from the fetus challenges the maternal immune system. Genetic studies have shown that pregnancies with PE are associated with specific KIR-HLA combinations, and that these PE-related combinations could cause inappropriate secretion of chemokines/ cytokines by dNK cells and ultimately impact trophoblast invasion (137, 141, 228). Proper placentation and spiral artery remodeling have been shown to be dependent on the cooperation between dNK cells and extravillous trophoblasts (228, 276). dNK cells have been shown to play a major role in cytotrophoblast regulation and invasion (137, 178) by releasing proinvasive factors that stimulate activation of MMP-2 and MMP-9. In early human pregnancy, uterine NK cells are the predominant source of MMP-2 (242). MMPs are important for their role in breaking down components of the extracellular matrix (ECM), thereby removing physical barriers for trophoblast migration. In addition to their role in cytotrophoblast invasion, dNK cells are important secretors of cytokines, growth factors, and angiogenic factors, such as VEGF and placental growth factor (PlGF), and do not express the aggressive cytotoxic phenotype (95). Studies have shown that cytolytic NK cell populations decrease during normal pregnancy, while regulatory NK cells increase, not only in the decidua (dNK cells) but also in the periphery; however, the opposite is true in PE (294).

Impaired cytotrophoblast migration and invasion in PE

Phase 1 in the pathogenesis of PE is hallmarked by abnormal placentation. Specifically, evidence supports a lack of proper trophoblast-mediated spiral artery remodeling in PE. Histological samples of placenta from PE pregnancies frequently depict shallow invasion and incomplete remodeling of these vessels compared to placenta from healthy pregnancies (49), where approximately 100 to 150 spiral arteries undergo complete remodeling (204). Human placental bed biopsies from PE patients indicate that abnormal vascular anatomy is characterized by a lack of decidual and myometrial vascular wall destruction and reductions in endovascular and intramural trophoblast cell counts (203, 204). Human placental tissues from PE patients show a reduction in MMP-2 and MMP-9 levels (265), suggesting a decreased trophoblast invasive/migratory ability (382).

Factors that impact dysregulation of cytotrophoblast function in PE is an active area of research. One study by Zhou et al. (384) showed that cytotrophoblasts do not appropriately transform to express the appropriate vascular adhesion molecules, including integrin and cadherin, during invasion in PE. Another source of cytotrophoblast dysfunction could be uncontrolled oxidative stress. Reactive oxygen species (ROS) production is critical in the signaling of several processes in normal pregnancy, from implantation to proper growth of the fetoplacental unit. However, ROS-generating enzymes are excessively increased, and antioxidant enzymes are decreased in both trophoblasts and placentas from PE pregnancies (385). There are multiple mechanisms whereby ROS are produced throughout PE, attributed mostly to hypoxia, inflammation, and reperfusion injury (121). The placenta undergoes prominent ischemia-reperfusion injury, resulting in ROS formation and endoplasmic reticulum (ER) stress. ER stress has been cited to trigger decidual cell and cytotrophoblast

apoptosis in PE (194). Upregulation of proapoptotic transcription factors as a result of ER stress has been shown to negatively regulate transcription of the proangiogenic factor, PlGF, in PE (227). Nuclear factor-kappa B (NF-κB), a redox-sensitive transcription factor, has also been implicated in the early stages of PE by impairing spiral artery remodeling and inducing trophoblast apoptosis (1, 26). In response to high levels of ROS, placental mitochondria become dysfunctional and may undergo degradation (fission) or rescue and repair (fusion) controlled by specific hydrolyzing proteins. Studies show dysregulation of profission and profusion factors in PE compared to normal pregnancy and also in PE with and without severe features (31, 101, 355). However, the full implications of these findings remain unclear. Antiphospholipid syndrome, which is linked to miscarriages and increased risk of PE, is caused by production of antiphospholipid antibodies. Recently, a study found that these antibodies are internalized by syncytiotrophoblasts, and that they specifically target mitochondria and induce ROS generation (354, 387). ROS also cause upregulation of proapoptotic pathways in mitochondria (257), and mitochondrial dysfunction itself leads to further ROS production (235). Ultimately, these disturbances lead to abnormal cytotrophoblast invasion, impaired spiral artery remodeling, poor perfusion of the placenta, and restricted oxygen and nutrient/waste exchange to the fetus.

Experimental animal studies linking trophoblast migration and invasion to spiral artery remodeling—Genetic-manipulation studies in mice have implicated the importance of cytotrophoblast-mediated spiral artery remodeling in pregnancy. Although the number of studies on this topic is too expansive for this article, a few are addressed. Trophoblasts expressing the *Tpbpa* gene are progenitors of trophoblasts that line most of the maternal vasculature and the sole progenitor of trophoblasts lining the spiral arteries. Ablation of *Tpbpa*-expressing trophoblasts, using genetically modified animals, decreases the number of trophoblasts lining the maternal placental vasculature, including the spiral arteries, which correlates to a reduction in maternal spiral artery diameters (147). As a likely consequence, these mice had reduced maternal blood volume within the labyrinth or villous layer, the placental layer where maternal-fetal gas and nutrient exchange occurs, consistent with placental insufficiency. All pups with a loss of this specific population of trophoblasts were not viable before the end of the second trimester.

Some studies have gone further to assess the effects of genetic manipulation on trophoblast migration/invasion and spiral artery remodeling. Notch 2 is an important paracrine signaling receptor for cell movements (270). Knockout of Notch 2 in *Tpbpa*-expressing trophoblast cells significantly reduced trophoblast invasion of spiral arteries. Moreover, altered spiral artery trophoblast invasion was associated with reduced canal diameters and placental perfusion, a key feature in PE, directly linking trophoblast migration and invasion with vascular remodeling (150). Therefore, it is probable to hypothesize that these trophoblast-specific modifications and subsequent abnormalities in placenta vascular remodeling would lead to PE-like symptoms such as hypertension in these mice, particularly because it has been shown that Notch 2 is reduced in placentas from women with PE (383). In another study, adoptive transfer of NK cells from Rag2$^{-/-}$ mice, which lack T or B lymphocytes, into BALB/c-Rag2$^{-/-}$Il2$^{-/-}$ mice, which lack T, B, and NK cells, corrected the uterine vascular

defects found in the latter mouse (144), suggesting that NK cells play a critical role in spiral artery remodeling.

Uterine blood flow is reduced up to 50% in patients with PE (280). As such, markers of placental ischemia and hypoxia, such as hypoxia inducing factors (HIF-1α and HIF-2α), are elevated in PE placental tissue (274). In mice, selective overexpression of HIF-1α in placenta is capable of inducing hypertension, a consequence of placental ischemia (155). In humans, the terminal villi of placentas associated with fetal growth retardation have elongated villous capillaries and inconspicuous loops, suggesting a larger surface area (180). This latter finding would be consistent with placental insufficiency, that is, inefficient nutrient/waste exchange between mother and fetus. In summary, these studies suggest that the pathogenesis of PE is mediated by a lack of trophoblast migration/invasiveness and spiral artery remodeling. The resulting fetal-placental ischemia induces the release of vasoactive factors from the placenta. Since these processes begin early in pregnancy, it is not surprising that circulating placenta factors in response to placental ischemia and vascular resistance are evident much earlier than the clinical manifestation of PE.

Clinical Manifestations of PE

Phase 2 in the pathogenesis of PE is the clinical manifestation of the maternal syndrome. Incomplete development of spiral arteries leads to placental ischemia and the subsequent release of pro-inflammatory and antiangiogenic factors into the maternal circulation. There is also evidence to suggest that PE is associated with increased complement levels (54, 261), which contributes to the excessively hypercoagulable state of this disease. In particular, mutations in the central complement gene, *C3*, were found to be associated with PE with severe features (153).

- *Reactive oxygen species in PE*. Oxidative stress plays a prominent role in the maternal syndrome. In phase 2, ROS are generated in a number of ways, including cellular injury and other biological processes, such as activation of the angiotensin II (Ang II) type 1 (AT1) receptor. *In vitro* studies have also shown that uterine arteries from rats that are isolated and incubated with serum from PE patients show greater superoxide staining than those incubated with serum from normal pregnant women. This can also be observed in vessels isolated from RUPP rats (165, 299). Ultimately, the increase in prooxidant molecules in PE causes organ injury and leads to endothelial dysfunction by directly inducing vasoconstriction, stimulating production of vasoactive factors, or inhibiting mechanisms for vasodilation.

- *Immune factors in PE*. The most well-studied immune factors that are increased in association with PE are the agonistic AT1-AA, TNF-α, interleukin (IL)-6, IL-17, T helper (Th)-1 cells, and Th-17 cells. In fact, infusion of AT1-AA, TNF-α, or IL-17 individually each increases MAP in pregnant rats (182, 183, 342). Also, blockade of the AT1-AA (Figure 6) or TNF-α in the RUPP rat model of PE has been shown to reduce blood pressure, improve angiogenic balance, and decrease expression of vasoconstrictive factors, such as endothelin-1 (ET-1) (71,

183). AT1-AA infusion into rats is associated with increases in the ET-1 precursor, prepro-ET, in the renal cortex and placenta (182, 236).

Animal models of PE have been used to assess specific immune cell types that are known to be involved in the pathogenesis of PE. Cornelius et al. showed that Th-17 cells isolated from the spleen of RUPP rats, cultured and injected interperitoneally into normal pregnant rats, induced a PE-like phenotype (66, 357). Furthermore, increasing the population of T regulatory cells (Tregs) in RUPP rats significantly reduces MAP, circulating levels of IL-17 and TNF-α, renal ROS, placental ROS, and prepro-endothelin-1 (prepro-ET-1) (65, 152). NF-κB is activated by Ang II, which is elevated in PE and in turn further increases release of pro-inflammatory cytokines and chemokines. PE is associated with an excess of these pro-inflammatory factors and a deficiency of IL-10 derived from Tregs. IL-10 plays an important role in normal pregnancy in regulating the polarization of T cells to a Th-2 phenotype over the pro-inflammatory Th-1 phenotype (293). Interestingly, supplementation of IL-10 alone in the RUPP rat is sufficient to attenuate MAP and pro-inflammatory factors (138). As discussed previously, NK cells have been shown to play a significant role in PE. Depletion of cytolytic NK cell in the RUPP rat lowers MAP, intrauterine growth restriction (IUGR), and inflammation (159). These data suggest that the increased pro-inflammatory immune cell populations play a deleterious role in PE. These factors all act to cause pathological activation of the maternal endothelium (Figure 7) as well as directly impacting multiple organ systems.

Endothelial dysfunction is a hallmark feature in PE

Endothelial dysfunction is an integral part of PE pathophysiology, specifically during the clinical manifestation of this disease. To understand endothelial dysfunction in PE, it is helpful to understand that during normal conditions, the endothelium (innermost layer of vessels composed of endothelial cells) produces factors that act to maintain vascular tone. Healthy pregnancy is associated with an increase in artery diameter and reductions in total peripheral resistance in early gestation, in part due to an increase in endothelial NO-induced vasodilation. In contrast, ET-1, another endothelium-derived factor, is the most potent pressor (or vasoconstrictor) known. ET-1 has been shown to be significantly elevated during PE pregnancy compared to normal pregnant women and correlates with the severity of the disease in some cases (113, 211). Furthermore, elevations in endothelium-derived vasoconstrictors, including ET-1, Ang II, and thromboxane A2, occur weeks prior to clinical onset of PE (122, 226, 339). Reduced peripheral resistance along with adequate perfusion of maternal organs and the uteroplacental unit are all vital for healthy pregnancy. Therefore, it is important to remember that these vasorelaxing and vasoconstricting factors are produced in a delicate balance, and aberrations to this system can have widespread implications. In the 1990s, *in vitro* studies confirmed that serum from PE women contained high levels of ET-1 (333), indicating that endothelial dysfunction could be the cause of hypertension and organ damage in this disease. Sera from both PE patients and animal models have been used to show that exposure to circulating placental factors induces ET-1 production (35, 183, 271). In addition, vessels from animal models of PE have been used to demonstrate resistance to mediators of vasorelaxation (acetylcholine; Figure 8) and increased sensitivity to vasoconstrictors (54).

There are a number of ways that ET-1 production (and its precursor big ET-1) is increased in PE. Reduced NO production has been shown to inhibit ET-1 production (167). Placental release of both ROS and TNF-α into the maternal circulation has been shown to induce ET-1 production. MMP-1 and MMP-2, which are increased in PE, cleave the ET-1 precursor, big ET-1, to active ET-1 within systemic blood vessels (3). In addition, MMP-1 activates the protease-activated receptor 1 (PAR-1) and mediates the release of ET-1 in endothelial cells (246). Another study found elevated endothelin-converting enzyme, which converts big ET-1 to vasoactive ET-1, in the maternal circulation of PE patients (9). It is most likely a combination of these pathways that pathologically increases vascular and circulating levels of ET-1 in PE women.

ET-1 acts on two G-protein-coupled receptors on the cell surface: ET-1 Type A (ET_A) and Type B (ET_B), which are localized to vascular smooth muscle cells and endothelial cells, respectively. Activation of the ET_A receptor causes vasoconstriction and cell proliferation, while the ET_B receptor facilitates vasodilation and natriuresis via NO and prostacyclin, which are significantly reduced in PE (85, 212). ET_A antagonism has been studied in a number of animal models of PE and is associated with reductions in MAP (Table 4; Figure 9) and ET-1 precursors in some cases (11, 182, 236). While the role of the ET_A receptor in PE is well established, less is known about the role of ET_B. However, studies have shown that ET_B expression is reduced in the RUPP rat, which could at least in part explain reduced ET_B-dependent vasorelaxation (136). Another study showed that ET_B-deficient pregnant rats have increased blood pressure during pregnancy (317). Interestingly, chronic infusion of the antiangiogenic factor, sFlt-1, into pregnant rats significantly increased prepro-ET in the renal cortex (182, 236).

Angiogenic imbalance and endothelial dysfunction in PE—One of the most intensely studied characteristic factors involved in endothelial dysfunction in PE is sFlt-1 and the angiogenic imbalance that exists in this disease. VEGF is a critical player in normal pregnancy, not only in the development of new vessels and angiogenesis but also in maintaining endothelial integrity. PlGF, a member of the VEGF family, is another angiogenic factor released by the placenta that serves to maintain proper endothelial function during pregnancy. These angiogenic factors bind to vascular endothelial growth factor receptors (VEGFRs) (267). VEGF binds to VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1), whereas PlGF binds exclusively to Flt-1 (98). The soluble form of Flt-1, called sFlt-1, is increased in the circulation of women with PE, where it antagonizes free VEGF and free PlGF. Depletion in the bioavailability of these circulating growth factors is at the detriment of the endothelium and blood pressure regulation (Figure 10). This was demonstrated by sFlt-1 overexpression and infusion into animal models, resulting in increased MAP and a PE-like phenotype (215, 236). Furthermore, PlGF administration has been shown to reduce blood pressure in the RUPP rat and a nonhuman primate model of PE, while VEGF administration has been shown to improve blood pressure in the RUPP model (198, 206, 323). It is important to note that normal pregnancy is associated with low levels of sFlt-1 that gradually increase toward term. Throughout gestation, sFlt-1 levels do not exceed the levels of VEGF and PlGF. Endothelial dysfunction occurs because PE is associated with uncontrolled excess of sFlt-1 that surpasses and antagonizes the available angiogenic factors.

Increased circulating levels of sFlt-1 and reduced PlGF levels have been documented in women with PE and, in fact, prior to the onset of clinical symptoms. In 2003, Maynard et al. (215) showed that elevated levels of sFlt-1 are present in PE patients and to a greater extent in PE with severe features. These data were accompanied by decreased circulating free levels of VEGF and PlGF in PE, with much lower concentrations in plasma from women with PE with severe features (Figure 10). Studies also support the presence of a susceptibility locus near the *FLT1* gene in neonates from PE pregnancies, suggesting that sFlt-1 is not simply released in response to placental ischemia but rather provides a genetic basis for this disease. Another antiangiogenic factor that is observed to be increased in PE is soluble endoglin (sEng). It is produced by the placenta and has been shown to reduce binding of transforming growth factor-β1 (TGF-β1), which is also important in cell proliferation, vasodilation, and angiogenesis.

Similar to the ROS and inflammatory factors discussed above, antiangiogenic factors act to dysregulate the NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway, which results in reduced vasorelaxation. One of the major outcomes of endothelium-bound VEGFR activation is the synthesis of NO, which diffuses to the vascular smooth muscle cell and binds to sGC to facilitate the conversion of the second messenger cGMP. cGMP is involved in a number of processes, including cell proliferation and vasodilation. Specifically, cGMP activates protein kinase G (PKG), which phosphorylates voltage-gated potassium channels and promotes relaxation (18, 297). In addition, increased cGMP levels inhibit calcium channel activity, blocking influx of calcium into the cell (156). In the absence of VEGFR stimulation, NO production is reduced, which has been reported in PE women in a number of studies (200, 212). Furthermore, increased levels of ROS in PE act on any available NO to produce peroxynitrite, an unstable, highly reactive, and damaging molecule. Studies show that sGC oxidation by ROS reduces signaling activity and cGMP production, diminishing vasodilatory activity. Studies in animal models have shown that improving NO signaling, by blocking the degradation of cGMP, attenuates hypertension (114, 118, 335). In addition, blockade of cGMP degradation is associated with reductions in circulating sFlt-1 (275) and increases in PlGF (161). Recent studies have investigated the link between the antiangiogenic environment and ET-1 in pregnant women and found that those with higher sFlt-1/PlGF ratio had greater levels of ET-1 (7, 352). All of the factors described in the sections above ultimately drive increases in ET-1 and decreases in NO bioavailability (Figure 11).

Another pertinent factor to consider in relation to increased oxidative stress and endothelial dysfunction are lipid peroxides. Circulating small, dense low-density lipoproteins (LDLs) have been shown to be increased in PE, which provide fatty acid substrates for lipid peroxidation (234). Oxidized low density lipoprotein (oxLDL) is increased in PE and binds to endothelial receptors, such as LOX-1 (lectin-like oxidized LDL receptor-1), to internalize and metabolize oxLDL particles. LOX-1 expression has been shown to be increased in response to TNF-α, IL-1, oxLDL, and Ang II, all of which are increased in PE (162, 252, 305). Increased LOX-1 activity is associated with increases in superoxide and peroxynitrite via activation of NADPH oxidase. Increased expression and activity of LOX-1 has been found to play a role in a number of pregnancy- and non-pregnancy-related diseases and thus is thought to contribute to vascular endothelial dysfunction in PE (316).

Sympathetic nerve activity in PE—The sympathetic nervous system tracks and innervates the adventitia of almost every blood vessel (57), and increased sympathetic nerve activity (SNA) is known to promote vasoconstriction and mediate the development of hypertension (102). However, research concerning this system has been relatively understudied in the field of pregnancy and PE. Much of what is currently known about this system in hypertensive pregnancies has been derived from associational studies using surrogate markers of SNA, including low frequency/high frequency (LF/HF) of heart rate variability (91, 231, 374), altered autonomic regulation of heart rate during orthostasis (191, 327), reduced baroreflex sensitivity (230, 281, 366), and circulating and uterine levels of vasoconstrictive substances such as catecholamines and neuropeptide Y (NPY) (2, 104, 169, 175, 248, 255). These markers are higher in PE versus control normotensive pregnancies and point to SNA being elevated in the former group of women, as reviewed by Spradley (319) and Reyes et al. (279). Far fewer studies have attempted to directly link SNA to hypertension in PE, but a study dating back to 1948 provided evidence that SNA drives increased blood pressure in superimposed PE (259). Those authors demonstrated that splanchnicectomy lowered blood pressure in women with superimposed PE. Since then, other investigations have detected that muscle (M)SNA is elevated in women with PE (124, 125, 298). These nerve-recording experiments are important but remain associational in nature and have not fully provided a cause-or-effect relationship between SNA and the pathogenesis of hypertension in PE.

As discussed throughout this article, the pathogenesis of PE is thought to originate from abnormal spiral artery remodeling and placental ischemia with subsequent release of prohypertensive factors such as sFlt-1. This antiangiogenic factor quenches the vasoprotective and antihypertensive actions of VEGF and PlGF (215), which ultimately causes endothelial dysfunction, vasoconstriction, and resultant hypertension. Preliminary experiments in rodents have implied that increased sympathetic drive leads to placental ischemia and alterations in circulating angiogenic factors. Pregnant rats subjected to a combination of chronic sonic, overpopulation, and immobilization stressors have reduced placental levels of the angiogenic factor, PlGF, and increased blood pressure (67). Such chronic stress-induced increases in SNA and blood pressure are supported by other studies and also been detected in rats encountering cold and fasting stress (164, 170, 328). Further evidence that neurological mechanisms initiate the development of PE is that acutely activating sympathetic centers within the brain using Kurotu's electrodes increased blood pressure in pregnant rats (205). Pregnant women destined to develop PE have increased blood pressure response to sympathetic outflow elicited by the cold-pressor test (369). This test has been shown to activate central pathways within the rostral ventrolateral medulla (RVLM), which increases sympathetic outflow and blood pressure in rats (240). Blockade of oxidative stress within the RVLM significantly reduced blood pressure in an animal model of PE, where desoxycorticosterone acetate (DOCA) is administered to pregnant rats (373). Based on these collective studies, it is feasible to hypothesize that elevated sympathetic drive promotes uteroplacental vasoconstriction, as there are increased nerve fibers observed in the placental bed myometrium in women with PE (99). This sympathetic signaling pathway would then incite placental ischemia and release of soluble placental factors, such as sFlt-1, to quench bioavailable angiogenic factors and cause maternal hypertension.

It is also likely that increased SNA is involved in the downstream hypertensive responses to placental ischemia. The involvement of SNA and its effector target, the adrenergic receptors, in placental ischemia-induced systemic vasoconstriction and hypertension had not been studied until Spradley et al. (321) tested the hypothesis that adrenergic receptor blockade would attenuate hypertension in the RUPP model of PE. They found that adrenergic receptor blockers significantly attenuated placental ischemia-induced hypertension and reported a lesser blood pressure response in normal pregnant control rats. Other researchers have provided suggestive evidence that SNA is increased in RUPP rats by finding that baroreflex sensitivity of blood pressure is reduced in this model of PE (142); this would implicate increased sympathetic drive to the systemic circulation. Indeed, Hines et al. found that the baroreflex was reset to a higher set point (i.e., reduced sensitivity) along with increased renal (R)SNA. It could be that the elevated SNA coupled to the endothelial dysfunction reduces the ability of the endothelium to buffer sympathetic flow-directed activation of adrenergic receptor-mediated vasoconstriction in PE. Overall, it is possible that elevated SNA is not only involved in the maintenance of vasoconstriction and increased blood pressure in PE but also the initiation of upstream placental ischemia and release of factors that cause endothelial dysfunction.

Multiorgan dysfunction in PE

In addition to widespread systemic endothelial dysfunction, PE is associated with multiorgan dysfunction and injury. Localized endothelial dysfunction itself is a major contributor to end-organ damage. Here, we discuss some of the major organ systems affected by this disease.

The kidney in PE—Normal pregnancy is associated with marked increases in renal hemodynamics. Renal plasma flow and glomerular filtration rate increase approximately 40% to 60% compared to nonpregnant women (181, 332). The clinical renal features of PE include reductions in renal hemodynamics, proteinuria, podocyturia, and glomerular endotheliosis that is identified by endothelial swelling and glomerular capillary narrowing (Figure 12) (214, 241). Excessive levels of sFlt-1 in PE are believed to cause glomerular membrane abnormalities by inhibiting VEGF binding to its receptors on glomerular endothelial cell and podocytes (214, 241). In support of this concept are animal studies demonstrating that increasing plasma sFlt-1 levels in pregnant mice or rats, via direct infusion of sFlt-1 or injection of adenovirus expressing the sFlt messenger RNA, results in an increase in blood pressure accompanied by proteinuria (Figure 13) and glomerular endotheliosis (Figure 14) (93, 215, 236, 326). Interestingly, anti-VEGF therapies given to nonpregnant rats or mice also cause glomerular endothelial injury and proteinuria (326). Glomerular disease characterized by proteinuria and glomerular endotheliosis has also been reported in a podocyte-specific VEGF knockout mouse (93). Collectively, these animal studies support the concept that sFlt-1-induced VEGF deficiency can produce a renal phenotype seen in women with PE.

Animal models used to examine the pathophysiology of PE have also been reported to exhibit reduced renal plasma flow and glomerular filtration rate. In RUPP rats, renal plasma flow (<23%) and glomerular filtration rate (<40%) are decreased as well as reductions in NO

synthase (NOS1 isoform) (16). A twofold increase in plasma TNF-α in pregnant rats produces significant reductions in renal function that is associated with significant decreases in renal NOS1 protein expression (14, 185). Inhibition of NOS1 in pregnant rats at midgestation results in decreases in renal plasma flow and glomerular filtration rate (5, 196). These data suggest that NOS1 plays a role in mediating the increases in renal hemodynamics that occur during pregnancy and may mediate the reduction in renal hemodynamics in response to placental ischemia. Other factors such as increases in sFlt-1, ET-1, and ROS may also contribute to the reduction in renal hemodynamics.

The liver in PE—Liver dysfunction in PE is caused by increased resistance within the hepatic vascular bed, resulting in ischemia, and elevated circulating liver enzymes, or transaminases. HELLP syndrome occurs in approximately 12% of patients with PE and is characterized by the presence of hemolysis, elevated liver aminotransferases, and low platelet counts. Importantly, transaminases can be elevated in PE patients both with and without HELLP syndrome (272). Another factor contributing to liver dysfunction is believed to be fibrin deposition within the hepatic sinusoids, resulting in sinusoidal obstruction, vasospasm of the liver vascular bed, and liver ischemia, leading to large hematomas, capsular tears, and intraperitoneal hemorrhage (225, 232). Histological changes in the liver in HELLP syndrome may include periportal abnormalities, such as with hemorrhage, sinusoidal fibrin deposition, and hepatocyte necrosis (225, 304).

The brain in PE—While PE can affect multiple organs, the brain is particularly vulnerable. Cerebrovascular dysfunction during PE can lead to acute and long-term cerebral complications in the mother. Acute cerebral complications include cerebral edema, stroke, or even eclampsia (378). Approximately 40% of maternal deaths that result from PE are attributed to cerebrovascular abnormalities (276). The underpinning mechanisms have yet to be fully elucidated; however, they are usually associated with endothelial cell injury and cerebrovascular overperfusion or in some cases vasospasm. Using angiography imaging, diffuse or multifocal segmental vascular narrowing has been observed in women having PE with severe features, which is consistent with some of the forms of cerebrovascular abnormalities listed above (378).

There is also substantial evidence in both PE patients and experimental animal models of PE that impaired regulation of cerebral blood flow, increased blood brain barrier (BBB) permeability, and cerebral edema play an important role in the acute and long-term consequences of cerebrovascular abnormalities. Overperfusion of the brain, due to decreased cerebrovascular resistance, is one mechanism whereby the BBB is disrupted to cause vasogenic edema and neurologic symptoms (Figure 15). In addition, reduced vascular resistance leads to diminished hypertensive remodeling of cerebral arteries during PE and may expose the maternal brain to significantly elevated blood pressure (135). Supporting this concept are studies reporting that pregnancy prevents hypertensive inward remodeling in animal models (135). Another potential mechanism contributing to the increased risk for cerebrovascular disease in women with PE is altered cerebral vascular autoregulatory index resulting from impaired vascular myogenic tone (Figure 16). Some, but not all studies, have

reported impaired cerebral blood flow autoregulation in patients with PE; this may be related to the difficulty in assessing cerebral blood flow in pregnant women.

As cerebrovascular function is difficult to monitor in pregnancies already complicated by PE, animal models have been useful tools in understanding the underlying mechanisms. Placental ischemia in the RUPP model leads to increased BBB permeability (Figure 17) and cerebral edema. In these studies, impaired cerebral blood flow regulation was particularly evident at higher perfusion pressures (Figure 18), as well as vascular myogenic reactivity (Figure 19) (291, 363). Furthermore, impaired vascular myogenic response in the RUPP rat is associated with reduced beta epithelial sodium channel (βENaC) expression in cerebral vessels. βENaC proteins form non-voltage-gated Na+ channels and are members of the degenerin protein family. They are expressed in vascular smooth muscle cells and involved in promoting vascular tone induced by changes in pressure. The importance of the altered βENaC proteins and cerebral hemodynamics on BBB function is currently unknown, but there is compelling evidence that placental factors may have a direct effect on cerebral vessels to enhance BBB permeability (135).

While placental ischemia leads to a number of cerebrovascular abnormalities that are also seen in women with PE, the various factors linking placental ischemia and cerebrovascular dysfunction are not fully known. Recent studies have implicated AT1-AA and TNF-α, which are both elevated in PE women and in the RUPP model. Warrington et al. (364) reported that the AT1 receptor plays a role in the development of hypertension and impaired cerebral blood flow autoregulatory function in placental ischemic rats. In addition, the AT1-AA impaired cerebral blood flow autoregulation in pregnancy. These findings indicate that activation of the AT1 receptor, in part due to circulating AT1-AA, may be involved in the cerebral vasculature dysfunction in PE. In another study, Warrington and colleagues showed that TNF-α infusion into pregnant rats, to levels reported in women with PE, increases brain water content, and that TNF-α blockade with Etanercept reduced brain water content and BBB permeability (363). Furthermore, a recent study by Duncan et al. (89) demonstrated that excess TNF-α in once normal pregnant rats also reduces cerebrovascular βENaC expression and impairs cerebral blood flow regulation, suggesting that TNF-α may contribute to cerebral edema, increased BBB permeability, and cerebral blood flow regulation. Taken together, these studies indicate that placental factors, particularly AT1-AA and TNF-α, stimulate degenerin-mediated vascular myogenic constriction and cerebral blood flow regulation.

The heart in PE—Pregnancy presents a significant challenge to cardiac function during the course of gestation, with cardiac output increasing 40% to 50% to meet the metabolic demands and support growth of the fetal-placental unit. Cardiac hypertrophy and associated increases in vascular density occur during normal pregnancy (55) and typically reverses within 7 days postpartum. Conversely, PE, particularly with low birth weight offspring, is typically associated with pathological hypertrophy, reduced ejection fraction, and reduced cardiac output. Numerous studies now highlight the prevalence of cardiac dysfunction in this cohort (83, 129, 221, 302, 309). Cardiac dysfunction in PE was historically thought to be the sole consequence of the hemodynamic forces of hypertension. However, recent studies have indicated a more severe cardiac phenotype in PE compared to gestational hypertension

(302), suggesting that cardiac dysfunction in PE could be a result of circulating placental factors and occurs independently of hypertension (Figure 20).

Diastolic dysfunction, based on predefined professional recommendations, occurs significantly more frequently in PE patients compared to gestational hypertensive pregnancies (220, 339). Systolic dysfunction, measured by global longitudinal strain (GLS), or deformation of the heart, has been reported to be reduced despite preserved ejection fraction (302). Incidentally, GLS is a sensitive measure that can detect subtle and subclinical cardiac dysfunction. Decreased GLS indicates stiffening of the ventricle and fibrosis and is therefore associated with age or disease. Similarly, the Tei Index, which is the ratio between contraction and relaxation time intervals, also typically increases under similar circumstances and is increased in PE women (45). A number of studies have investigated whether cardiac abnormalities are related to severity of PE. In a study of 192 patients, women with prepregnancy cardiac remodeling as a result of chronic hypertension were more likely to develop cardiac complications during pregnancy (350). Another study reported that eccentric ventricular hypertrophy, which is typically associated with physiological remodeling and exercise, was most associated with adverse outcomes such as admission to neonatal intensive care unit, low birth weight, and use of ventilator for the first 24 h (21). Similar to previous publications, ejection fraction was preserved in these patients, suggesting that current methods of monitoring cardiac dysfunction in PE using crude measures such as ejection fraction may not be conducive in this cohort.

The development of cardiac dysfunction in PE is not well understood; however, placental ischemic factors have been implicated. Animal studies show that the RUPP rat exhibits reduced ejection fraction and GLS during pregnancy (Figure 17) as well as apoptosis, histological measures of fibrosis, and reductions in vascular density (34, 131). Importantly, cardiac dysfunction only develops in animal models of hypertension after 2 weeks; however, these changes in the RUPP rat are observed after only 5 days of placental ischemia, suggesting that placental factors could be contributing to these cardiac abnormalities. The antiangiogenic properties of sFlt-1 could impact cardiac function in PE. Overexpression of sFlt-1 has been shown to induce cardiac dysfunction in mice. Mice with knockout of PCG-1α, which is a pro-angiogenic transcription factor, exhibit systolic dysfunction within 3 weeks (258), suggesting that an antiangiogenic environment is sufficient to induce cardiac dysfunction, independent of elevated blood pressure. Moreover, clinical studies show that the impaired cardiac angiogenesis compares to the levels of circulating sFlt-1.

Circulating Activin A, a profibrotic factor and member of the transforming growth factor TGF-β family, is produced by the placenta, is significantly increased during pregnancy, and correlates with cardiac dysfunction in PE (301). Shahul et al. showed that levels of Activin A with clinical characteristics of PE were the most accurate predictor of abnormal GLS, suggesting that Activin A has a direct role in mediating cardiac dysfunction in PE. Activin A infusion into mice also results in significant impairment to cardiac function (289). Despite previous theories that cardiac dysfunction is a consequence of chronic hypertension, these data suggest that placental factors could have a direct impact on the heart in PE.

Fetal Outcomes

A number of circumstances during pregnancy, such as maternal undernutrition, alcohol consumption, gestational hypertension, maternal obesity, preexisting cardiovascular disease, and PE, can impact fetal outcomes during childhood and adulthood (Figure 21). Pregnancies complicated with hypertension are at the highest overall risk of fetal mortality (134). Of those, PE is the leading cause of perinatal morbidity and mortality. As the only current therapy for PE is delivery of the fetus and placenta, premature birth is particularly common in this disease, which poses severe and long-term risks for the baby. PE is also associated with IUGR and small for gestational age (SGA) births. In addition to the immediate risks of underdevelopment, more recent studies have shown significantly increased risk for the development of cardiovascular disease during child- and adulthood in SGA offspring. In 1990, British epidemiologist Dr. David Barker postulated that the high prevalence of low birth weight babies and subsequent disease during adulthood in the same geographical area was due to the programming of disease during fetal life (38). What is now commonly referred to as the Barker Hypothesis, or the developmental origins of fetal programming, has since been widely studied and considered a critical time frame for therapeutic intervention to improve long-term outcomes on fetal outcomes (15).

Impact of the prenatal environment on fetal outcomes

Placental insufficiency, such as is present in PE, is thought to play a central role in programing cardiovascular disease in offspring. This insufficiency occurs when the placenta cannot appropriately deliver amino acids, oxygen, and nutrients to the growing fetus. In the case of PE, this is due to impaired spiral artery remodeling, which leads to poor perfusion of the placenta and placental ischemia. Although it is widely accepted that placental insufficiency is an initiating event in the programing of disorder, the exact mechanisms are not completely understood. Barker postulated a "brain-sparing" effect where, in the presence of restricted nutrients, blood flow is redistributed away from other organs as an adaptive mechanism for survival. As a result, other major organs remain underdeveloped, resulting in changes to structure and physiology, thereby ultimately "programming" the development of cardiovascular risk and disease. The brain-sparing effect can be observed by enlarged cranial circumference compared to body circumference in 70% to 80% of offspring. Hemodynamically, brain sparing can be detected by reduced middle cerebral artery resistance in the offspring *in utero*, allowing for increased perfusion. While this compensatory mechanism most likely increases survival, it does not improve the long-term cardiovascular and metabolic risk in later life (103, 140). It is important to note that not all preclinical studies where cardiovascular risk is increased in offspring are associated with maternal hypertension (as is present in PE), whereas this risk is consistently found in models of placental insufficiency, suggesting it is placenta insufficiency in PE that is the key factor in the programming of long-term cardiovascular disease in these offspring.

Postnatal and long-term outcomes for offspring

PE is most notably associated with IUGR, which leads to low birth weight and development of cardiovascular, metabolic, and neurological diseases (Table 5) (201). Some studies in infants born at term suggest that exposure to PE *in utero* is adequate to lead to these

disturbances and are not due solely to preterm delivery (239). Increased risk of cardiovascular disease in offspring exposed to PE has been relatively well established. Studies show a significantly increased risk of elevated blood pressure in childhood through to young adulthood (12, 19, 82, 249). A number of studies have found increased risk of congenital heart disease (CHD) in PE offspring (29, 46, 48, 375), with one study estimating an eightfold greater risk for offspring of PE women. In that study, 30% of infants from PE pregnancies were diagnosed with CHD by day 7 of life and 21% at day 28, as compared to 12% and 3%, respectively, in infants born from healthy pregnancies (375). Some studies have also showed increased prevalence of metabolic disease in children and adults exposed to PE pregnancies, such as insulin insensitivity, obesity, and type 2 diabetes mellitus (19, 160, 300).

Despite the brain-sparing effect observed in pregnancies with placental insufficiency, several preclinical and clinical studies have reported neurodevelopmental impairment in offspring. Clinical studies have demonstrated increased autism spectrum disorder and attention deficit/ hyperactivity disorder, as well as cognitive impairments, such as reduced academic performance. In addition, infants born from PE pregnancies are at an increased risk of developing neurological diseases such as epilepsy and stroke (72, 90, 130, 238). In another study, adults from PE pregnancies exhibited much greater tendencies for depressive symptoms (344).

The RUPP model has been useful in understanding some of the cardiovascular aberrations that occur in infants from PE pregnancies. Interestingly, male offspring from RUPP pregnancies develop hypertension, similar to the human population. Female offspring exhibit age-dependent increases in blood pressure, which can be attenuated by androgen receptor blockade or estradiol supplementation in association with reduced AT1a receptor activity, implicating androgen-mediated activation of the AT1 receptor in the development of PE-induced hypertension in offspring (76–78). Studies have shown that renal oxidative stress, renal expression of renin, angiotensinogen, and angiotensin-converting enzyme activity, are increased in male IUGR offspring. Furthermore, blockade of the renin angiotensin system (126), renal denervation (251), or chronic antioxidant administration (250) attenuates the development of hypertension in RUPP offspring.

Long-term Risk for Mother

In 2011, the American Heart Association released guidelines for the prevention of cardiovascular disease and recognized PE as a risk factor. Indeed, several studies now highlight the profound long-term effect of a PE pregnancy on the mother, and in doing so, negate theories of this being a disease that is cured at delivery (Table 5). A meta-analysis of over 20 studies determined that the long-term risk of developing hypertension and ischemic heart disease is increased four- and twofold, respectively (43). In addition, the strong association between PE and subsequent risk for hypertension could potentially account for incidence of chronic kidney disease in formerly PE patients in the long term, as they are both known risk factors for renal injury.

While some studies have found little association between previous PE and later chronic kidney disease, others reported strong associations, with up to ninefold increases in risk of chronic kidney disease (199, 214, 241). Little is known with regard to the underpinning causes of long-term renal disease in PE, but a number of animal models have been reported to have sustained decline in renal function. Paauw et al. (254) reported that placental ischemia in pregnant rats is associated with a decline in renal function and persistent cardiac dysfunction 8 weeks postpartum that was independent of blood pressure. Turbeville et al. (345) showed in a model of superimposed PE that pregnancy exaggerates postpartum renal damage despite no difference in blood pressure long term. Utilization of these animal models may provide a better understanding of the mechanisms linking PE and long-term chronic kidney disease as well as could help in developing preventive, diagnostic, and therapeutic strategies for women who develop chronic kidney disease after a preeclamptic pregnancy.

As seizures during pregnancy are a severe complication of PE, it is not surprising that this disease has long-term implications on the brain. Studies showed that the long-term consequences of cerebrovascular impairment include persistent white matter lesions and chronic cognitive abnormalities in mothers with a history of PE (378). White matter lesions are thought to be a result of posterior reversible encephalopathy syndrome, where edema is thought to compress the cerebral tissue causing ischemia and cell death (379). PE itself is a prominent risk factor for long-term cerebrovascular disease risk, but whether white matter lesions increase this risk further is not clear. It is important to note that not all women who experience later cerebrovascular damage experienced seizures during pregnancy. However, white matter lesions are particularly associated with early-onset PE (30).

Mounting evidence indicates that cardiac dysfunction is present in women long after delivery. In a meta-analysis of 22 studies and 6.4 million women, PE was associated with a fourfold increase in the development of postpartum heart failure after pregnancy and a twofold increased risk of coronary heart disease, stroke, and death due to cardiovascular disease (371). Another study showed persistent diastolic and systolic dysfunction 12 months following parturition in the absence of hypertension (220). The same study reported that PE patients were more likely to develop essential hypertension within 2 years of giving birth (220). A 2019 study of 149,712 PE patients observed 18,624 first-time cardiovascular events including heart failure, stroke, and cardiovascular deaths over a 9-year period after PE pregnancy (190). A recent report highlighting the high rate of pregnancy-related heart failure admissions also showed that postpartum heart failure hospitalizations increased by 7% between 2001 and 2006, which have since continued to steadily rise (229). The same report showed that, in over 50 million hospitalizations, almost 40% of women were also patients diagnosed with PE or superimposed PE. Although a number of placental factors have been implicated in the development of cardiac dysfunction during PE, Activin A is the only factor that has been studied to date and found to correlate with long-term systolic dysfunction (301). These large cohort studies suggest that cardiac dysfunction is independent of hypertension during PE, and that elevated circulating placental factors may have a long-term impact on the heart.

While the direct cause of long-term disease in women with a history of PE is not well understood, some factors have been shown to remain increased in this cohort, despite the fact that the placenta is removed and thus can no longer contribute to the circulating milieu. Ang II, AT1-AA, and Activin A have all been shown to remain increased in women with a history of PE (149, 301, 324), suggesting that these factors continue to act on the maternal endothelium and organ systems years after delivery. In addition, a second PE pregnancy has been shown to further increase risk of cardiovascular disease. Some theories of long-term cardiovascular disease in PE are centered around the concept that pregnancy is a physiological "stress test" and that the subsequent cardiovascular disease that is seen in these women was simply dormant or subclinical previously. Nevertheless, this is unlikely because the studies discussed above suggest that new damage occurs during a PE pregnancy.

Clinical Management of PE

Predicting the development of PE

Many studies have attempted to predict the onset of PE (245). There is no single test that can definitively identify women who will develop this disorder; however, measurement of sFlt-1/PlGF ratio has been extensively studied with promising results. Currently, the most accurate predictive measurement of early-onset PE is the sFlt-1/PlGF ratio accompanied by uterine artery Doppler assessment (307). The PROGNOSIS (Prediction of Short-term Outcome in Pregnant Women with Suspected Preeclampsia Study) trial found that women with an sFlt-1/PlGF ratio 38 did not develop PE in the subsequent week (380). Furthermore, repeated measurements of this ratio improved risk stratification and could rule out onset of PE for up to 4 weeks (381). A recent article reported that aspirin treatment was effective in reducing the sFlt-1/PlGF ratio in women who were considered to be at risk of developing PE during their first trimester (213).

While efforts to predict PE could improve management of this disease, there is still no effective intervention to prevent its onset. However, a number of micronutrients, particularly those that have been shown to be depleted in PE women, have been studied in this area of research. Selenium, an essential micronutrient, represents a promising candidate, particularly because it is a nonpharmacological option and can be administered as a dietary supplement. It has been shown to improve mitochondrial function, *in vitro* (171, 269), and has been associated with reduced incidence of PE in a number of studies (262, 372). Other micronutrients, such as magnesium, which is an important antioxidant coefficient, had little to no effect in women at high or low risk of developing PE (80, 81). This area of research requires further investigation and highlights the importance of basic research for the development of appropriate therapeutic options.

Current therapeutic avenues

Currently, treatment for PE is limited to managing symptoms and in severe cases premature delivery of the fetus, which poses significant risk to both mother and baby. Aspirin therapy in high-risk women, betamethasone (<34 weeks), and magnesium sulfate in women at risk for developing eclampsia are the only medications currently administered for management of this disease. In addition, blood pressure monitoring is important both during pregnancy

and following delivery, in case the patient develops *de novo* postpartum PE (276). Antihypertensive therapy is carefully regulated during pregnancy. Based on ACOG guidelines, mild to moderate hypertension (<160/110 mmHg) should not be treated pharmacologically, because there is no evidence that reducing hypertension will improve disease progression or outcomes. In circumstances where antihypertensives must be administered, the recommended therapy is labetalol (beta blocker), nifedipine (calcium channel blocker), or methyldopa (adrenergic receptor blocker) (282).

Despite tremendous advances in understanding the pathophysiology of PE, therapeutic options remain limited. One of the primary reasons for this is the posed risk of teratogenic effects on the fetus. In fact, this further highlights the necessary use of animal models to study PE and potential therapeutic targets. A summary of preclinical and clinical trials that will be discussed in this section can be found in Table 6.

The NO-sGC-cGMP signaling pathway has garnered much interest in the treatment of PE. NO donors and precursors stimulate this pathway and are a well-established therapy for cardiovascular disease. For PE, NO donors/precursors have been successful in preclinical models (17, 237, 253) but yield mixed findings in clinical trials (128, 158, 202, 209, 244). These studies involve administration of L-arginine (an NO precursor) or a molecule that will release, or "donate," NO molecules. Preclinical studies in the RUPP (17), sFlt1-infusion (237), and L-NAME model (253), where NO synthesis is suppressed, found that MAP is reduced and angiogenic balance is improved in response to l-arginine. In some clinical studies, MAP and maternal vascular resistance are improved, but most show minimal improvement in parameters for infants (128, 202, 244). One explanation for these findings is that the high levels of ROS that are present in PE may result in oxidation of the exogenous NO to produce peroxynitrite and thus have minimal effect on the downstream vasoprotective pathways such as cGMP signaling.

More recent studies focused on blocking cGMP degradation as a mechanism to sustain NO-pathway activity. A number of preclinical studies showed profound improvements to MAP and other characteristics in the mother, including increased pup weight in response to Sildenafil administration (a phosphodiesterase type 5 inhibitor) (114, 118, 275, 335). It is important to acknowledge that in preclinical studies in animal models, increases in pup weight is a crude measure that indicates improved flow and implies better fetal outcomes, but this can only truly be determined through long-term studies in the offspring. In contrast to the findings of preclinical studies, recent clinical trials did not show any benefit, including prolonging gestation or improving IUGR. A 2017 randomized trial for Sildenafil was halted following mortality in 11 offspring due to pulmonary disease. It is important to note that these deaths were not directly attributed to Sildenafil (127, 303). A novel class of drug, sGC stimulators and activators, increases cGMP by promoting sGC activity. In addition to reducing bioavailable NO, ROS can oxidize sGC and inhibit its function, leading to further downregulation of this pathway. In the RUPP rat, sGC activators significantly reduce MAP and endothelial function by increasing cGMP production (36).

Another important avenue to attenuate the clinical manifestation of PE is to improve angiogenic imbalance. One possibility could be to administer PlGF, which has been

successful in preclinical models (206, 323). Another method could be to reduce circulating sFlt-1. Thadhani et al. showed that removal of sFlt-1 from serum using an apheresis device delayed delivery by an average of 8 days with a single treatment and a maximum of 21 days (range 11–21) with multiple treatments. This is compared to induction of delivery by 3 to 4 days in the control group. Interestingly, following each apheresis treatment, a reduction in sFlt-1 was associated with a transient decrease in blood pressure, which was followed by a gradual increase as circulating sFlt-1 levels rose again likely due to the ischemic placenta continuing to secrete this factor. Still, these findings represent a hopeful avenue for the treatment of PE (336).

Statins are a commonly prescribed therapy for lowering cholesterol in cardiovascular disease. In addition to this well-established effect, statins have also been shown to have anti-inflammatory properties and protect endothelial function (247). Numerous studies in rodent models of PE have demonstrated the potential beneficial effects of pravastatin therapy in PE. Garrett et al. (108) found that pravastatin improved placental flow and reduced placental insufficiency, resulting in decreased release of vasoactive factors, and in fact, protected both mother and offspring from long-term adverse cardiovascular outcomes. Another study in a mouse model of PE showed that pravastatin activates antiapoptotic pathways in the placenta (292). In RUPP rats treated with pravastatin, MAP and oxidative stress were reduced and angiogenic balance was improved (42). Interestingly, one study reported that statin treatment in another rat model of PE led to amelioration of cardiac fibrosis and capillary rarefaction and improved cardiac function 28 days after pregnancy. Animals in this study were treated during pregnancy (gestational day 15) and postpartum (28 days postpartum) (179). Currently, statins are not recommended during pregnancy; however, a pilot clinical study to test safety and pharmacokinetics did not report any adverse effects in the mother or offspring (69). This pilot study did not report any cholesterol-lowering effects in the fetus. A randomized trial of early-onset PE patients did not find any evidence that pravastatin reduced plasma sFlt-1 or length of gestation (8). As neither of these studies found any adverse effects attributed to pravastatin, this drug continues to be intensively researched.

Several studies have shown that some vitamins are deficient in PE women and have anti-inflammatory and antioxidant properties (33). The RUPP model has been used to examine vitamin D_2 and vitamin D_3 and demonstrated that both were successful in reducing blood pressure, Th-17 cells, ET-1, sFlt-1, and AT_1-AA; however, these vitamins did not have any effect to improve fetal or placental weight (74, 100, 341). In another model of PE that is induced by blocking NO production, vitamin D supplementation reduced TNF-α and sFlt-1 (315). Vitamin B_3 (nicotinamide) also has anti-inflammatory properties and significantly reduces MAP, oxidative stress, glomerular endotheliosis, and fetal growth restriction in numerous mouse models of PE (54, 105). Clinically, vitamin supplementation to treat PE has had mixed findings. There are studies suggesting that multimineral-vitamin D during pregnancy can reduce the risk of PE (32). In contrast, one meta-analysis of 30 clinical trials and 7,289 women reported that, while vitamin D supplementation above the current recommendations during pregnancy is safe and may reduce risk of gestational diabetes, overall, it has little to no effect on the risk of PE and IUGR (256).

In addition to the above therapies that have reached clinical trials, a number of interventions have been tested in preclinical models with promising results. ET_A antagonism has been tested in rat models of PE and is associated with decreases in MAP and improvement in the angiogenic balance (11, 182, 236). Progesterone is a hormone that typically increases over the course of normal pregnancy and is produced primarily by the placenta. In PE, levels of progesterone do not increase at the same rate, and in fact, its administration is used to prevent spontaneous preterm birth (223). In the RUPP model, progesterone treatment for only 24 h using 17-α-hydroxyprogesterone caproate improves hypertension and suppresses inflammation while improving uterine artery blood flow and litter size (20, 351). Another molecule that has been shown to be reduced in PE and has anti-inflammatory, antiapoptotic, and angiogenic properties is heme-oxygenase-1 (HO-1). RUPP rats treated with CoPP (a known HO-1 inducer) have attenuated hypertension and reduced endothelial dysfunction (112). Further studies in these animals suggested that HO-1 improves cytotrophoblast migration by increasing βENaC expression (362), and that CoPP has a direct effect in blocking TNF-α-induced ET-1 production from glomerular endothelial cells (35). HO-1 treatment also has similar effects in sFlt-1- and TNF-α-infusion models of PE (111, 115). During the development and pathogenesis of PE, both mother and baby are exposed to high levels of oxidative stress where the HO-1 pathway could also be protective. Hypoxia modifies phosphorylation of proteins that regulate survival and injury. Indeed, one study showed that HO-1 treatment following placental ischemia promotes prosurvival responses (110) through activation of ERK and the MAPK pathway. While these interventions have not yet reached clinical trials, the success of preclinical studies, such as those described above, remains invaluable in the search for an appropriate treatment for PE.

Conclusions

PE is a complex, multifaceted disease during pregnancy. It develops in two phases (1) impaired cytotrophoblast migration and uterine invasion causing deficient perfusion of the placenta and (2) the release of factors from the ischemic placenta into the maternal circulation, leading to endothelial and vasculature dysfunction and the maternal clinical syndrome (Figure 22). Throughout this article, we have discussed the many factors and pathways playing a critical role in the development of PE. Specifically, antiangiogenic factors and pro-inflammatory cytokines are at the center of PE pathogenesis in phase 2 by inducing endothelial dysfunction. Endothelial dysfunction is associated with reduced NO availability and upregulation of the endothelin system. The brain, kidneys, liver, and heart are particularly vulnerable to the circulating placental factors associated with PE. Moreover, some adverse effects during PE have been shown to persist postpartum. Thus, PE also poses significant risk for long-term diseases in both mother and her baby. Notably, women and infants born from PE pregnancies are at increased odds for cardiovascular, renal, cerebrovascular, and/or neurological diseases. It is thought that the adverse environment during preeclamptic pregnancies impacts these offspring well into adulthood (50+ years). These findings highlight the need for novel cures to treat the immediate and chronic effects of this maternal disorder. Currently, pharmacological treatment for PE is limited to managing symptoms through antihypertensives, betametasome, and magnesium sulfate. Preclinical studies in animal models have been instrumental not only in understanding the

pathophysiology of PE but also in the search for novel therapeutic options for the treatment of this disease. These studies have shown that blockade of excessive placental ischemic factors, such as the antiangiogenic factor, sFlt-1, can improve maternal outcomes. Attenuation of the endothelin system and stimulation of the NO-sGC-cGMP pathway are among other targets that could be important in the treatment of PE. In a clinical trial, clearance of the antiangiogenic factor, sFlt-1, increased length of gestation, substantiating additional larger trials. Basic science and clinical studies investigating the treatment of PE remain an active and promising area of research.

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Further Reading

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Didactic Synopsis

Major teaching points

- Incidence, diagnosis criteria, and risk factors for pre-eclampsia (PE)

  – Major contributor of maternal and fetal morbidity and mortality

  – New-onset hypertension with new onset of one or more other features

- Understand the pathophysiology of PE

  – Phase 1: Shallow and reduced cytotrophoblast invasion, resulting in impaired uterine spiral artery remodeling and placental ischemia

  – Phase 2: Clinical manifestations resulting from release of placental factors into the maternal circulation

- PE is associated with multiorgan dysfunction and injury

- Pathologies in offspring from preeclamptic pregnancies

  – Intrauterine growth restriction

  – Increased risk of cardiovascular, metabolic, and neurological diseases

- Risk of cardiovascular disease is significantly increased in women with a history of PE

- There is currently no definitive treatment to cure PE other than early delivery of baby and importantly, the placenta

- Animal models are instrumental in understanding mechanisms of pathophysiology and therapeutic options for PE
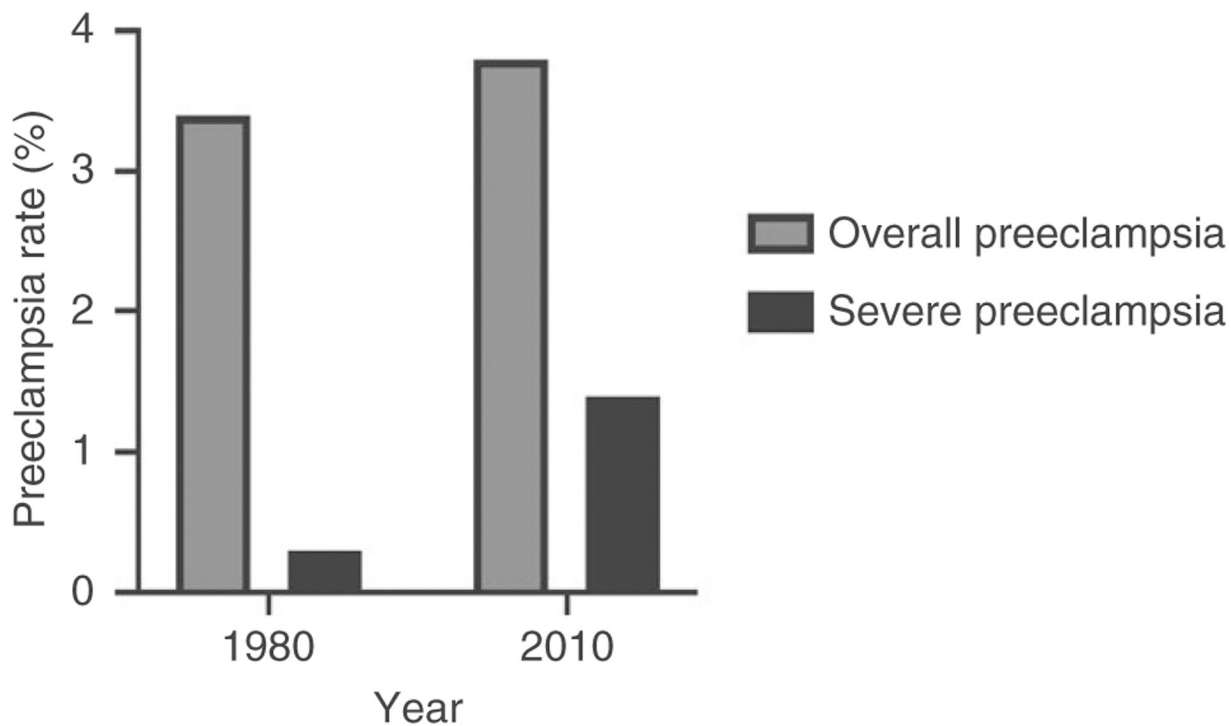
Figure 1. Rates of preeclampsia over the past decades.
This figure illustrates the rates of preeclampsia (PE) in 1980 and 2010. These rates may be influenced by the change in definition of PE over time but are also certainly affected by the global increase in risk factors for this disease, including obesity and preexisting cardiovascular disease. Notably, rates of severe PE have significantly increased since 1980. Adapted from Ananth CV, et al., 2013 (22).
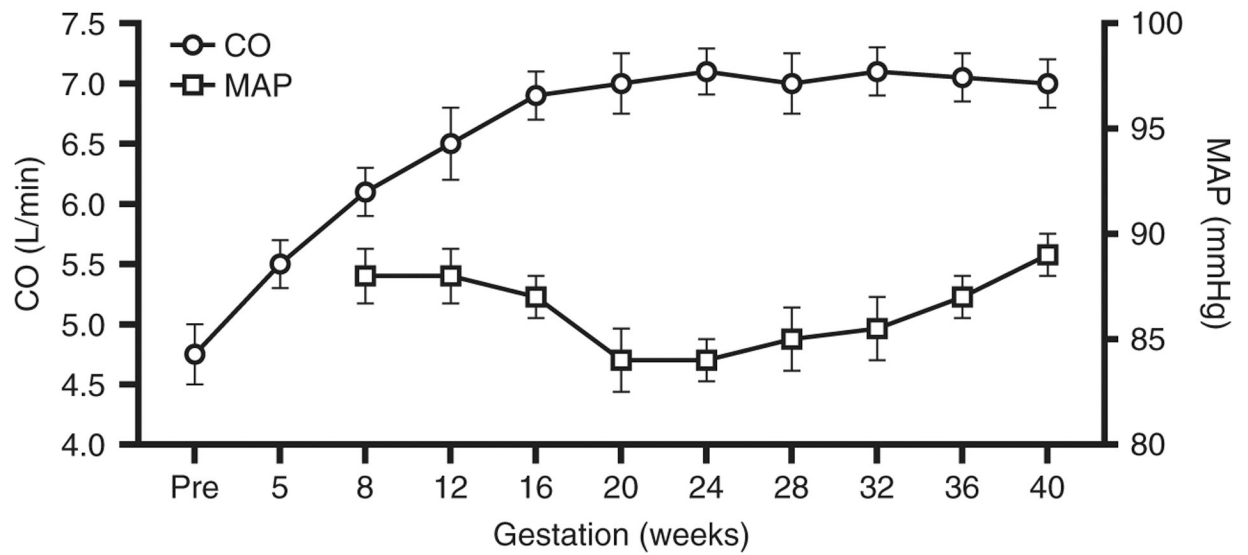
Figure 2. Hemodynamic changes during normal pregnancy.
This figure illustrates the gradual increase of cardiac output (CO; circles) and a gradual decrease in mean arterial pressure (MAP; squares) over the first and second trimesters of normal pregnancy. Data are presented as mean ± SEM. Adapted from Moutquin JM, et al., 1985 (233).
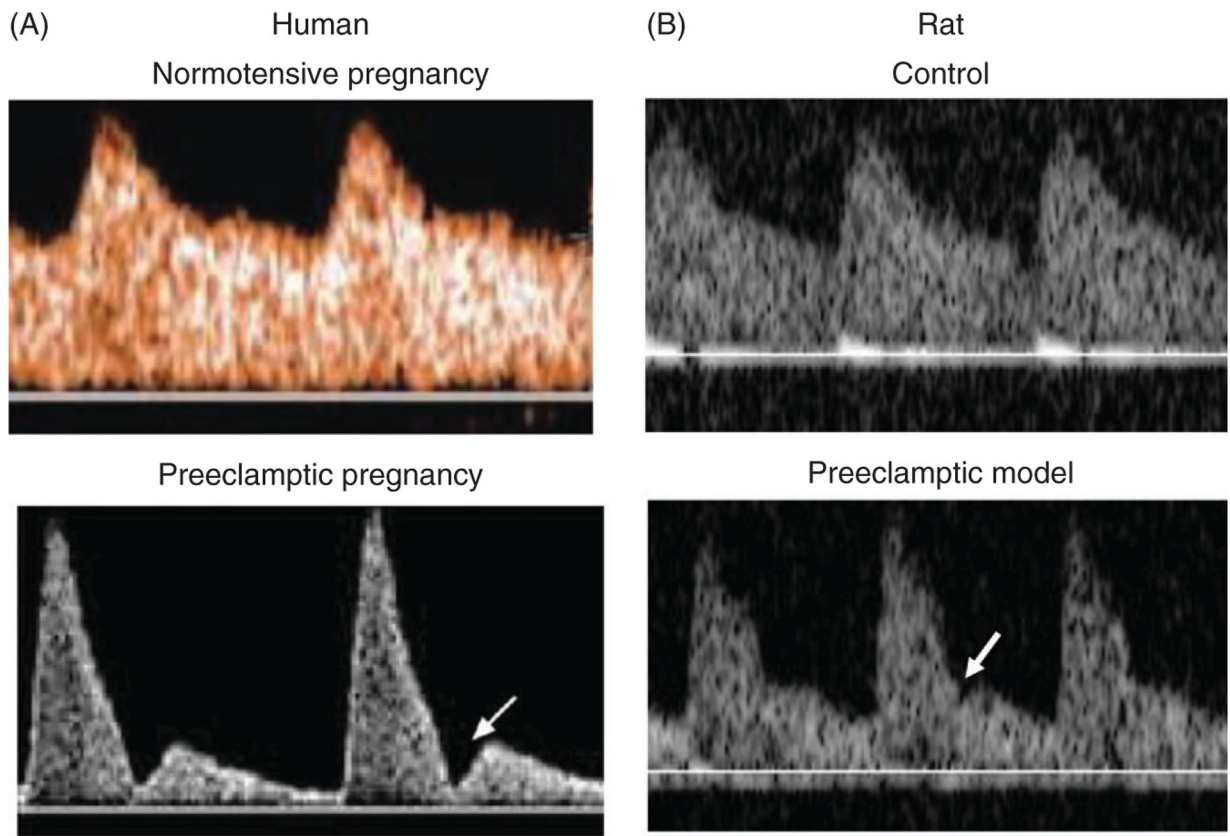
Figure 3. Uterine artery resistance in humans and an animal model of superimposed preeclampsia.

This figure illustrates the difference between Doppler waveforms (velocity) during normal pregnancy and preeclampsia (PE) in (A) humans and (B) rats. In normal pregnancy, resistance in uterine arteries is low as evidenced by high peak during systole followed by a fall during diastole. In contrast, Doppler waveforms from PE pregnancies have a peak during systole followed by a sharp fall during diastole. The arrows in the figure indicate the characteristic notch found in PE and the rat model of superimposed PE (Dahl S Rat). Adapted from McLeod L, 2008 (219) and Gillis EE, et al., 2015 (119).
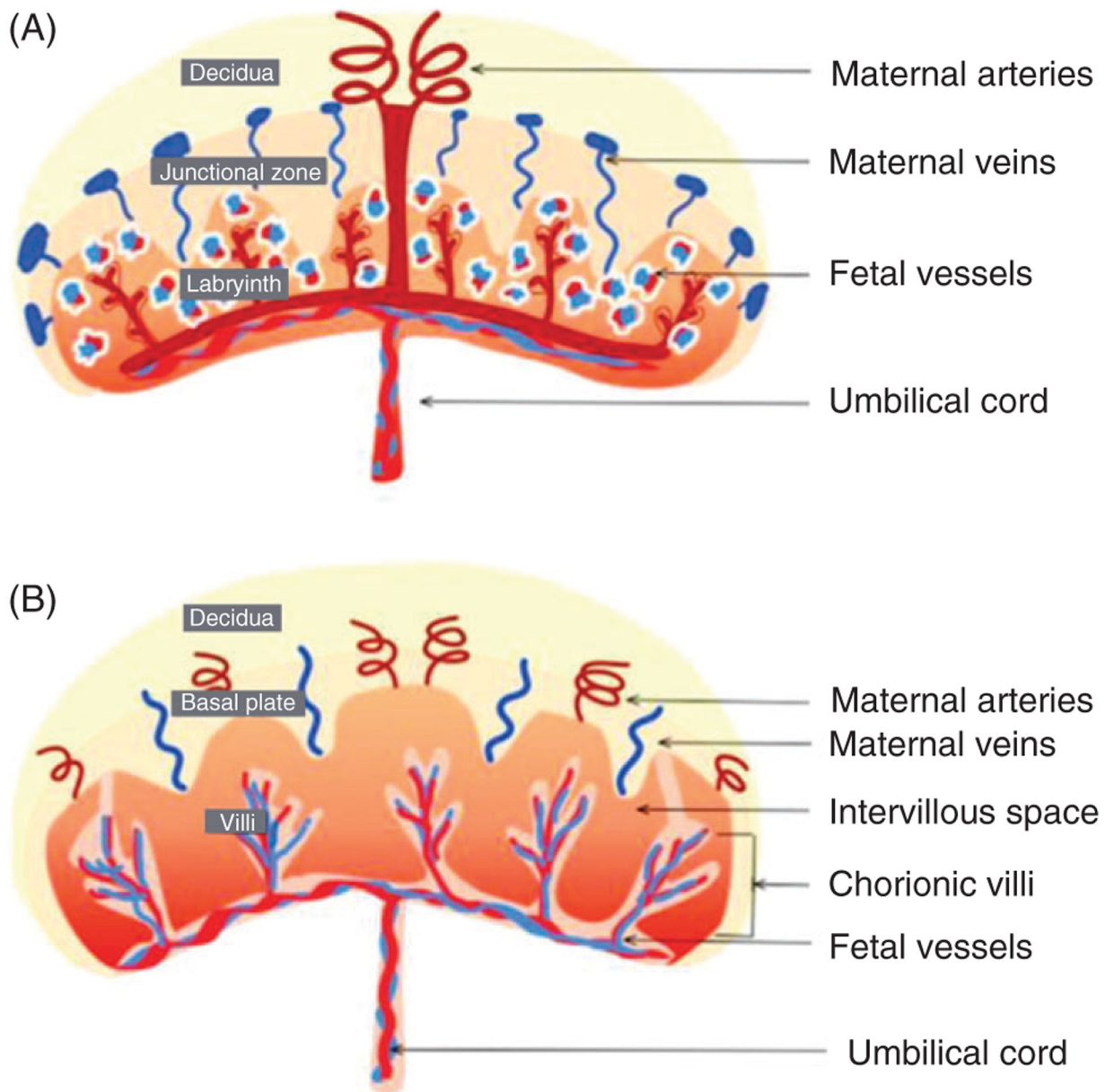
Figure 4. Illustrations of mature placenta in rodents and humans.
This figure illustrates the differences between the (A) rodent and (B) human placenta.
Rodent models of preeclampsia are valuable tools in understanding the pathogenesis of this
maternal disorder. The decidua on the "maternal side" can be seen housing the spiral arteries
in both placentas. The "fetal side," closest to the umbilical cord, in the rodent is termed the
labyrinth, and the villous layer in the humans. Villi form large surface areas where
nutrient/gas exchange can occur between mother and baby. In terms of vascular anatomy,
human spiral arteries drain directly into the intervillous space to surround the villi and allow
for this nutrient/waste exchange to occur. In rodents, spiral arteries converge into one or
more canals that pass through the junctional zone to the base of the villous layer and then
branch out to feed the sinusoid/intervillous spaces. Adapted from Rai and Cross, 2014 (273).
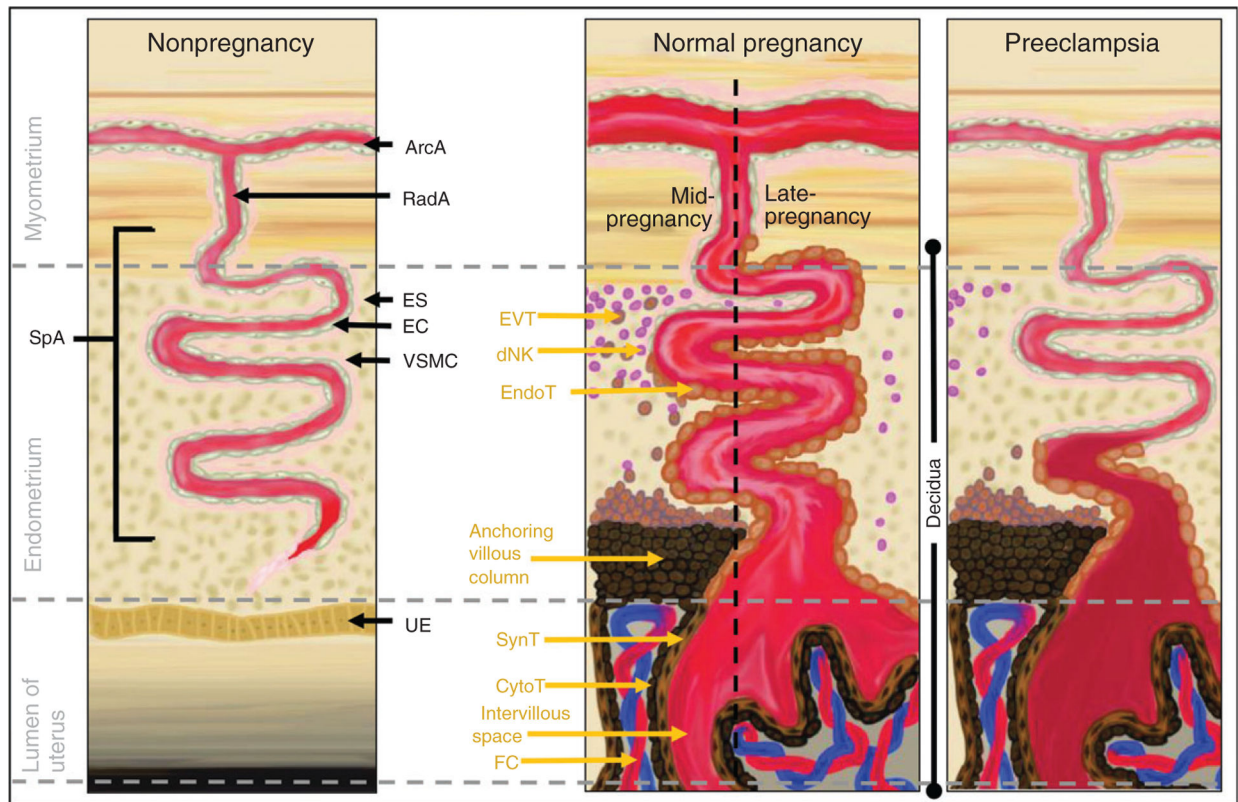
Figure 5. Illustrations of spiral artery remodeling during normal pregnancy and attenuation of this process in preeclampsia.

Spiral arteries are depicted during nonpregnancy (left panel), mid-to-late gestation during normal pregnancy (middle panel), and preeclampsia (PE) (right panel). Spiral arteries originate in the myometrium and proceed through the endometrium. Placentation during normal pregnancy is noted by decidualization and significant changes to stromal cells of the uterus, and spiral artery remodeling, which involves invasion of fetal-derived cytotrophoblast cells. Early trophoblast lineages fuse to form the overlying and multinucleated syncytiotrophoblast layer that progressively invades the uterus and forms the barrier between maternal blood and the fetal capillaries. These capillaries are developed via vasculogenesis and are housed within the placental villi. Villi are floating or anchored to the uterine wall. The cytotrophoblasts within the anchoring villous column break through the syncytium and eventually depolarize into extravillous (interstitial) trophoblast cells. The latter cells invade and replace the vascular smooth muscle and endothelium of the spiral arteries of the endometrium and the first third of the myometrium while becoming endovascular trophoblast cells. The spiral arteries are remodeled to form conduits promoting blood flow toward the intervillous space to surround and deliver oxygen and nutrients to the placental villi. Attenuations in this process promote placental ischemia and PE. Recent research indicates that resident decidual natural killer cells secrete factors that promote trophoblast function and remodel the spiral arteries, which is reduced in PE. SpA, spiral artery; ArcA, arcuate artery; RadA, radial artery; ES, endometrial stroma; EC, endothelial cells; VSMC, vascular smooth muscle cell; UE, uterine epithelium; EVT, extravillous trophoblast; dNK,

decidual natural killer cell; EndoT, endovascular trophoblast; SynT, syncytial trophoblast; FC, fetal capillary.
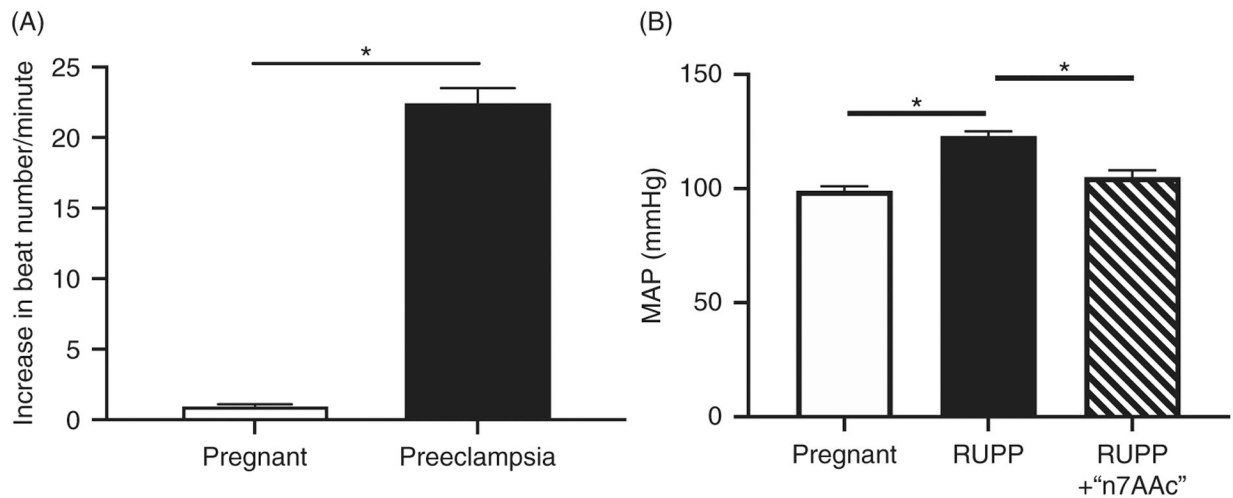
Figure 6. Angiotensin II Type 1 receptor autoantibodies are increased in preeclampsia.
Panel (A) illustrates that levels of the agonistic angiotensin II type 1 receptor autoantibody
(AT1-AA) are significantly increased in serum from preeclamptic women. For these data,
spontaneous beating of neonatal rat cardiomyocytes in response to serum exposure was
used. Panel (B) shows that when the AT1-AA, which is elevated in the reduced uterine
perfusion pressure (RUPP) rat model of preeclampsia (PE), is inhibited (with "n7AAc"),
mean arterial pressure (MAP) is reduced, suggesting that AT1-AA has a role in increasing
blood pressure in PE. Data are mean + SEM. $*P < 0.05$. Adapted from Wallukat G, et al.,
2008 (359) and Cunningham MW, et al., 2018 (71).
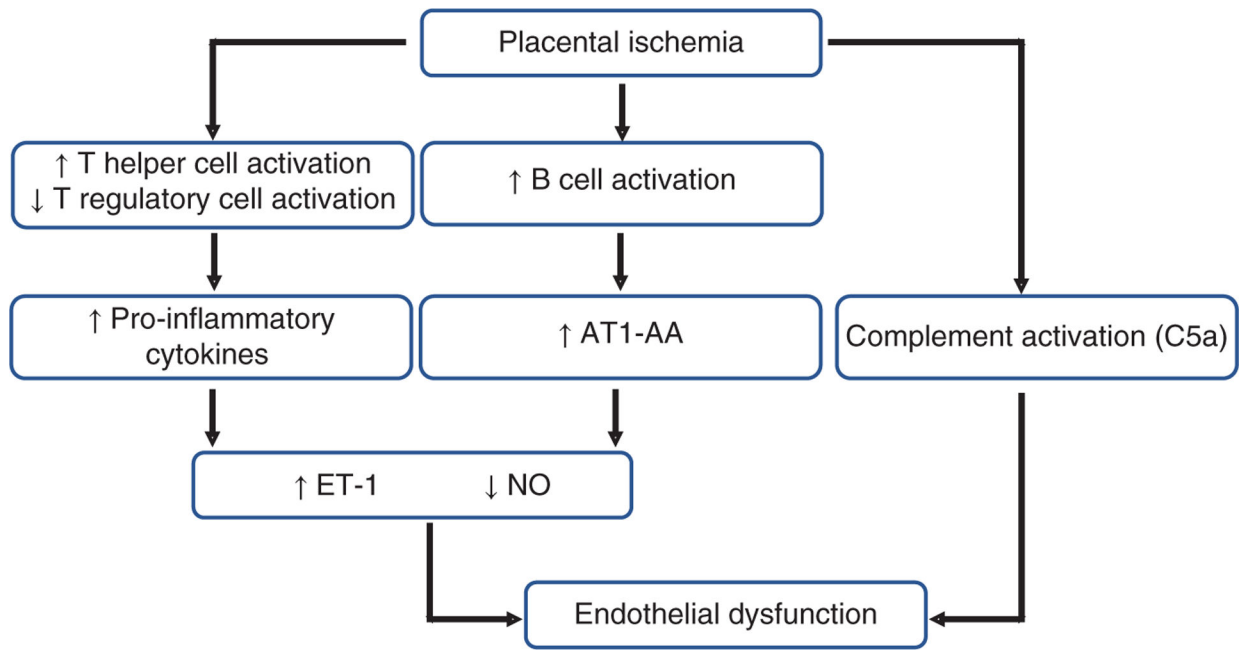
Figure 7. Role of immune factors in the development of endothelial dysfunction in preeclampsia.
This figure illustrates that pro-inflammatory T- and B-cell activation results in elevated prohypertensive cytokines and the angiotensin II type 1 receptor autoantibody (AT1-AA). These factors cause endothelial dysfunction by increasing endothelin-1 (ET-1) production and reducing nitric oxide (NO) bioavailability.
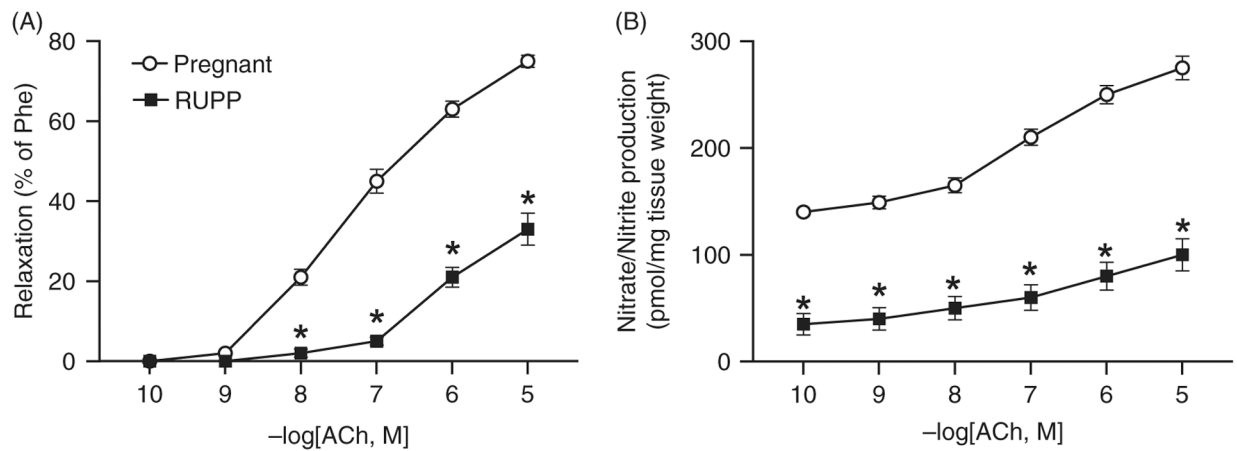
Figure 8. Endothelial dysfunction in placental ischemic rats.
(A) This figure illustrates blunted endothelial-dependent vasorelaxation in response to increasing concentrations of acetylcholine (Ach) in phenylephrine (Phe)-constricted aortic tissue isolated from rats with reduced uterine perfusion pressure (RUPP). (B) ACh at these concentrations induces NO production in normal pregnancy, and this effect is attenuated in aortic strips from placental ischemic rats. Data are mean ± SEM. *$P < 0.05$ versus pregnant. Adapted from Barron LA, et al., 2001 (39).
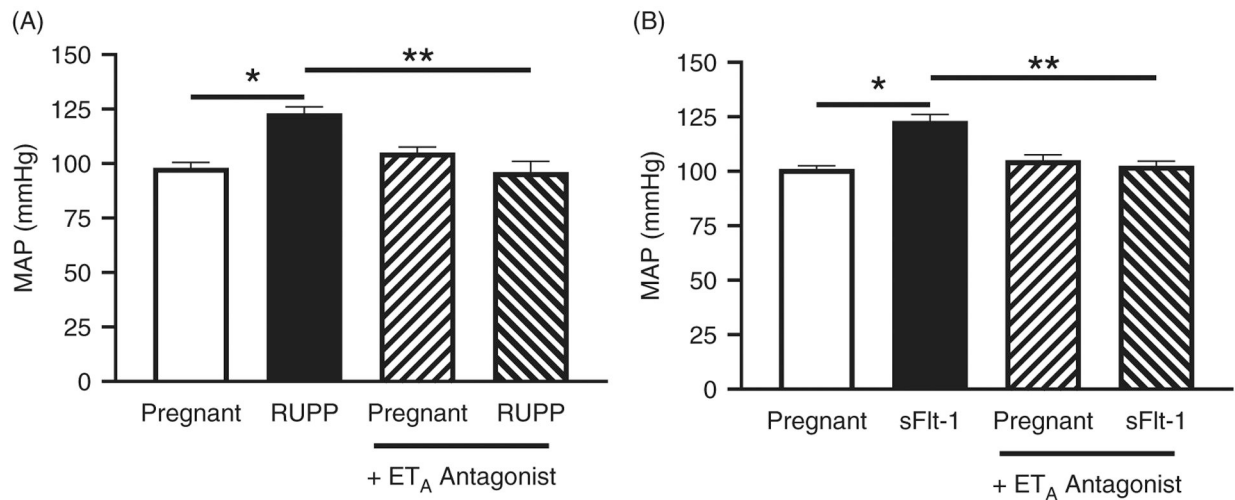
Figure 9. Endothelin type A receptor blockade reduces blood pressure in animal models of preeclampsia.

This figure illustrates that endothelin type A (ET_A) antagonism reduces mean arterial pressure (MAP) in (A) the reduced uterine perfusion pressure (RUPP) model and (B) the sFlt-1 infusion (sFlt-1) model of preeclampsia. Data are mean + SEM. *$P < 0.05$ versus pregnant. **$P < 0.05$ versus sFlt-1/RUPP. Adapted from Murphy S, et al., 2010 (236) and Alexander B, et al., 2001 (11).
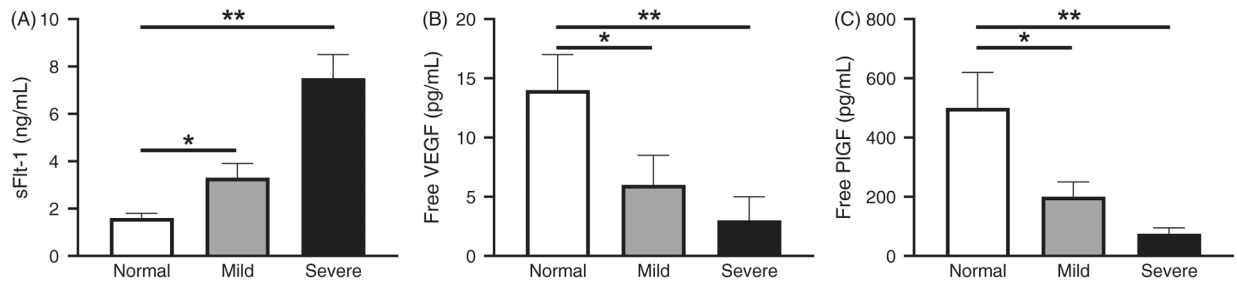
Figure 10. Circulating levels of angiogenic factors in preeclampsia.
These data depict the antiangiogenic environment that exists in preeclampsia (PE), whereby (A) sFlt-1 is increased and (B) free vascular endothelial growth factor (VEGF) and (C) placental growth factor (PlGF) are decreased. Importantly, these changes are exaggerated as the severity of PE increases. Data are mean ± SEM. *$P < 0.05$ versus Mild. **$P < 0.05$ versus Severe. Adapted from Maynard SE, et al., 2003 (215).
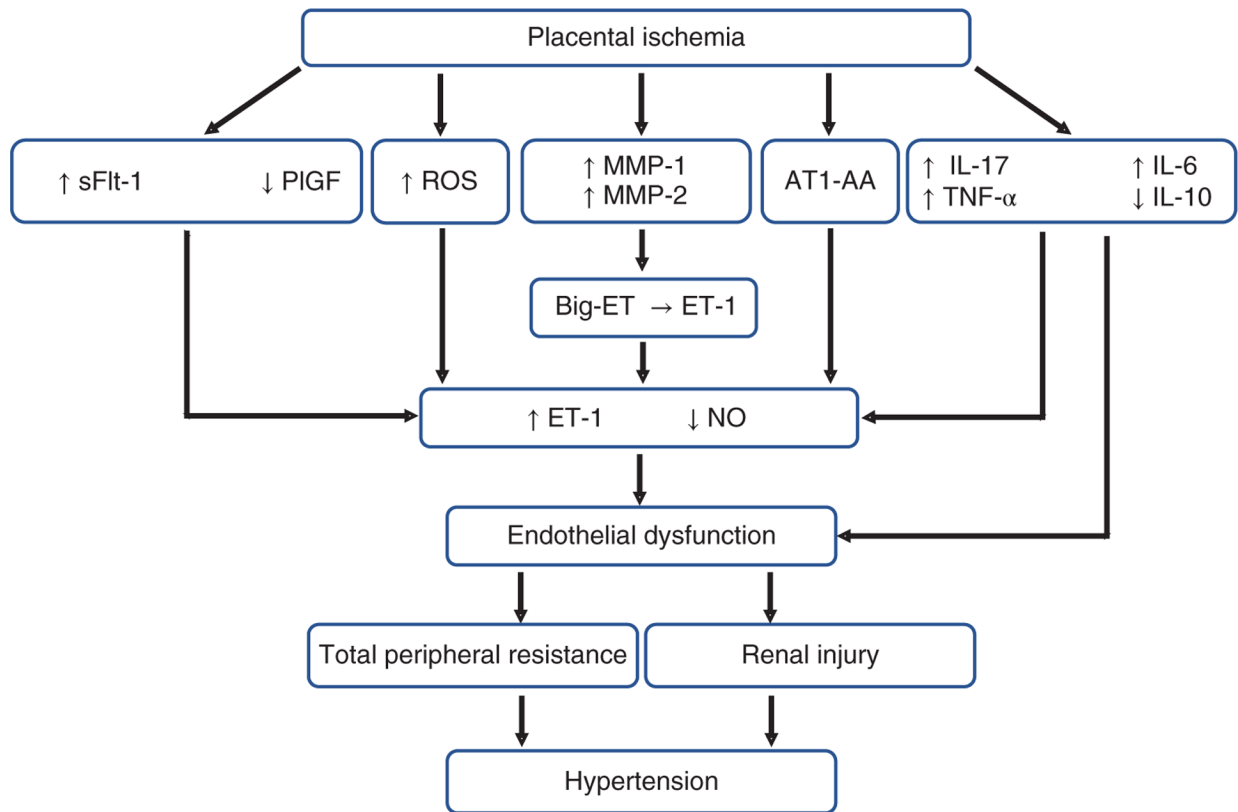
Figure 11. Factors that impact endothelial dysfunction in preeclampsia.
This figure illustrates the development of endothelial dysfunction and hypertension in preeclampsia. The release of factors from the ischemic placenta, such as antiangiogenic factors, reactive oxygen species (ROS), matrix metalloproteinases (MMPs), angiotensin II type 1 receptor autoantibody (AT1-AA), and pro-inflammatory cytokines, play a central role in depleting nitric oxide (NO) bioavailability and increasing endothelin-1 (ET-1) production, which drives this prohypertensive pathway.
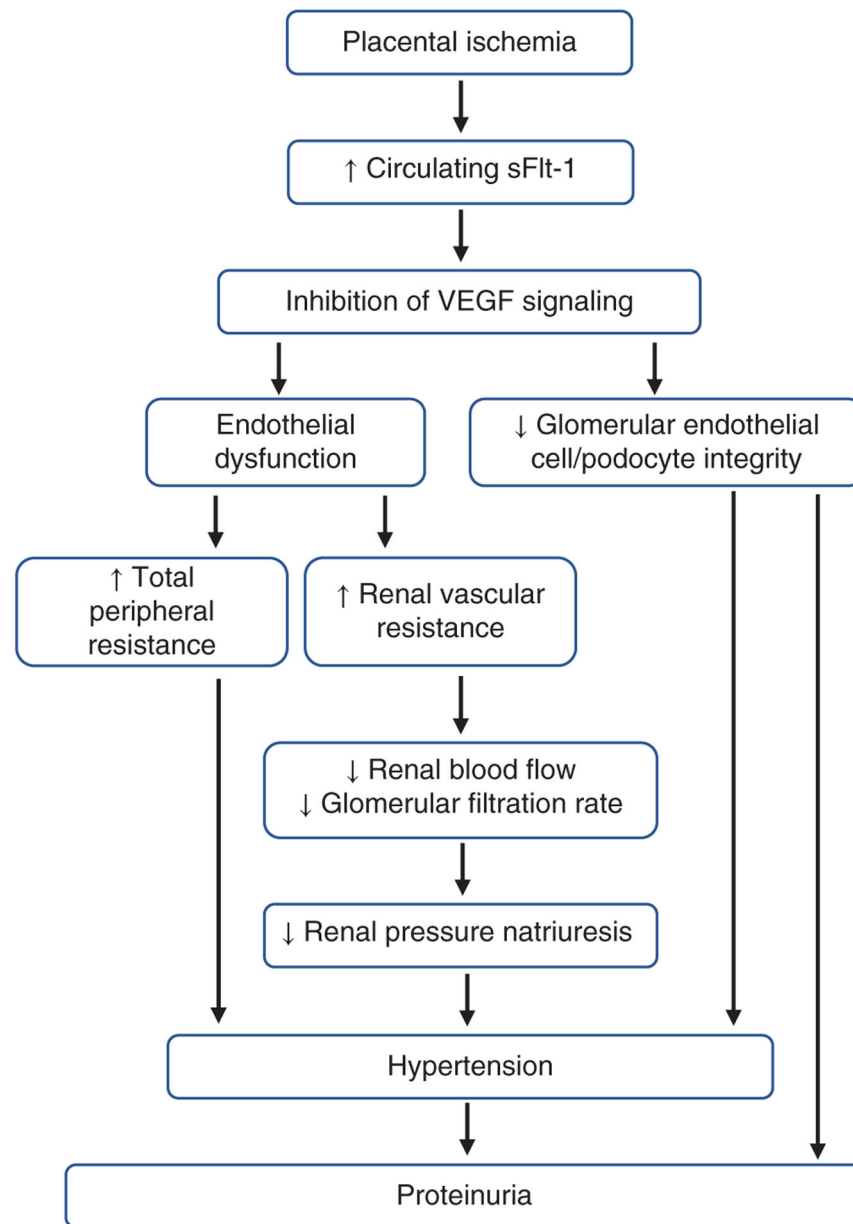
Figure 12. The development of renal dysfunction in preeclampsia.
This figure illustrates the development of renal injury and dysfunction in preeclampsia, resulting in hypertension and proteinuria. Endothelial cell dysfunction and damage in the kidney leads to increased renal vascular resistance, impaired pressure natriuresis, hypertension, and proteinuria.
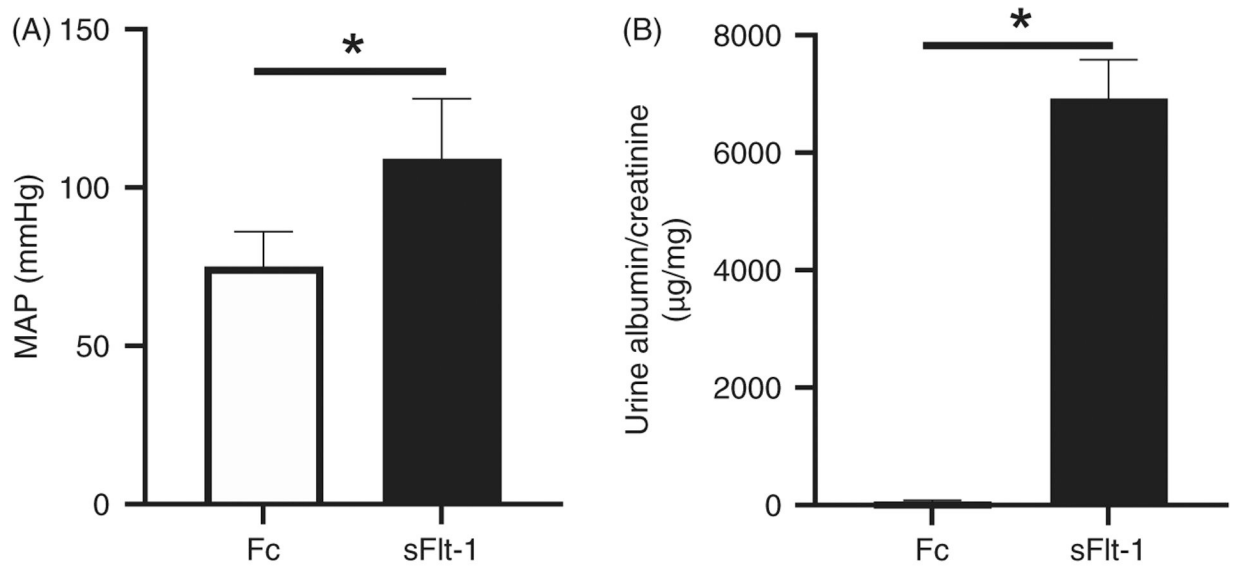
Figure 13. Elevated sFlt-1 induces a preeclampsia-like phenotype in rats.
This figure illustrates that rats injected with sFlt-1 (via sFlt-1-adenovirus construct) develop (A) elevated mean arterial pressure (MAP) and (B) proteinuria, as measured by urine albumin/creatinine, compared to controls (Fc). Data are presented as mean + SEM. *$P <$ 0.05. Adapted from Maynard SE, et al., 2003 (215).

EM   IF (fibrin)

Fc
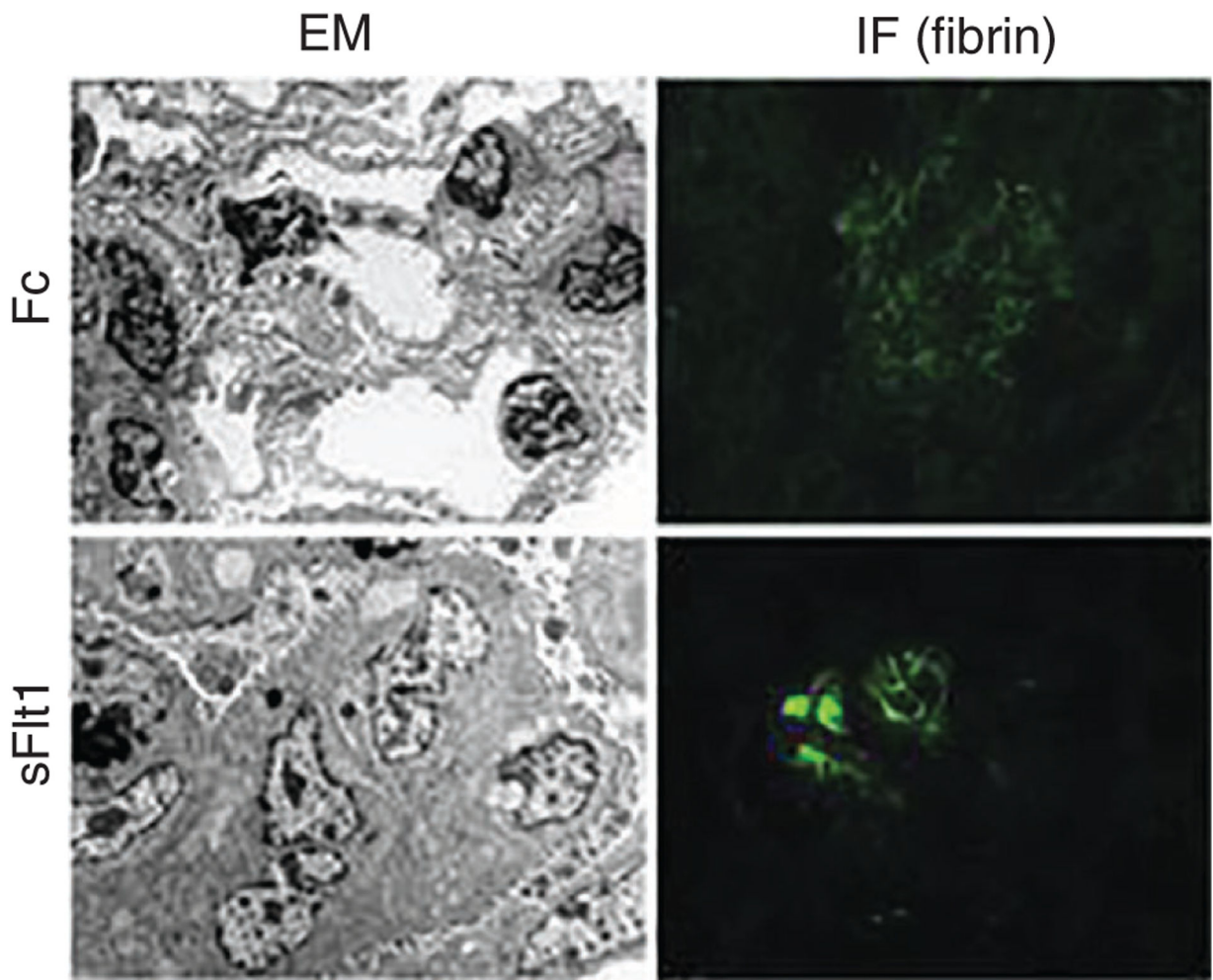
sFlt1

Figure 14. Elevated sFlt-1 causes fibrin deposition in the glomeruli of rats.
This figure illustrates fibrin deposition within the glomeruli of rats treated with sFlt-1 (sFlt-1) compared to control rats (Fc). Electron microscopy (EM) from an sFlt1-treated rat confirms glomerular injury. Immunofluorescence (IF) for fibrin shows foci of fibrin deposition in glomeruli of sFlt1 rats. The IF images were collected at 40×, and the EM images were collected at 2400× magnification. Adapted from Maynard SE, et al., 2003 (215).
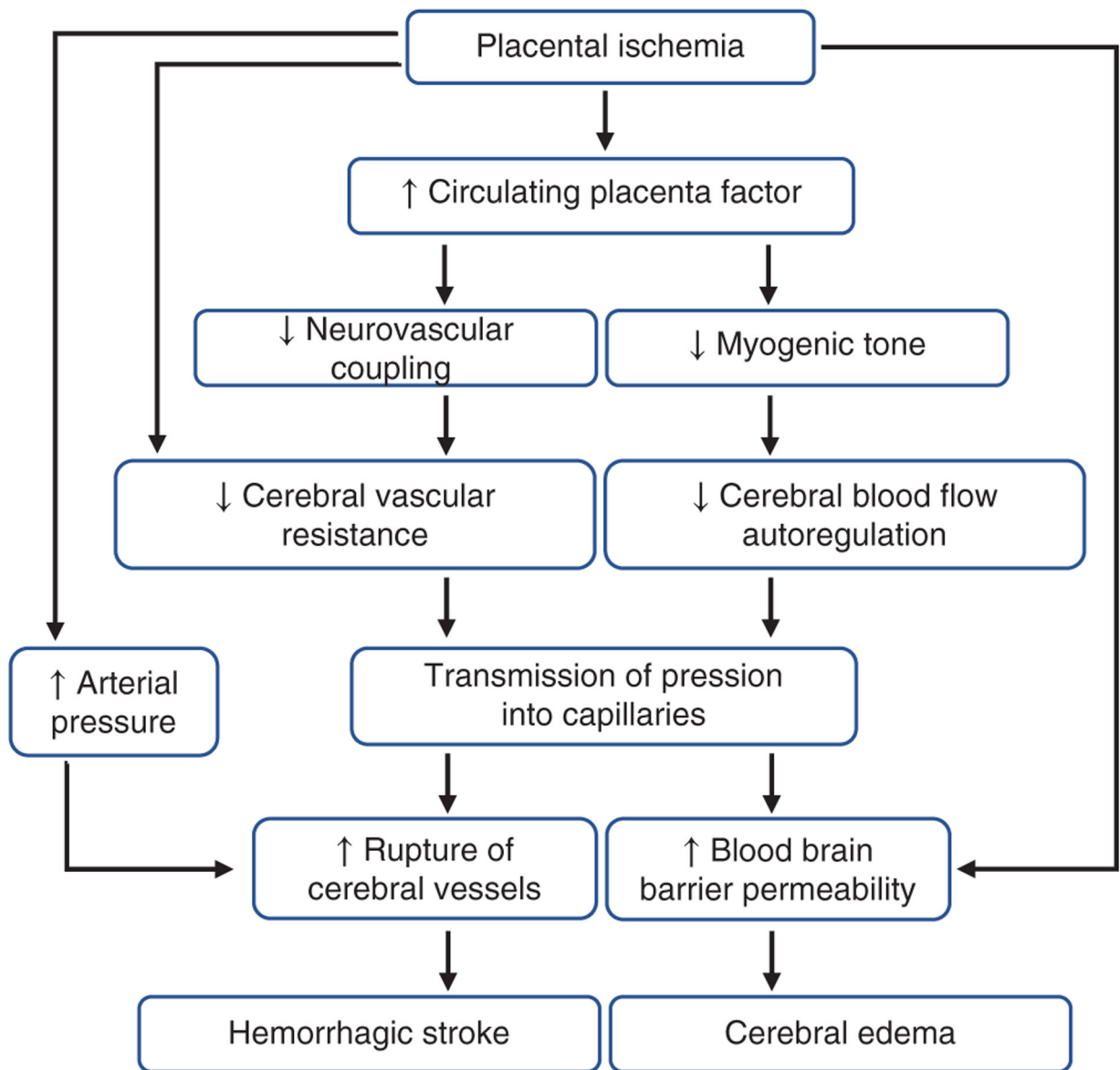
Figure 15. The development of cerebral dysfunction in preeclampsia.
Hypertension and placental factors in preeclampsia cause cerebrovascular dysfunction, resulting in impaired cerebral blood flow autoregulation, vessel rupture, and blood brain barrier permeability, leading to hemorrhagic shock and cerebral edema.
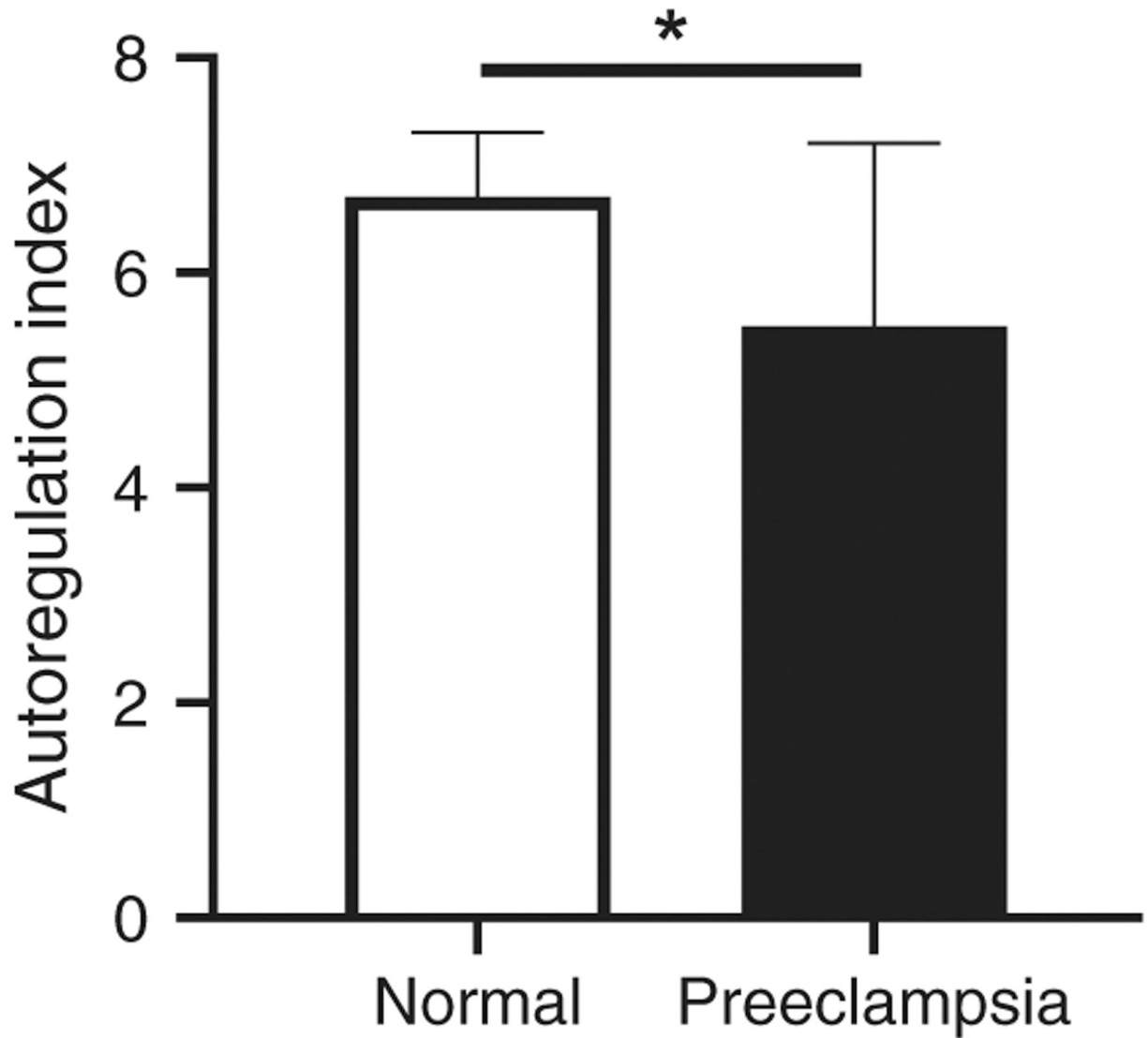
Figure 16. Autoregulation in human preeclampsia.
This figure illustrates middle cerebral artery blood flow autoregulation in normal and preeclamptic pregnancy at 35 to 37 weeks of gestation and shows that the autoregulatory index is impaired in preeclampsia. Data are mean + SD. *$P < 0.05$. Adapted from Van Veen TR, et al., 2013 (349).
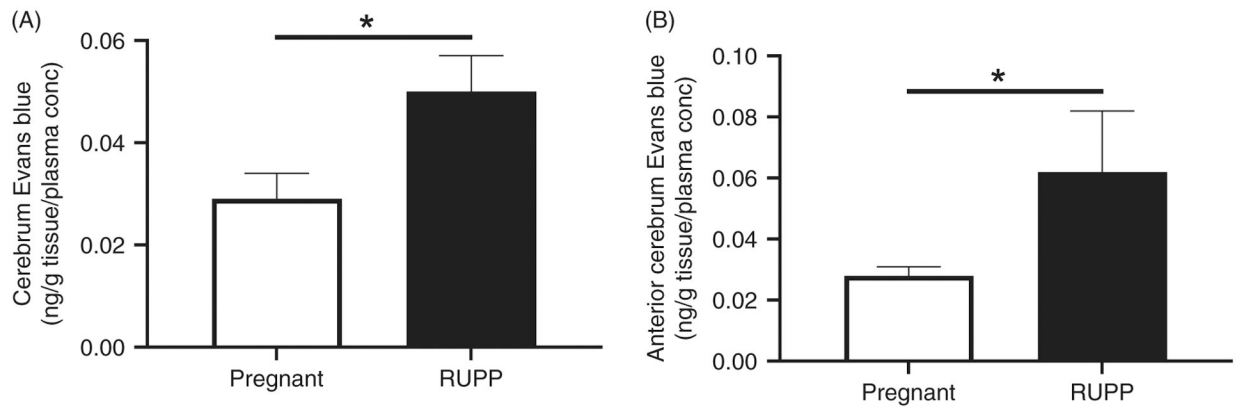
Figure 17. Blood-brain permeability in placental ischemic rats.
This figure illustrates increased blood-brain permeability in (A) cerebrum and (B) anterior cerebrum of reduced uterine perfusion pressure (RUPP)-operated rats, as measured by extravasation of Evans blue dye. Data are presented as mean + SEM. *$P < 0.05$. Adapted from Warrington JP, et al., 2015 (363).
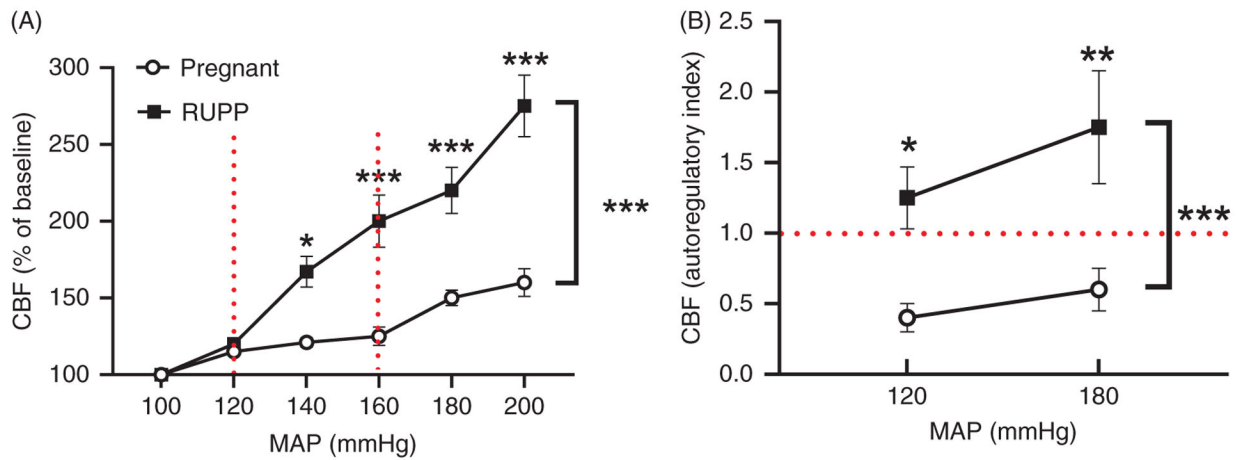
Figure 18. Cerebral blood flow and autoregulation index in placental ischemic rats.
This figure illustrates that (A) cerebral blood flow (CBF), as measured by laser Doppler flowmetry, and (B) autoregulation are significantly impaired in placental ischemic rats (reduced uterine perfusion pressure; RUPP), as evidenced by increases in blood flow at elevated mean arterial pressures (MAP). Data are mean ± SEM. *$P < 0.05$ versus pregnant, **$P < 0.01$ versus pregnant. Adapted from Warrington JP, et al., 2014 (365).
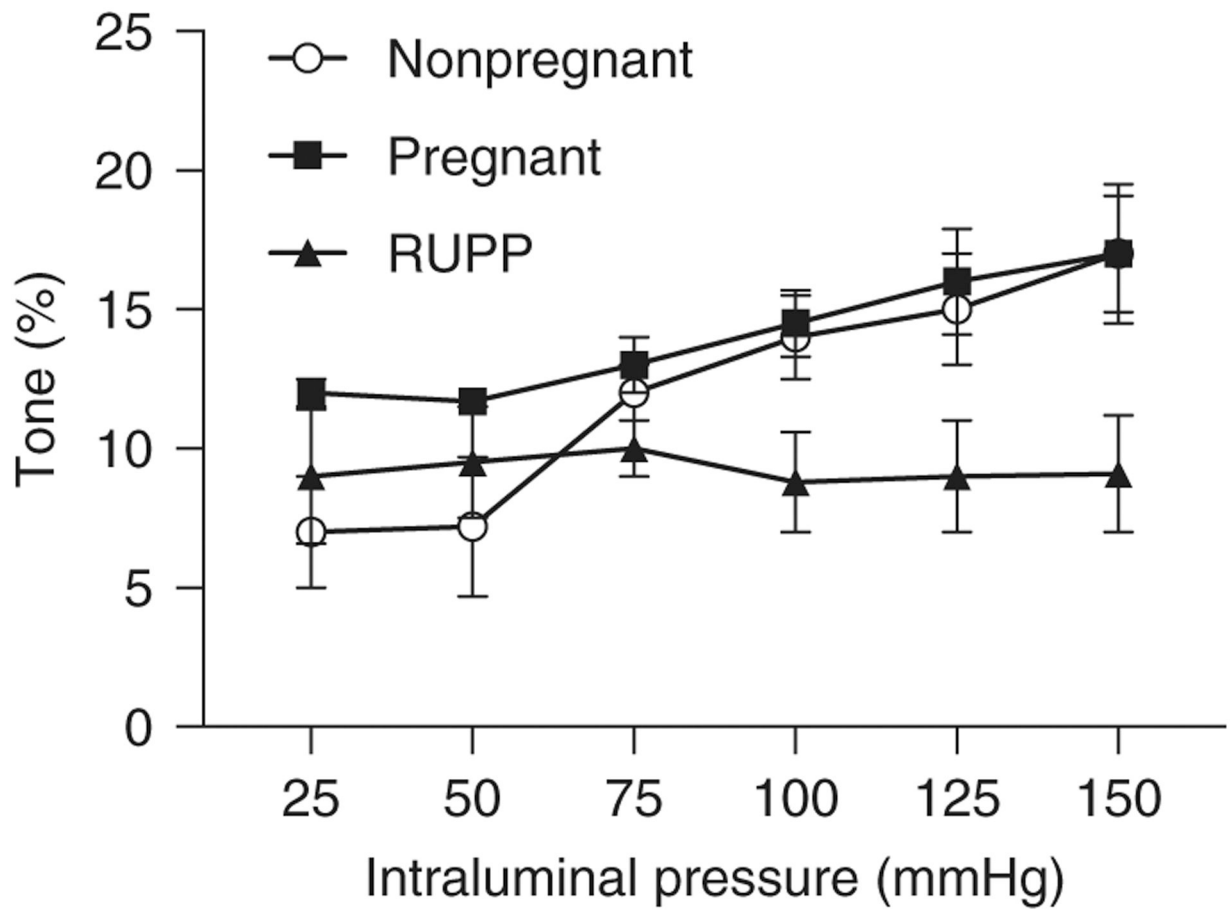
Figure 19. Vascular myogenic tone in placental ischemic rats.
This figure illustrates that the relationship between middle cerebral artery tone and pressure is blunted in reduced uterine perfusion pressure (RUPP) rats compared to nonpregnant and normal pregnant rats. Data are presented as mean ± SEM. Adapted from Ryan MJ, et al., 2011 (291).
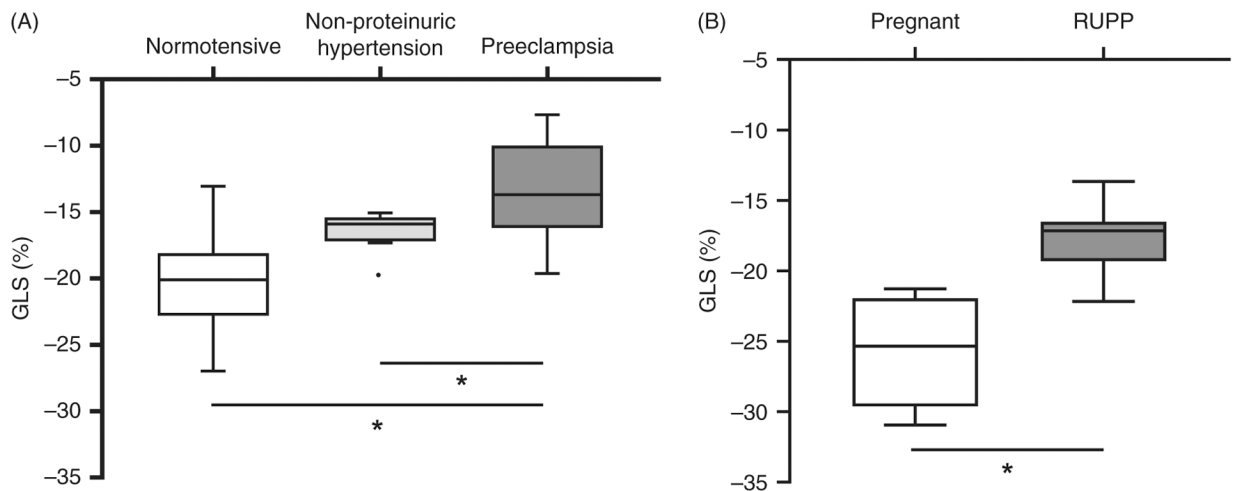
Figure 20. Global longitudinal strain in humans and placental ischemic rats.
This figure illustrates the development of cardiac global longitudinal strain (GLS) in humans and in the reduced uterine perfusion pressure (RUPP) rat model of preeclampsia (PE). Importantly, Panel (A) also shows significantly reduced GLS in PE compared to nonproteinuric hypertension (gestational hypertension), suggesting more than hypertension (potentially placental factors) plays a role. In animal models, cardiac dysfunction typically only emerges after 2 weeks in hypertensive models; therefore, data in the RUPP rat in Panel (B) also suggests that placental factors could play a role in the development of cardiac dysfunction in PE. The lower (25th percentile) and upper (75th percentile) limits of each box represent the interquartile range; the line across the box indicates the median. The lowest and highest values within 1.5 interquartile ranges below and above the interquartile range are indicated by the whiskers. Dots represent values that lie outside this range. $*P < 0.05$. Adapted from Shahul S, et al., 2012 (302) and Bakrania BA, et al., 2019 (34).
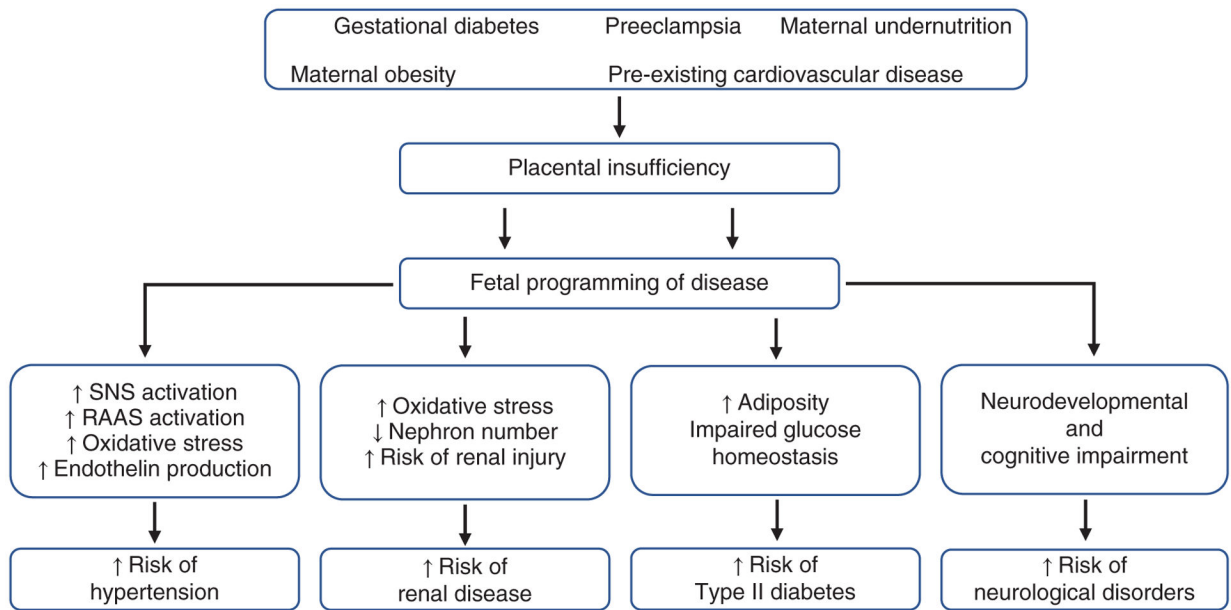
Figure 21. Factors involved in long-term cardiovascular risk in offspring from preeclamptic pregnancies.

This figure illustrates how fetal programming leads to increased risk of cardiovascular, metabolic, and neurological disease in infants and adults born from preeclamptic pregnancies. SNS, sympathetic nervous system; RAAS, renin angiotensin aldosterone system. Adapted from Alexander BT, et al., 2015 (15).
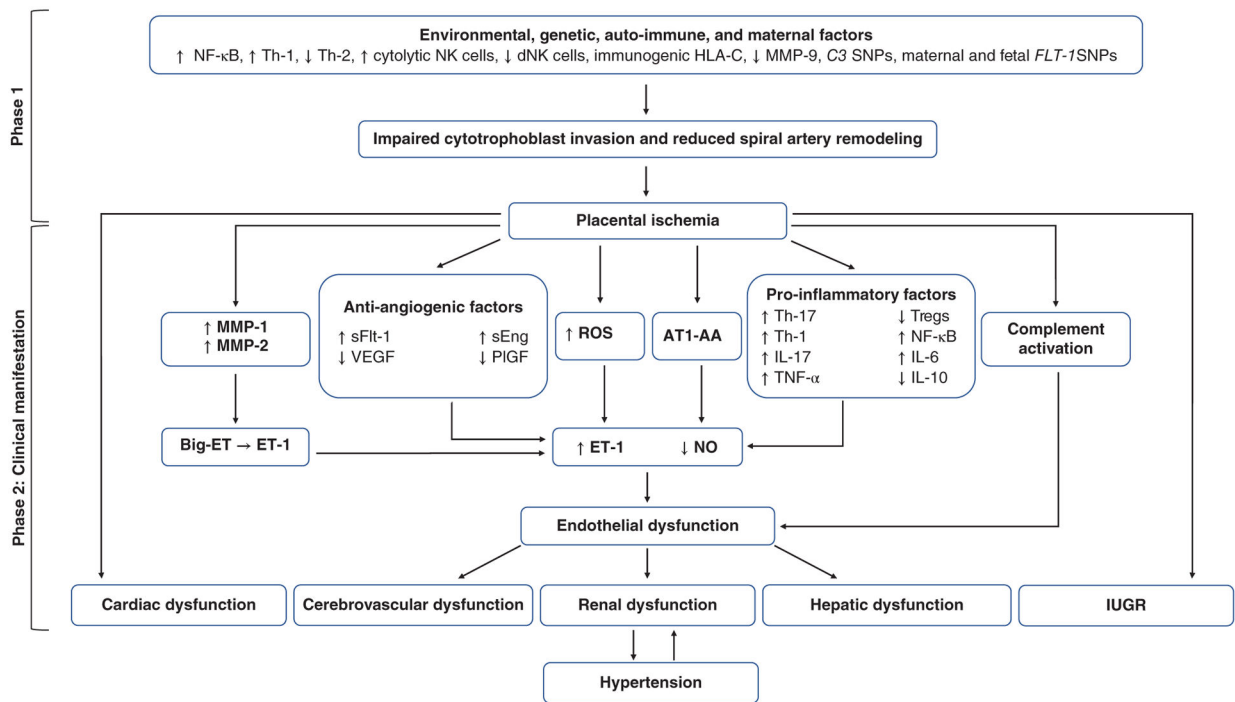
Figure 22. Schematic of the pathogenesis of preeclampsia.
This figure illustrates the pathways involved in the pathophysiology of preeclampsia (PE), from abnormal placentation to the development of hypertension and end-organ dysfunction and injury. Phase 1 of the pathogenesis of PE involves impaired and shallow cytotrophoblast invasion, resulting in impaired spiral artery remodeling, poor placental perfusion, and placental ischemia. Phase 2 is clinical manifestation, which presents >20 weeks of gestation. As a result of placental ischemia, several factors are released into the maternal circulation causing widespread endothelial dysfunction, hypertension, and multiorgan dysfunction. It is important to note that hypertension is the only symptom that occurs in *every* incidence of PE and is typically coupled with other disturbances/organ dysfunction. NF-κB, nuclear factor-kappa B; Th, T helper cell; NK, natural killer cell; dNK, decidual natural killer cell; HLA-C, human leukocyte antigen-C; MMP, matrix metalloproteinases; *C3*, complement 3; SNPs, single nucleotide polymorphisms; *FLT-1*, fms-like tyrosine kinase-1; sFlt-1, soluble Flt-1; sEng, soluble endoglin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; ROS, reactive oxygen species; AT1-AA, angiotensin II Type 1 receptor autoantibody; Tregs, T regulatory cells; IL, interleukin; TNF-α, tumor necrosis factor-α; ET, endothelin; NO, nitric oxide; IUGR, intrauterine growth restriction.

Table 1

Diagnostic Criteria for Preeclampsia Based on American College of Obstetrics and Gynecology Guidelines

Hypertension	140/90 mmHg on two occasions at least 4 h apart
	or
	160/110 mmHg on two occasions within minutes
The new onset of hypertension and one of the following can be used for diagnosis:	
Proteinuria	300 mg/24 h (or this amount extrapolated from a timed collection)
	or
	Protein/creatine (each mL/dL) ratio 0.3
	Dipstick reading of 1 + (used only if other measures are unavailable)
Thrombocytopenia	Platelet count < 100,000/μL
Renal insufficiency	Serum creatine 1.1 mg/dL
	or
	Doubling of serum creatine in the absence of other renal disease
Impaired liver function	Twice the normal blood concentration of liver transaminases
Pulmonary edema	–
Cerebral or visual symptoms	–

Table 2

Severe Features of Preeclampsia Based on American College of Obstetrics and Gynecology Guidelines (282)

Any of the following findings are considered severe features of PE

- Blood pressure   160/110 on two occasions at least 4 h apart while patient is on bed rest (unless antihypertensive therapy is administered)

- Thrombocytopenia (platelet count <100,000/μL)

- Impaired liver function (twice normal blood concentration of liver transaminases), severe persistent right upper quadrant pain or epigastric pain, unaccounted for alternative diagnosis and/or unresponsive to medication

- Progressive renal insufficiency (serum creatine   1.1 mg/dL or doubling of serum creatine in the absence of other renal disease)

- Pulmonary edema

- New-onset cerebral or visual disturbances

Table 3

Risk Factors for the Development of Preeclampsia Based on the American College of Obstetrics and Gynecology Guidelines (282)

Risk factor	Additional references
Primiparity	(86, 266)
Previous preeclamptic pregnancy	(266)
Chronic hypertension, renal disease or both	(266)
History of thrombophilia	(41, 97)
Multifetal pregnancy	(86)
In vitro fertilization	(64, 210, 353)
Family history of preeclampsia	(94, 266)
Type I or Type II diabetes mellitus	(86)
Obesity	(216, 318, 376)
System lupus erythematosus	(54, 62)
Advanced maternal age (>40 years)	(22, 86)

Table 4

Summary of Studies that Inhibit Key Pathways and Placental Factors in Animal Models of Preeclampsia

Intervention	Model/Animal	MAP	References
sFlt-1 inhibition			
PlGF supplementation	RUPP—rat	↓	(323)
	UPI—nonhuman primate	↓	(206)
VEGF supplementation	RUPP—rat	↓	(198)
ROS inhibition	RUPP—rat	↓	(299)
AT1-AA inhibition	RUPP—rat	↓	(71)
TNF-α inhibition	RUPP—rat	↓	(183)
ET$_A$ antagonism	RUPP—rat	↓	(11)
	sFlt-1 infusion—rat	↓	(236)
	AT1-AA infusion—rat	↓	(182)
	TNF-α infusion—rat	↓	(186)

PlGF, placental growth factor; VEGF, vascular endothelial growth factor; RUPP, reduced uterine perfusion pressure; UPI, uteroplacental ischemia; ROS, reactive oxygen species; AT1-AA, angiotensin II type 1 autoantibody; TNF-α, tumor necrosis factor-α; ET$_A$, endothelin type A receptor.

Table 5

Long-Term Risks for Mother and Baby Following a Preeclamptic Pregnancy

Risk factor	References
Long term risks for offspring	
Hypertension	(12, 19, 82, 249)
Congenital heart disease	(29, 46, 48, 375)
Insulin sensitivity	(19, 300)
Obesity	(19)
Type 2 diabetes mellitus	(19, 160)
Autism spectrum disorder	(55, 207, 356)
Attention deficit/hyperactivity disorder	(133, 308)
Epilepsy	(72, 90, 130, 238)
Stroke	(72, 90, 130, 238)
Depression	(344)
Long term risks for mother	
Hypertension	(43, 338)
Ischemic heart disease	(43)
Cardiac dysfunction	(220, 301)
Heart failure	(190, 229, 371)
Coronary heart disease	(190, 371)
Chronic kidney disease	(199, 214, 241)
Stroke	(43, 190, 338)
Cognitive impairment	(378)
Alzheimer's disease	(338)

Table 6

Summary of Clinical Studies Being Researched for the Treatment of Preeclampsia

Therapy	Preclinical studies in animal models of PE	Clinical trials
NO precursors/ donors	↓ MAP, ↔ pup weight (17)	↔ MAP, trend toward reduced incidence of PE and neonatal complications with L-arginine treatment (244)
	↓ MAP, ↓ prepro-ET-1 (237)	↓ MAP, ↓ umbilical artery PI, ↔ uterine artery PI (128)
	↓ MAP, ↓ proteinuria, ↑ fetal weight, ↓ sFlt-1, ↑ VEGF (253)	↓ MAP, ↓ uterine artery PI, ↓ umbilical artery PI ↔ fetal heart rate, ↔ fetal MCA PI (202)
		↓ Diastolic blood pressure, ↔ fetal heart rate (209)
Sildenafil	↓ MAP, ↔ sFlt-1, ↔ pup weight (114)	STRIDER trial (260):
	↓ MAP, ↓ proteinuria, ↓ kidney injury, ↓ TNF-α, ↓ ET-1, ↓ UARI, ↑ pup weight (118)	↔ Angiogenic factors, ↔ fetal death, ↔ birth weight, ↔ ability to prolong pregnancy, any adverse effects not attributed to Sildenafil (303)
	↓ sFlt-1, ↓ sEng (275)	↔ Fetal outcomes, no adverse outcomes (127).
	↓ MAP in offspring (335)	
PIGF administration	↓ MAP, ↓ sFlt-1, ↓ oxidative stress, ↑ GFR, ↔ pup weight (323)	—
	↓ MAP, ↓ proteinuria, ↓ sFlt-1 mRNA, ↔ sFlt-1 (206)	
sFlt-1 removal	—	↓ sFlt-1, transient ↓ MAP, transient ↓ proteinuria (337)
		↓ sFlt-1, transient ↓ MAP, ↓ proteinuria, gestations prolonged by 8 or 15 days following 1 or multiple treatments, respectively, no adverse effects (336)
Statins	↓ MAP, ↓ sFlt-1, ↑ VEGF, ↑ pup weight, ↓ oxidative stress (42)	StAmP trial:
	↓ MAP in dams and offspring, ↓ sFt-1, ↑ PlGF, ↓ cardiac fibrosis and hypertrophy during pregnancy and postpartum, improved endothelial function in dams and offspring, ↓ ET-1, ↓ oxidative stress, ↑ NO, ↓ glomerular injury during pregnancy and postpartum, ↓ IL-6 and TNF-α (108)	↔ Fetal cholesterol levels, no adverse effects (69)
	Activation of antiapoptotic pathway (292)	↔ sFlt-1, gestation prolonged by 4 days, no adverse effects related to pravastatin (8)
	↑ Cardiac output postpartum, ↓ cardiac fibrosis postpartum, ↓ cardiac hypertrophy postpartum (179)	
Vitamin D	↓ MAP, ↓ sFlt-1, ↓ IL-6, ↔ TNF-α, ↓ AT1-AA, ↓ PPET-1 (100)	Meta-analysis of 30 clinical trials—little to no effect to treat PE and IUGR overall (256)
	↓ MAP, ↓ proteinuria, ↓ oxidative stress, ↓ ER stress, ↓ apoptosis, ↑ pup weight, ↓ renal injury, ↓ cardiac remodeling (341)	Multimineral-vitamin D reduced incidence of PE (32)
	↓ sFlt-1, ↓ TNF-α, ↑ VEGF, ↓ oxidative stress (315)	
	↓ MAP, ↓ CD4+ T cells, (74)	
Vitamin B	↓ sFlt-1, ↓ proteinuria, prolongs gestation, ↑ pup weight (54)	—
	↓ MAP, ↓ proteinuria, ↓ glomerular injury, ↑ pup weight, ↓ HIF1α (105)	

Therapy	Preclinical studies in animal models of PE	Clinical trials
HO-1	↓ MAP, ↑ VEGF, ↔ pup weight, ↓ oxidative stress, ↔ PPET-1 (112) ↓ MAP, ↔ sFlt-1, ↔ VEGF, ↔ pup weight, ↔ TNF-α (115) ↓ MAP, ↑ VEGF, ↔ sFLt-1, ↓ PPET-1 (111)	–
ETₐ antagonist	↓ MAP (11, 182, 236) ↓ MAP, ↓ UARI (329)	–

PE, preeclampsia; ↑, increase; ↓, decrease; ↔, no change; MAP, mean arterial pressure; PI, pulsatility index; MCA, middle cerebral artery; TNF-α, tumor necrosis factor-α; ET-1, endothelin-1; UARI, uterine artery resistive index; sEng, soluble endoglin; STRIDER, Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction; GFR, glomerular filtration rate; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; NO, nitric oxide; IL–6, interleukin-6; StAmP, Statins to Ameliorate Preeclampsia; AT1-AA, angiotensin II type 1 receptor autoantibody; PPET-1, prepro-endothelin-1; ER, endoplasmic reticulum; CD4+, cluster of differentiation 4 positive; IUGR, intrauterine growth restriction; HIF1 α, hypoxia-inducible factor 1α.